Evidence Report/Technology Assessment

Number 224

Omega-3 Fatty Acids and Maternal and Child Health: An Updated Systematic Review

Agency for Healthcare Research and Quality

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Omega-3 Fatty Acids and Maternal and Child Health: An Updated Systematic Review

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Omega-3 Fatty Acids and Maternal and Child Health: An Updated Systematic Review

Structured Abstract

Objectives. To update a prior systematic review on the effects of omega-3 fatty acids (n-3 FA) on maternal and child health and to assess the evidence for their effects on, and associations with, additional outcomes.

Data sources. MEDLINE®, Embase®, the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Centre for Agriculture and Biosciences (CAB) Abstracts from 2000 to August 2015; eligible studies from the original report; and relevant systematic reviews.

Review methods. We included randomized controlled trials (RCTs) of any defined dose of n-3 FA (or combination) compared to placebo, any other n-3 FA, or alternative dose with an outcome of interest conducted in pregnant or breastfeeding women or neonates (preterm or term). We also included prospective observational studies that analyzed the association between baseline n-3 FA intake or biomarker level and followup outcomes. Postnatal interventions began within a week of birth for term infants and within a week of beginning enteral or oral feeding for preterm infants. Standard methods were used for data abstraction and analysis, according to the Evidence-based Practice Center Methods Guide.

Results. We identified 4,275 potentially relevant titles from our searches, of which 95 RCTs and 48 observational studies met the inclusion criteria. Risk of bias was a concern with both RCTs and observational studies. Outcomes for which evidence was sufficient to draw a conclusion are summarized here with the Strength of Evidence (SoE). (Outcomes for which the evidence was insufficient to draw a conclusion are summarized in Appendix G of the report.)

Maternal Exposures and Outcomes

Gestational length and risk for preterm birth: Prenatal algal docosahexaenoic acid (DHA) or DHA-enriched fish oil supplementation had a small positive effect on length of gestation (moderate SoE), but no effect on risk for preterm birth (low SoE). Prenatal EPA (eicosapentaenoic acid) plus DHA-containing fish oil supplementation has no effect on length of gestation (low SoE). Supplementation with DHA, or EPA plus DHA-, or DHA-enriched fish oil does not decreaserisk for preterm birth (low SoE).

Birth weight and risk for low birth weight: Changes in maternal n-3 FA biomarkers were significantly associated with birth weight. Prenatal algal DHA or DHA-enriched fish oil supplementation had a positive effect on birth weight among healthy term infants (moderate SoE), but prenatal DHA supplementation had no effect on risk for low birth weight (low SoE). Prenatal EPA plus DHA or alpha-linolenic acid (ALA) supplementation had no effect on birth weight (low SoE).

Risk for peripartum depression: Maternal n-3 FA biomarkers had no association with risk for peripartum depression. Maternal DHA, EPA, or DHA-enriched fish oil supplementation had no effect on risk for peripartum depression (low SoE).

Risk for gestational hypertension/preeclampsia: Prenatal DHA supplementation among high-risk pregnant women had no effect on the risk for gestational hypertension or preeclampsia

(moderate SoE). Prenatal supplementation of any n-3 FA in normal-risk women also had no significant effect on risk for gestational hypertension or preeclampsia (low SoE).

Fetal, Infant, and Child Exposures and Outcomes

Postnatal growth patterns: Maternal fish oil or DHA plus EPA supplementation had no effect on postnatal growth patterns (attainment of weight, length, and head circumference) when administered prenatally (moderate SoE) or both pre- and postnatally (low SoE). Fortification of infant formulas with DHA plus arachidonic acid (AA, an n-6 FA) had no effect on growth patterns of preterm or term infants (low SoE).

Visual acuity: Prenatal supplementation with DHA had no effect on development of visual acuity (low SoE). Supplementing or fortifying preterm infant formula with any n-3 FA had no significant effect on visual acuity assessed by visual evoked potentials (VEP) at 4 or 6 months corrected age (low SoE). Data conflicted on the effectiveness of supplementing infant formula for term infants with n-3 FA depending on when and how visual acuity was assessed (i.e. by VEP or by behavioral methods) and the type of essential FA provided (low SoE).

Neurological development: Prenatal or postnatal n-3 FA supplementation had no consistent effect on neurological development (low SoE).

Cognitive development: Prenatal DHA supplementation with AA or EPA had no effect on cognitive development (moderate SoE). Supplementing breastfeeding women with DHA plus EPA also had no effect on cognitive development in infants and children (low SoE). Supplementing or fortifying preterm infants' formula with DHA plus AA had a positive effect on infant cognition at some short-term followup times (moderate SoE). Supplementing or fortifying infant formula for term infants with any n-3 FA had no effect on cognitive development (low SoE). Evidence is insufficient to support any effect of n-3 FA infant supplementation on long-term cognitive outcomes.

Autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), and learning disorders: Maternal or infant n-3 FA supplementation had no effect on risk for autism spectrum disorders or ADHD (low SoE). No studies on other learning disorders were identified.

Atopic dermatitis (AD), allergies, and respiratory disorders: Pre- and postnatal (maternal and infant) n-3 FA supplementation had no consistent effect on the risk for AD/eczema, allergies, asthma, and other respiratory illnesses (moderate SoE). Biomarkers and intakes had no consistent association with the risk for AD, allergies, and respiratory disorders (low SoE).

Adverse events: Prenatal and infant supplementation with n-3 FA or fortification of foods with n-3 FA did not result in any serious or nonserious adverse events (moderate SoE); with the exception of an increased risk for mild gastrointestinal symptoms.

Conclusions. Most studies in this report examined the effects of fish oil (or other combinations of DHA and EPA) supplements on pregnant or breastfeeding women or the effects of infant formula fortified with DHA plus AA. As with the original report, with the exception of small increases in birth weight and length of gestation,n-3 FA supplementation or fortification has no consistent evidence of effects on peripartum maternal or infant health outcomes. No effects of n-3 FA were seen on gestational hypertension, peripartum depression, or postnatal growth. Apparent effects of n-3 FA supplementation were inconsistent across assessment methods and followup times for outcomes related to infant visual acuity, cognitive development and prevention of allergy and asthma. Future RCTs need to assess standardized preparations of n-3 and n-6 FA, using a select group of clinically important outcomes, on populations with baseline n-3 FA intakes typical of those of most western populations.

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Executive Summary

Introduction

The n-3 FA (including alpha linolenic acid [ALA], stearidonic acid [SDA], eicosapentaenoic acid [EPA], docosapentaenoic acid [DPA], and docosahexaenoic acid [DHA]) are a group of essential long-chain and very-long-chain polyunsaturated fatty acids (PUFA). Along with the n-6 FA (including linoleic acid [LA] and arachidonic acid [AA]), they are involved in the eicosanoid pathway and are incorporated into cell membranes. Eicosanoids (including AA, prostaglandins, thromboxanes, and leukotrienes) have wide ranges of physiologic effects and play a key role in inflammation regulation. ALA is the simplest n-3 FA from which all other n-3 FA are metabolically derived. ALA must come from the diet as it cannot be made by the body. ALA is found in plants, such as leafy green vegetables, nuts, and vegetable oils such as canola, soy, and flaxseed. SDA can be formed from ALA via Δ-6 desaturase, the rate-limiting enzyme in the pathway. When SDA enters the metabolic pathway, it is rapidly converted to EPA. EPA can be converted to DPA and vice versa. The conversion rates from ALA to EPA or DHA are highly variable. Good sources of EPA and DHA in the diet include fish, other seafood, other marine sources (e.g., algae and phytoplankton), and organ meats.

A role for n-3 FAs in prenatal and postnatal growth and development and risk for certain chronic diseases has been suggested by a variety of evidence from prospective cohort studies and randomized controlled trials (RCTs). In 2002, the Institute of Medicine (IOM) considered the evidence inadequate to establish an estimated average requirement (EAR) for n-3 FAs.[1] Thus, in the absence of sufficient evidence, the IOM set only Adequate Intake values (AIs), based on current population intake in the apparent absence of deficiency symptoms.[a] The IOM set the following AIs for n-3 FA (ALA, whose primary dietary sources are plant foods and algae) for healthy pregnant women and children:

Pregnant women: 1.4 grams(g)/day (d) of ALA
Infants (≤12 months): 0.5 g/d of n-3 FAs
Children (1 to 3 years): 0.7g/d of ALA
Children (4 to 8 years): 0.9 g/d of ALA

In 2004, at the request of the National Institutes of Health's (NIH) Office of Dietary Supplements (ODS), three Evidence-based Practice Centers (EPCs) conducted 11 systematic reviews (SRs) of the evidence for the health effects of n-3 FAs. Included among these SRs was one that encompassed outcomes related to the health of pregnant women and their children.[2] Maternal outcomes included gestational length, the risk for preterm birth, birth weight, intrauterine growth retardation ([IUGR], small-for-gestational age [SGA], and low birth weight [LBW]); birth length, head circumference, pregnancy hypertension and preeclampsia. Child health outcomes included neurological development; visual function in the first year of life; and various indices of cognitive development. This review found insufficient evidence to draw definitive conclusions about the effects of n-3 FA on maternal or child outcomes. Since the original review, many new studies and a number of SRs have examined the role of n -3 FAs in these outcomes. In addition, recent studies have suggested a potential role for n-3FAs in some

[a] The use of an AI instead of an EAR indicates the need for more research to determine, with confidence, the mean and distribution of requirements for that nutrient; AIs are based on much less data and more scientific judgment than are EARs.

related outcomes, e.g., the development of attention and working memory.[3] Thus ODS requested an update to the original report.

Scope and Key Questions

Scope of the Review

The current systematic review has four aims: 1) to update the original review on the topic of the effects of n-3 FAs on maternal and child outcomes,[2] 2) to identify the literature for several additional outcomes of interest (see below) not included in the original review; 3) to include prospective observational studies that were excluded from the original report when two or more RCTs were identified for an outcome of interest; and 4) to use this new review to collect additional information such as baseline intakes of or exposures to n-3 FAs and associations between exposure dose and response that would enhance the usefulness of this report for policy and clinical applications. Therefore, it is of interest to systematically compare results across different exposure/intervention products and study types (e.g., interventional vs. prospective cohort studies), and to account for differences in background n-3 FA intake.

This update includes the addition of seven new outcomes: (maternal) ante- and postnatal depression, and pediatric attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), learning disabilities, atopic dermatitis, allergies, and respiratory disorders, specifically looking at the risk for (or prevention of) these conditions in otherwise healthy individuals and their offspring, rather than the efficacy of n-3 FA in treating affected individuals.

Key Questions

The Key Questions address both issues of efficacy (i.e., causal relationships from trials) as well as associations (i.e., prospective cohort study results and outcomes or risk factors from RCTs for which the randomization may not be applicable). Compared with the Key Questions from the 2005 report, they expand the scope of the review to include additional maternal and child outcomes, as noted above and described below (shown in bold face).

Key Question 1: Maternal Exposures

- What is the efficacy of maternal interventions involving—or association of maternal exposures to—n-3 FAs (EPA, DHA, EPA+DHA, DPA, ALA, SDA, or total n-3 FA) on the following:
  - duration of gestation in women with or without a history of preterm birth (less than 37 weeks gestation),
  - incidence of preeclampsia/eclampsia/gestational hypertension in women with or without a history of preeclampsia/ eclampsia/gestational hypertension
  - Incidence of birth of small-for-gestational age human infants
  - **Incidence of ante- and/or postnatal depression in women with or without a history of major depression or postpartum depression**

- What are the associations of maternal biomarkers of n-3 intake during pregnancy and the outcomes identified above?
- What are the effects of potential confounders or interacting factors (such as other nutrients or use of other supplements, or smoking status)?
- How is the efficacy or association of n-3 FA on the outcomes of interest affected by the ratio of different n-3 FAs, as components of dietary supplements or biomarkers?
- How does the ratio of n-6 FA to n-3 FA intakes or biomarker concentrations affect the efficacy or association of n-3 FA on the outcomes of interest?
- Is there a threshold or dose-response relationship between n-3 FA exposures and the outcomes of interest or adverse events?
- How does the duration of the intervention or exposure influence the effect of n-3 FA on the outcomes of interest?

Key Question 2: Fetal/childhood exposures

- What is the influence of maternal intakes of n-3 fatty acids or the n-3 fatty acid content of maternal breast milk (with or without knowledge of maternal intake of n-3 FA) or n-3 FA-supplemented infant formula or intakes of n-3 FA from sources other than maternal breast milk or supplemented infant formula on the following outcomes in term or preterm human infants?
  - Growth patterns
  - Neurological development
  - Visual function
  - Cognitive development
  - **Autism**
  - **Learning disorders**
  - **ADHD**
  - **Atopic dermatitis**
  - **Allergies**
  - **Respiratory illness**
- What are the associations of the n-3 FA content or the n-6/n-3 FA ratio of maternal or fetal or child biomarkers with each of the outcomes identified above?

Key Question 3: Maternal or childhood adverse events:

- What are the short and long-term risks related to maternal intake of n-3 fatty acids during pregnancy or breastfeeding on
  - Pregnant women
  - Breastfeeding women
  - Term or preterm human infants at or after birth
- What are the short and long-term risks associated with intakes of n-3s by human infants (as maternal breast milk or infant formula supplemented with n-3 FA)?
- Are adverse events associated with specific sources or doses?

Methods

The present review evaluates the effects of—and the associations between—n-3 FAs intakes (including EPA, DHA, DPA, ALA, SDA, and n-3 biomarkers) and maternal and child health outcomes. The Evidence-based Practice Center (EPC) conducted the review based on a systematic review of the published scientific literature using established methods as outlined in the Agency for Healthcare Research and Quality (AHRQ)'s Methods Guide for Comparative Effectiveness Reviews.[4]

This review is conducted in parallel with a systematic review of n-3 FA and cardiovascular disease, conducted by another EPC. Several aspects of the reviews are being coordinated, including eligibility criteria regarding interventions and exposures, search strategies, structure of the reviews, and assessments of the studies' risk of bias, strength of the bodies of evidence, and abstraction of study characteristics needed to assess causality.

We convened a Technical Expert Panel (TEP) to help refine the research questions and protocol. We discussed the Key Questions, analytic framework, study eligibility criteria, literature search, and analysis plans. The protocol was entered into the PROSPERO register (registry number CRD42015020638).

Literature Search Strategy

We modified the existing search strategies from the original report (see Appendix A) to include a complete set of terms for the new outcomes of interest based on searches we have conducted on these topics for previous reviews and consultation with colleagues. We conducted literature searches in Medline (Pubmed), Embase, the Cochrane Collection, Web of Science and Centre for Agriculture and Biosciences (CAB). For the topics of depression; ADHD; autism; and cognitive, neurological, and visual function development, we searched PsychInfo. We did not search for unpublished (grey) literature; however a notice was published in the Federal Register requesting unpublished data from manufacturers of omega-3 fatty acid-fortified infant formulae and dietary supplements. Searches for all topics began with the year 2000. For the newly added topics, we "reference mined" articles that we identified to determine whether any studies conducted and published prior to 2000 should be obtained and included. Studies in the original report deemed eligible for pooling with newly identified studies were included, as were prospective cohort and nested case control studies excluded from the original report that met current inclusion criteria.

The search was updated upon submission of the draft report for peer and public review.

Inclusion and Exclusion Criteria

The eligibility criteria applied to the search results were mostly similar to the criteria used in the original (2005) review. The populations were expanded to accommodate the expanded outcomes of interest. The interventions and exposures remain the same as those in the original report, with the addition of two n-3 FA (DPA and SDA). Included study designs have also been modified slightly.

The Eligibility Criteria are outlined here according to the PICOT framework, with indications of the Key Questions to which they apply.

- **Population(s):**
  - Key Question (KQ) 1(Maternal exposures and outcomes)
    - Healthy pregnant women (for outcomes of birth weight, intrauterine growth restriction/small for gestational age, duration of gestation, risk of pre-eclampsia, eclampsia, or pregnancy hypertension)
    - Pregnant women with a history of pre-eclampsia, eclampsia, or pregnancy hypertension (only for outcome of risk of pre-eclampsia, eclampsia, or pregnancy hypertension)
    - Pregnant women with a history of major depressive disorder or postpartum depression (only for the outcome of risk for peripartum depression)
  - Key Question 2 (In utero and postnatal (through the first year of life) exposures and outcomes)
    - Healthy preterm or full term infants of healthy women/mothers whose n-3 fatty acid exposures were monitored during pregnancy
    - Breastfed infants of healthy mothers whose n-3 fatty acid exposure was monitored and/or who participated in an n-3 fatty acid intervention during breastfeeding beginning at birth
    - Healthy preterm or full term infants with and without family history of respiratory conditions (for outcomes related to atopic dermatitis, allergy, respiratory conditions) of mothers whose n-3 exposures were monitored during pregnancy and/or breastfeeding
    - Healthy children or children with a family history of a respiratory disorder, a cognitive or visual development disorder, autism spectrum disorder, ADHD, or learning disabilities, age 0 to 18 years who participated in an n-3 fatty acid-supplemented infant formula intervention or an n-3 supplementation trial during infancy
  - Key Question 3 (Adverse events associated with n-3 interventions)
    - Healthy pregnant women or pregnant women in the other categories described above
    - Offspring of women enrolled in an n-3 fatty acid intervention during pregnancy
    - Offspring of women whose exposure to n-3 fatty acids was assessed during pregnancy

        - Children whose exposure to n-3 fatty acids (through breast milk, infant formula, or supplementation) was monitored during the first year of life

- **Interventions/Exposures:**
    - Interventions (KQ1, 2, 3 unless specified):
        - N-3 fatty acid supplements (e.g., EPA, DHA, ALA, singly or in combination;
        - N-3 fatty acid supplemented foods (e.g., eggs) with quantified n-3 FA content
        - High-dose pharmaceutical grade n-3 fatty acids, e.g., Omacor®, Ropufa®, MaxEPA®, Efamed, Res-Q®, Epagis, Almarin, Coromega, Lovaza®, Vascepa® (icosapent ethyl)
            - Exclude doses of more than 6g/d, except for trials that report adverse events
        - N-3 fatty acid fortified infant formulae (KQ2,3)
            - E.g., Enfamil® Lipil®; Gerber® Good Start DHA & ARA®; Similac® Advance®
            - N-3 FA fortified follow-up formulae
            - Exclude parenterally administered sources
        - Marine oils, including fish oil, cod liver oil, menhaden oil, and algal with quantified n-3 FA content
        - Algal or other marine sources (e.g., phytoplankton) of omega-3 fatty acids with quantified n-3 content
    - Exposures (KQ1,2)
        - Dietary n-3 fatty acids from foods if concentrations are quantified in food frequency questionnaires
        - Breast milk n-3 fatty acids (KQ2)
        - Biomarkers (EPA, DHA, ALA, DPA, SDA), including but not limited to the following:
            - Plasma fatty acids
            - Erythrocyte fatty acids
            - Adipocyte fatty acids.

- **Comparators:**
    - Inactive comparators:
        - Placebo (KQ1, 2, 3)
        - Non-fortified infant formula (KQ2)
    - Active comparators
        - Different n-3 sources
        - Different n-3 concentrations (KQ1, 2, 3)
        - Alternative n-3 fortified infant formulae (KQ2)
        - Soy-based infant formula (KQ2)
        - Diet with different level of Vitamin E exposure

- **Outcomes:**
    - Maternal outcomes (KQ1)
        - Blood pressure control

            - Incidence of gestational hypertension
            - Maternal blood pressure
            - Incidence of pre-eclampsia, eclampsia
        - Peripartum depression
            - Incidence of antepartum depression[5]
            - Incidence of postpartum depression, e.g.,
                - Edinburgh Postnatal Depression scale
                - Structured Clinical Interview (SCI)
        - Gestational length
            - Duration of gestation
            - Incidence of preterm birth
        - Birth weight
            - Mean birth weight
            - Incidence of low birth weight/small for gestational age
    - Pediatric Outcomes (KQ2)
        - Neurological/visual/cognitive development
            - Visual development, e.g.,
                - Visual evoked potential (VEP) acuity
                - Behavioral visual acuity testing
                    - Teller's Acuity Card test and others
                - Electroretinography
            - Cognitive development, e.g.,
                - Bayley's Scale of Infant and Toddler Development Mental Development Index (MDI)
                - Griffith Mental Developmental Scale
                - Kauffman Assessment Battery for Children
                - Neonatal Behavioral Assessment
                - Wechsler Scales
                - MacArthur Communicative Development Inventory
                - Fagan Test of Infant Intelligence
                - Ages and Stages Questionnaire
                - Stanford-Binet IQ
                    -
            - Neurological development
                - Bayley's Scale of Infant and Toddler Development Psychomotor Development Index (PDI)
                - Electroencephalograms (EEGs) as measure of maturity
                - Neurological/movement impairment assessment
                - Active sleep, quiet sleep, sleep-wake transition, wakefulness
                - Nerve conduction test
                - Latency Auditory evoked potential
        - Risk for ADHD
            - Validated evaluation procedures
                - E.g., Wechsler Intelligence Scale for Children,

            - Behavioral rating scales, e.g., Connors, Vanderbilt, and Barkley scales
        - Risk for Autism spectrum disorders
            - Validated evaluation procedures
                - E.g., Modified Checklist of Autism in Toddlers
        - Risk for learning disabilities
            - Validated evaluation procedures
        - Risk for atopic dermatitis
        - Risk for allergies
            - Validated allergy assessment procedures, preferably challenge (skin prick test or validated blood tests accepted)
        - Incidence of respiratory disorders
            - Spirometry in children 5 and over (peak expiratory flow rate [PEFR] and forced expiratory volume in 1 second [FEV_1])
    - Key Question 3: Adverse effects of intervention(s)
        - Incidence of specific adverse events reported in trials by study arm

- **Timing:**
    - Duration of intervention or follow-up
        - Key Question 1,3 (maternal interventions/exposures):
            - Interventions implemented anytime during pregnancy but preferably during the first or second trimester
            - Follow-up duration is anytime during pregnancy (for maternal outcomes of pre/eclampsia or maternal hypertension); term (for outcomes related to birth weight, duration of pregnancy); or within the first 6 months postpartum (for the outcome of postpartum depression)
        - Key Question 2, 3 (infant exposures):
            - Interventions implemented within one month of birth or exposures measured within 1 month of birth
            - Follow-up duration is 0 to 18 years

- **Settings:**
    - Community-dwelling individuals seen by primary care physicians or obstetricians in private or academic medical practices (KQ1, 3)
    - Community dwelling children seen in outpatient health care or educational settings (KQ2, 3)

We limited the study designs of interest to RCTs of any size, and to prospective cohort studies and nested case control studies of sample size 250 or greater (cross-sectional, retrospective cohort, and case study designs were excluded; studies must have measured intake/exposure prior to outcome). Only peer-reviewed studies published in English language were included. Unpublished studies were not included.

Study Selection

The DistillerSR software package was used to manage the search outputs, screening, and data abstraction. Title/abstract screening was conducted in duplicate). All title selections were accepted without reconciliation for further full-text review. Second-level screening of full text articles was conducted by two reviewers and differences reconciled (the project leaders settle disagreements, if needed).

Data Extraction

Accepted studies underwent single abstraction of study-level data and risk-of-bias assessment in Distiller, with audit by an experienced reviewer. Outcome data were abstracted by a biostatistician and audited by an experienced reviewer. We re-extracted data from studies included in the original report that are to be included in new pooled analyses as needed.

Methodological Quality (Risk of Bias) Assessment of Individual Studies

We assessed the methodological quality of each study based on predefined criteria. Risk of bias among RCTs was assessed using the Cochrane Risk of Bias tool,[6] which evaluates risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential sources of bias. Risk of bias among observational studies was assessed using questions relevant for prospective studies from the Newcastle-Ottawa tools.[7] Both tools were supplemented with nutrition-specific items in consultation with the TEP (e.g., those related to uncertainty of dietary assessment measurements and compliance).[8-10]

Data Synthesis/Analysis

We considered meta-analyses when there were at least three trials with similar intervention (i.e. DHA, DHA+EPA, DHA+AA), follow-up time (i.e. birth, 12 months of age), and population (i.e. pregnant women, term infants, preterm infants). For trials that had groups with the same intervention but with varying doses, we averaged the outcome across doses for the main analysis. Forest plots were provided for random effects meta-analysis. We used the Hartung-Knapp-Sidik-Jonkman method for our random effects meta-analysis.[11-13] It has been shown that the error rates from this method are more robust than the previously used DerSimonian and Laird method.[14] Heterogeneity was assessed using the I2 statistic.[15] All statistical analyses were performed in R 3.2.0.[16]

New trial results were added to original meta-analyses, when appropriate, based on similarity of participants, interventions (including doses), and outcomes.[4]

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

The strength of evidence was assessed for each outcome and exposure type using the method outlined in the AHRQ Methods Guide,[4] in which the body of evidence for each outcome is assessed based on the following dimensions: study limitations (risk of bias), reporting bias, consistency (within and across study designs), directness (of study outcome measures), and precision, as well as the number of studies by study design. Based on these assessments, we assigned a strength of evidence rating (i.e., insufficient, low, moderate, or high level of evidence). The data sources, basic study characteristics, and each strength-of-evidence dimensional rating were summarized in a “Summary of Evidence Reviewed” table detailing our reasoning for arriving at the overall strength of evidence rating. Peer Review and Public Commentary

A draft version of this report was reviewed by a panel of expert reviewers, including representatives from the American Academy of Pediatrics and the American College of Obstetrics and Gynecology, and the general public. The reviewers included experts in prenatal and postnatal development and in the clinical effects of n-3FA and representatives of dietary supplement trade organizations. These experts were either directly invited by the EPC Program or offered comments through a public review process. Revisions of the draft were made, where appropriate, based on their comments. The draft and final versions of the report were also reviewed by AHRQ. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Results

For this systematic review, we identified 95 RCTs and 48 eligible prospective longitudinal studies and nested case-control studies that were eligible for inclusion based on the prespecified inclusion criteria. Most of the RCTs evaluated the effects of marine oil supplements on weight gain during pregnancy (risk for low birth weight) and length of gestation (risk for preterm birth) or the effects of DHA with or without arachidonic acid ([AA], an n-6 FA) as supplements or added to infant formulas on infant neural, visual, and cognitive development. Most observational studies assessed the association between the status of particular n-3 FA and developmental outcomes.

We summarize the results of our review below by the outcomes of interest (maternal outcomes, childhood outcomes, adverse events), and within each outcome, by the target population for the intervention (e.g., pregnant women, preterm infants, term infants) where relevant, and further by the intervention or exposure. Findings included in this summary are those for which evidence was determined to be sufficient to draw a conclusion. Findings for all interventions/exposures across all outcomes and time points are described in full in the main text and the conclusions and strength of evidence are provided in Appendix G.

Maternal Exposures and Outcomes

Length of Gestation and the Risk for Preterm Birth

The original report found inconsistent effects of prenatal maternal n-3 FA supplementation on length of gestation or the risk for preterm birth and a consistent finding of no effects of prenatal maternal supplementation with EPA+DHA among a large number of RCTs. The current report identified a moderate level of evidence that maternal supplementation of DHA or DHA-enriched fish oil may increase gestational length, and a low level of evidence that maternal supplementation with EPA+DHA-containing fish oils may not have significant effects on infants' gestational length compared with placebo.

For the current report, pooled analysis of 11 RCTs among healthy pregnant women found a significant increase in length of gestation among mothers who received algal DHA or DHA-enriched fish oil (weighted mean difference [WMD] +0.34 week [95% CI 0.02, 0.67]) compared to placebo. Pooled analysis of seven RCTs showed no significant effect of DHA or DHA-enriched fish oil on the risk for preterm birth.

Two RCTs in healthy pregnant women showed that maternal fish oil supplementation (EPA+DHA) had no significant effects on length of gestation, while one RCT in at-risk pregnant women found that maternal fish oil supplementation significantly increased the infants' mean gestational age compared with placebo. Pooled analysis of nine RCTs (in four publications) found no effects of EPA+DHA supplementation in pregnant women who were at risk for preterm birth on the incidence of preterm birth.

Random-effects meta-regression found no significant linear dose-response relationships between doses of DHA, EPA, or DHA to EPA ratio (beta coefficient [SE]=-0.04 [0.09], P=0.67, n=9) and the effect sizes.

Prospective studies are sparse and found no consistent associations of maternal exposures with outcomes related to length of gestation or preterm birth.

Birth Weight and the Risk for Low Birth Weight or Small-for-Gestational Age Birth

The original report did not find a significant effect of maternal n-3FA supplementation on the risk for low birth weight (LBW) or small-for-gestational age (SGA) birth or a clear association of any maternal biomarkers with risk for low birth weight or birth weight itself.

For the current report, we found a moderate level of evidence that maternal supplementation with DHA may increase birth weight and a low level of evidence that maternal supplementation with EPA+DHA may not have significant effects on birth weight compared with placebo. Pooled analysis of 12 RCTs showed significantly higher birth weights among infants (mixed term and preterm) whose mothers received algal DHA or DHA-enriched fish oil compared with placebo (WMD [95% CI]=90.12 [2.62-177.62] grams). Pooled analysis of five RCTs found no significant effect of maternal EPA+DHA supplementation on infant birth weight. One RCT that assessed the effects of ALA on infant birth weight also showed no effects. These findings are consistent with prospective observational studies, which found that higher maternal blood DHA concentrations were associated with higher birth weight.

We also found a low level of evidence that maternal supplementation with EPA+DHA may not have significant effects on risk for delivering a LBW infant among healthy pregnant women. Pooled analysis of five RCTs showed no significant effects of fish or fish oil supplementation (doses ranged from 0.49 to 3 g/d) on birth weight compared with placebo or control (WMD [95% CI]=37.89 [-19.53, 95.31]) grams). Similarly, there is a low level of evidence that maternal n-3 FA supplementation may not have significant effects on the incidence of SGA. Two RCTs identified in our search found no effect of DHA alone or DHA-enriched fish oil on SGA outcomes in healthy pregnant women. Pooled analyses of four RCTs also found no significant effects of fish oil supplementation (DHA+EPA) on SGA/IUGR among women at increased risk for preterm delivery (OR [95% CI]=1.00, CI[0.70, 1.43]). Pooled analysis of four RCTs identified for the current review that assessed the effects of DHA alone or DHA-enriched fish oil showed no significant effects on the risk for delivering a LBW infant among women who were not at risk. Observational studies were sparse and showed mostly no associations between n-3FA intake or biomarkers and these outcomes.

Risk for Antenatal and Postnatal Depression

The outcome of risk for antenatal and postnatal depression was a new one for this review. Outcome measures for depression were heterogeneous so meta-analysis is not appropriate. Three RCTs that assessed the effects of prenatal supplementation with DHA alone, DHA+AA, or EPA-enriched fish oil or postnatal supplementation with DHA alone found no effects on risk of developing perinatal depression among healthy pregnant women. One small RCT showed that women who received prenatal DHA supplementation had significantly fewer symptoms of postpartum depression compared to the placebo group. Prospective studies mostly found no significant associations of maternal n-3 FA levels and risk of developing postnatal depression.

Risk for Gestational Hypertension or Preeclampsia

The original report found no consistent effect of maternal supplementation with n-3FA on the risk for gestational hypertension or preeclampsia.

For the current report, pooled analysis of three RCTs (one study identified for the current report and two studies from the original report) that randomized women not at high risk for poor pregnancy outcomes to DHA supplements or placebo showed no difference in the risk for gestational hypertension or preeclampsia among the DHA-treated women compared with the placebo-treated women (OR 0.94[0.66, 1.34], I^2=0% (n=2,818); pooling studies of high-risk women who were randomized to fish oil or placebo also showed no effect (OR 1.04 [0.76 , 1.42], $I^{2=}$ 0%).

Childhood Outcomes

Postnatal Growth Patterns

The original report found no or inconsistent effects of maternal supplementation or infant formula fortification on postnatal growth patterns. The present review identified 24 additional RCTs and three observational studies that included pediatric growth pattern outcomes.

Seven RCTs and two observational studies that evaluated prenatal maternal n-3 FA interventions or exposures found no or mixed effects on growth patterns. Four RCTs examined a combination of prenatal and postnatal maternal n-3 FA interventions or exposures and found no or mixed effects on growth patterns. One RCT examined the effects of a postnatal maternal n-3 FA intervention and found higher body mass index (BMI) and head circumference in the intervention group at 2.5 years, but no effects were observed in an observational study of postnatal maternal exposures. Two RCTs examined a mixed set of postnatal maternal and postnatal infant n-3 FA interventions or exposures and found inconsistent effects of supplementation on growth. Six RCTs that assessed the effects of n-3 FA supplementation in infants on growth patterns were conducted among healthy infants or infants born to healthy women and found inconsistent associations with supplementation and growth patterns. Four RCTs conducted among preterm or LBW infants found inconsistent correlations of n-3 FA supplementation with growth pattern outcomes. Pooled analysis of four RCTs of prenatal (maternal) supplementation alone with DHA and EPA or fish oil (no postnatal supplementation) showed no significant effects on weight, length, or head circumference at 18 months. Pooled analysis of three studies of fortification of infant formula with DHA and AA also showed no effects on postnatal weight gain and length at 4 months among preterm infants.

Neurological Development

The original report found no consistent effect of maternal or infant supplementation with n-3 FA on neurological developmental outcomes and inconsistent associations with biomarkers.

Likewise, 17 RCTs identified for the current report found no consistent effects of n-3 FA alone or in combination with AA or linoleic acid (LA) on any of these outcomes compared with placebo. Two studies reported a positive effect of formula supplemented with DHA and AA on

Bayley's Psychomotor Development Index (PDI) scores (an index of motor development) in preterm infants at 12 and 18 months, and two RCTs reported positive effects on brainstem maturation, but the remaining studies reported mixed effects on measures of motor development, including the PDI, in term infants supplemented with DHA and similarly mixed effects of DHA plus AA on other outcomes.

Visual Acuity

The original report found inconsistent effects of maternal and infant supplementation with n-3 FA on development of visual acuity, and differences between effects on behavioral measures of visual function and effects on electrophysiological measures (visual evoked potentials [VEP]).

Four RCTs that assessed the effects of prenatal maternal supplementation with DHA found no effects on infant visual acuity.

The current report identified one RCT that found that DHA supplementation of breast-feeding mothers resulted in improvement in one VEP outcome (transient VEP amplitude) at 4 and 8 months of age but not at 5 years of age; No differences were seen in other VEP measures, including sweep VEP and transient VEP latency, and no differences were seen using behavioral measures at any age.

Supplementation of preterm infants with any n-3 FA was assessed in nine RCTs identified for the original report and three RCTs identified for the current report. Pooling five studies that assessed VEP at 4 and 6 months showed insignificant effects of n-3 FA supplementation on VEP at 4 months (WMD -0.06 [-0.12, 0.01]; I^2=1.7%) and 6 months corrected age (WMD -0.04[-0.09, 0.01] I^2=0%).

Pooling studies that assessed supplementation of healthy term infants with formula containing any n-3 FA showed inconsistent effects on visual acuity. At two months follow-up, the pooled effect size for behavioral measurements was significant in favor of n-3 FA (WMD 0.07 [0.00, 0.14] six RCTs); the pooled effect size for VEP was insignificant (WMD 0.07[-0.03, 0.17], six RCTs). At 4 months follow-up, the pooled effect size for behavioral measurements was significant in favor of placebo treatment (WMD -0.05 [-0.08, -0.01], six RCTs); the pooled effect size for VEP was significant in favor of n-3 FA (WMD -0.10[-0.14, -0.07], eight RCTs). At 12 months follow-up, the pooled effect size for behavioral measures was insignificant (WMD -0.01[-0.04, 0.01]); the pooled effect size for VEP was significant in favor of n-3 FA (WMD -0.14 [-0.17, -0.12]).

Supplementation of healthy term infants with formula containing DHA+AA also showed inconsistent results. Eight studies identified for the original report showed no differences at 2, 4, 6, 8 and 9 months; however four studies that assessed VEP at 12 months showed a significant pooled effect size in favor of DHA+AA (p=0.01). Two new studies were identified for the current report that assessed the effect of supplementation with DHA+AA on VEP at 4 and 12 months. At 4 months, the pooled effect size for VEP was significant in favor of DHA+AA (WMD -0.10 [-0.14, -0.07], five RCTs). At 12 months follow-up, the pooled effect size for VEP was also significant in favor of DHA+AA (WMD -0.14 [-0.17, -0.12] six RCTs). None of the analyses showed evidence for publication bias.

A small number of trials assessed the association between maternal or infant biomarkers of n-3 FA status and subsequent visual acuity, with inconsistent findings.

Cognitive Development

The original report found inconsistent effects of n-3 FA supplementation on cognitive development. follow-up. We identified ten RCTs of pregnant women that reported cognitive outcomes in their offspring (including the only RCT identified in the original systematic review); only two reported significant results.

Six RCTs, including two from the original review, reported on supplementation for lactating women, including fish oil, cod liver oil, or high-DHA algal oil (two studies each); none reported significant results.

The original review included six RCTs in preterm infants that reported cognitive outcomes, while the current one identified an additional six reports on five RCTs. Seven RCTs of preterm infants reported the Bayley MDI score at 18 to 24 months of age; the pooled difference between the intervention and placebo groups was significant. The other RCTs reported mixed results.

Regarding healthy infants, the original review reported that six of eight RCTs did not find a significant difference between intervention and placebo groups in Bayley MDI scores. The current review identified five additional reports on four RCTs that measured cognitive outcomes. The pooled difference in MDI scores at 18 months was not significant when 3 RCTs were pooled. The RCTs that could not be pooled reported insignificant results regarding cognitive outcomes.

Among six observational studies identified for the current report, almost no associations between biomarker levels of n-3FAs and cognitive outcomes were noted. In one observational study that controlled for 18 potential confounders, low levels of AA in erythrocytes of pregnant women were associated with lower performance IQ; high levels of adrenic acid were associated with lower verbal IQ; and low levels of DHA were associated with lower verbal and full scale IQ at age 8; however, the authors caution that the effect sizes were small.

Risk for Autism, Learning Disorders, and Attention Deficit Hyperactivity Disorder

Developmental outcomes newly included for the current report were the risk for Autism Spectrum Disorders (ASD), Learning Disorders, and Attention Deficit Hyperactivity Disorder (ADHD). Long-term follow-up on one RCT of pregnant women and one RCT of preterm infants found no association between n-3 FA and reduced risk of ASD. One large observational study on ASD was identified; women with the highest quartile of total PUFA intake while pregnant were at lower risk of having a child with ASD than women in the lowest quartile (after controlling for many important potential confounders). The authors advised that the results should be interpreted with caution, given the small number of cases. Two RCTs of preterm infants and one RCT of pregnant women measured attention or reported diagnoses of ADHD at long-term follow-up; no association was found with earlier interventions or biomarker levels. No studies of other learning disorders were identified.

Allergy, Atopic Dermatitis, and Respiratory Conditions

Additional outcomes newly included in the current report were risks for atopic dermatitis/eczema, risks for allergies, and risks for respiratory illnesses, including asthma. A number of studies were conducted in mothers or infants at high familial risk for allergies or asthma.

Atopic dermatitis/eczema: Four prenatal and three postnatal RCTs showed inconsistent effects of maternal n-3 FA supplementation on the risk for atopic dermatitis/eczema: Only one of the prenatal studies found a significant reduction in eczema risk. Only one of seven prospective observational studies found higher concentrations of breast milk n-3 FA to be significantly associated with a lower risk of developing atopic dermatitis; the remaining six studies found no associations between n-3 FA exposures (measured through maternal dietary intake or breast milk composition) and risk for atopic dermatitis/eczema. Studies that assessed the association of biomarkers with this risk observed inconsistent associations of risk for atopic dermatitis with plasma levels of DHA, erythrocyte EPA, AA levels, and EPA/AA ratios. One of four prospective observational studies of n-3 FA biomarkers (in cord blood or maternal blood sample) found decreased risk of eczema and increasing AA levels, with the remaining three studies showing no effects.

Food allergies: Metaanalysis of three RCTs that assessed the effect of maternal supplementation with DHA plus EPA showed a reduction in the risk for food allergies that was not statistically significant. Use of infant formula fortified with DHA and AA or tuna oil or administration of fish oil capsules did not influence the risk for allergies. Prospective observational studies showed no consistent associations of maternal or infant n-3 FA exposures with risk for allergies.

Respiratory illness/asthma: Among 8 RCTs and follow-up studies that assessed the effect of prenatal n-3 FA supplementation on the risk for respiratory illnesses (including wheeze, asthma, persistent cough, inflammation, and respiratory infections), only two reported significant effects—decreases in the risk for asthma—but these effects were not consistent over time. A metaanalysis of three postnatal interventions that assessed the effects of DHA-supplemented formula on risk for wheeze found no significant effect. Prospective observational studies and biomarker studies reported inconsistent associations between various postnatal n-3 FA and n-6 FA exposures and risk for respiratory illnesses, with some studies showing an association between lower DHA, EPA, or total n-3 FA exposures or higher n-3 FA to n-6 FA ratios and lower risk for respiratory conditions (wheeze or asthma) but some studies of the same exposures showing no effects.

Adverse Events

The original report identified 21 RCTs that reported on adverse events with n-3 FA supplementation in pregnant women, breastfeeding mothers, and preterm and term infants. Overall they found that n-3 FA supplements and fortified formulas were well tolerated. Pregnant and breastfeeding women reported no serious adverse events, and adverse events in these groups were limited to mild GI symptoms. Among both preterm and term infants, adverse events were largely limited to GI symptoms also, with most serious adverse events attributable to morbidities associated with prematurity.

The current report identified 20 RCTs that reported on adverse events. The profile of both non-serious and serious adverse events in this report was identical to that of the original report. None of the observational studies identified for the current report described adverse events.

Discussion

Overall Summary and Strength of Evidence

As with the original report, most of the studies identified for the current report assessed the effects of n-3 FA interventions (or associations with exposures) on birth weight (or risk for low birth weight or intrauterine growth retardation), gestational length (or risk for preterm birth), and cognitive outcomes among children. Among studies reporting on the same outcomes, results were often inconsistent across studies.

The current study identified a small but statistically significant effect of DHA supplementation of pregnant women on the length of gestation, strengthening a non- statistically significant finding in the original report. As in the original report, the current report found no effect of DHA- or other n-3 FA supplementation on the risk for preterm birth, and observational studies provided inconsistent results. The difference in findings with respect to length of gestation (a continuous variable) and the risk for preterm birth (a dichotomous variable) may be attributable to any of several factors. Many more studies assessed length of gestation than assessed risk for preterm birth. The effect size for the increase in gestational length may not have been large enough to translate to an observable decrease in risk for preterm birth. Alternatively, the exclusion of preterm infants from some studies that assessed effects of supplementation on length of gestation could have skewed the results, or the populations enrolled in studies that assessed risk for preterm birth may have had sufficient baseline n-3 FA status. Too few studies assessed baseline status to examine this possibility.

The current study also found a significant effect of maternal DHA supplementation on birth weight in a pooled analysis of twelve studies, in contrast to the original report, which saw no effect from pooling two studies. Similar to the original report, a pooled analysis for the current report saw no significant effect of supplementation with DHA on the risk for low birth weight among women who were not at risk due to a prior low-birth-weight pregnancy. Reasons for the difference in these two outcomes may be similar to those posited for length of gestation. In addition, a study by Makrides and colleagues included in this review reported that the increase in birth weight that resulted from DHA supplementation was largely attributable to the increase in gestational age at birth.[17]

This review also identified no significant effects of n-3 FA supplementation of pregnant women on perinatal depression and gestational hypertension/preeclampsia.

The current report identified effects of supplementing formula with n-3 FA on visual acuity of preterm infants at 4 and 6 months corrected age that were not statistically significant but approached borderline significance. The report also found small, statistically significant effects of supplementing infant formula with n-3 FA, mainly DHA plus AA, on visual acuity development in term infants at 4 and 12 months but not at 2 months, when assessed using VEP. However, when behavioral measurements were used, an increase in visual acuity was observed in supplemented infants only at 2 months but not at 4 or 12 months.Thus the observed effects were inconsistent across time and assessment methods.

The current report identified a significant effect of supplementing infant formula with n-3 FA on indices of cognitive development among preterm infants at 18 and 24 months corrected age, but no differences were seen on longterm followup (8 to 10 years). No significant effects of supplementations were seen on cognitive development among term infants. The findings regarding the effects of n-3 FA supplementation on other childhood neurodevelopmental outcomes (e.g. psychomotor development, autism spectrum disorder, attention deficit hyperactivity disorder, and learning disorders) and respiratory outcomes (atopic dermatitis/eczema, allergy, and respiratory disorders) were either lacking in evidence or too inconsistent across studies as well as within studies at different follow-up time points to draw any high strength conclusions.

A random-effects meta-regression showed no dose-response effects for n-3 FA and birth weight. Too few studies assessed the effects of n-3 FA using similar populations and outcome measures to enable dose-response or threshold estimation for other outcomes.

Few studies stratified outcomes according to risk groups, so it was usually not possible to assess whether the effectiveness of omega-3 interventions depended on level of risk. In addition, no RCTs stratified outcomes by baseline n-3 FA status, so it is not possible to assess whether adequacy of n-3 FA status might account for differences in outcomes across (or lack of outcomes within) studies.

Table A summarizes the findings for which we identified a low, moderate, or high strength of evidence (SoE) for an effect or no effect of n-3 FA.

Table A. Conclusions with strength of evidence for an effect or lack of effect

Outcome	Intervention/Exposure	Study Design[a]	Strength of Evidence[b]	Conclusion[c]
Maternal outcomes				
Length of gestation	Healthy pregnant women: n-3 FA*[d] supplementation	12 RCTs 4 observational studies	Moderate	RCTs: Increase in gestational length compared with placebo Meta-analysis of 12 RCTs in update: WMD 0.33 (95% CI 0.04, 0.62) weeks. Observational studies: No associations. Original report: mixed findings .
Length of gestation	Healthy pregnant women: Algal DHA or DHA-enriched fish oil supplementation	11 RCTs 4 observational studies	Moderate	RCTs: Increase in gestational length compared with placebo Meta-analysis of 11 RCTs in update: WMD 0.34 (95% CI 0.02, 0.67) weeks Observational studies: No associations. Original report: mixed findings
Length of gestation	Healthy pregnant women: EPA+DHA fish oil supplementation	7 RCTs 4 observational studies	Low	RCTs: No significant effects on gestational length compared with placebo Observational studies: 3 of 4 found no association. Original report: no effects found[e]
Risk for preterm birth	Healthy pregnant women: Algal DHA or DHA-enriched fish oil supplementation	7 RCTs	Low	RCTs: No significant effects on the incidence of preterm birth compared with placebo Meta-analysis of 7 RCTs: OR 0.87 (95% CI 0.66, 1.15)
Risk for preterm birth	At-risk pregnant women: EPA+DHA fish oil supplementation	9 RCTs 2 observational studies	Low	RCTs:No significant effects on the incidence of preterm birth compared with placebo Meta-analysis of 9 RCTs: 0.86 (95% CI 0.65, 1.15)

Outcome	Intervention/Exposure	Study Design[a]	Strength of Evidence[b]	Conclusion[c]
				Observational studies showed mixed results.
Birth weight	Healthy pregnant women: n-3 FA* supplementation	16 RCTs 10 observational studies	Moderate	RCTs: Significant Increase in birth weight compared with placebo Meta-analysis of 16 RCTs in update: WMD 74.8 (95% CI 12.4, 137.17) grams. Observational studies of dietary intake, supplement use, and biomarkers generally showed positive associations with birth weight. Original report: Mixed findings
Birth weight	Healthy pregnant women: Algal DHA or DHA-enriched fish oil supplementation	12 RCTs 3 observational studies	Moderate	RCTs: Significant Increase in birth weight compared with placebo Meta-analysis of 12 RCTs: WMD 90.12 (95% CI 2.62, 177.62) grams Observational studies showed associations between DHA intake and biomarkers and birth weight. Original report: mixed findings
Birth weight	Healthy pregnant women: EPA+DHA fish oil supplementation	5 RCTs 4 observational studies	Low	RCTs: No significant effects on birth weight compared with placebo Meta-analysis of 5 RCTs: WMD 37.89 (95% CI -19.53, 95.31) grams Observational studies showed mixed associations with birth weight. Original report: no effects
Low birth weight	Healthy pregnant women: Algal DHA or DHA-enriched fish oil supplementation	4 RCTs	Low	RCTs: No significant effects on risk of low birth weight compared with placebo Meta-analysis of 4 RCTs: OR 0.72 (95% CI 0.43, 1.11)

Outcome	Intervention/Exposure	Study Design[a]	Strength of Evidence[b]	Conclusion[c]
SGA/IUGR	At-risk pregnant women: EPA+DHA or fish oil supplementation	4 RCTs 2 observational studies	Low	RCTs: No significant effects on SGA/IUGR compared with placebo Observational studies: no consistent association with SGA Meta-analysis of 4 RCTs: OR 1.00 (95% CI 0.70, 1.43)
Gestational hypertension	Normal-risk pregnant women: DHA supplementation	3 RCTs	Low	RCTs: No significant effect on risk for gestational hypertension in normal risk women Meta-analysis of 3 RCTs OR 0.94 (95% CI 0.66, 1.34)
Gestational hypertension	High-risk pregnant women: Marine oil supplementation	3 RCTs	Moderate	RCTs: No significant effect on risk for gestational hypertension among high-risk women Meta-analysis of 3 RCTs OR 1.04 (95% CI 0.76 , 1.42)
Peripartum depression	Pregnant women: Prenatal DHA, DHA-rich fish oil, DHA+AA, EPA+DHA/fish oil, or any n-3 FA	4 RCTs 8 observational studies	Low	RCTs: Nosignificant effect on risk for peripartum depression across studies. Observational studies showed no associations with risk for depression.[e]
Infant and child outcomes				
Postnatal growth patterns	Pregnant women: Fish oil or DHA+EPA supplementation	7 RCTs 2 observational studies	Moderate	RCTs: No significant effect on postnatal growth patterns among healthy term infants. Observational studies: Consistent with RCTs[e]
Postnatal growth patterns	Breastfeeding women: Supplementation with any n-3FA	6 RCTs 1 observational study	Low	RCTs: No significant effect on postnatal growth patterns Observational study: consistent with RCTs[e]
Postnatal growth patterns	Preterm or term infants: Feeding infant formula fortified with DHA+AA	47 RCTs	Low	RCTs: No significant effect on postnatal growth patterns[e]
Visual acuity	Pregnant women: Supplementation with DHA-enriched fish oil	4 RCTs	Low	RCTs: No significant effect on development of visual acuity in infants.[e]

Outcome	Intervention/Exposure	Study Design[a]	Strength of Evidence[b]	Conclusion[c]
Visual acuity	Preterm infants: Feeding infant formula supplemented with any n-3 FA	5 RCTs	Low	VEP RCTs: No significant effect in preterm infants 4 months corrected age WMD -0.06 (−0.12; 0.01)
Visual acuity	Preterm infants: Feeding infant formula supplemented with any n-3 FA	5 RCTs	Low	VEP RCTs: No significant effect on development of visual acuity in preterm infants 6 months corrected age WMD -0.04 (-0.09, 0.01)
Visual acuity	Term infants: Feeding infant formula supplemented with any n-3 FA	6 RCTs	Low	Behavioral measures RCTs: Significant effect at 2 months WMD 0.07 (0.00, 0.14) six RCTs
Visual acuity	Term infants: Feeding infant formula supplemented with any n-3 FA	6 RCTs	Low	VEP RCTs: No significant effect at 2 months WMD 0.07[-0.03, 0.17], six RCTs
Visual acuity	Term infants: Feeding infant formula supplemented with any n-3 FA	6 RCTs	Low	Behavioral measures RCTs: No significant effect at 4 months WMD -0.05 (-0.08, 0.01) six RCTs
Visual acuity	Term infants: Feeding infant formula supplemented with any n-3 FA	6 RCTs	Moderate	VEP RCTs: Significant effect at 4 months WMD -0.10(-0.14, -0.07), six RCTs
Visual acuity	Term infants: Feeding infant formula supplemented with any n-3 FA	8 RCTs	Low	Behavioral measures RCTs:No significant effect of n-3 FA at 12 months WMD -0.10 (-0.14, -0.07)
Visual acuity	Term infants: Feeding infant formula supplemented with any n-3 FA	8 RCTs	Moderate	VEP RCTs: Significant effect of n-3 FA at 12 months WMD -0.14 (-0.17, -0.12)
Visual acuity	Term infants: Feeding DHA plus AA-fortified infant	7 RCTs	Low	VEP RCTs: Significant effect of

Outcome	Intervention/Exposure	Study Design[a]	Strength of Evidence[b]	Conclusion[c]
	formula			DHA+AAat 4 months. WMD -0.10 (-0.14, -0.07)
Visual acuity	Term infants: Feeding DHA plus AA-fortified infant formula	6 RCTs	Moderate	VEP RCTs: Significant effect of DHA+AA at 12 months WMD -0.14 (-0.17, -0.12)
Neurological development	Pregnant women: Supplementation with any n-3 FA	17 RCTs 5 observational studies	Low	RCTs: No significant effects on measures of neurological development across studies (insufficient numbers of studies of any outcomes to pool) consistent with observational studies.[e]
Cognitive development	Pregnant women: Supplementation with DHA+EPA or DHA + AA	10 RCTs	Moderate	RCTs: No significant effects on cognitive development across studies[e]
Cognitive development	Preterm infants: Supplementation with any n-3 FA	11 RCTs	Moderate	RCTs: Significant increase in cognitive (MDI) scores WMD 2.24; (95% CI 0.05, 4.43)
Cognitive development	Term infants: Supplementation with DHA+ AA	12 RCTs	Low	RCTs: No significant effect on cognitive development at 18-24 months WMD 0.75, 95% CI -9.29, 10.79
Autism Spectrum Disorders (ASD)	Pregnant women or preterm infants: Supplementation with DHA	2 RCTs 1 observational study	Low	RCTs: No significant effect on risk for ASD; association shown for intake of n-3 FA in observational study[e]
ADHD	Pregnant women or preterm infants: Supplementation with DHA	3 RCTs	Low	RCTs: No significant effect on risk for ADHD[e]
Atopic dermatitis/ eczema	Pregnant women: Supplementation with any n-3 FA or exposures as assessed by biomarkers	4 RCTs	Low	RCTs: No significant (and inconsistent) effects on risk for atopic dermatitis/eczema
Atopic dermatitis/ eczema	Breastfeeding women or infants: Supplementation of mothers or infants through formula fortification with any n-3 FA or exposure as assessed with biomarkers	3 RCTs 7 observational studies	Low	RCTs: No significant (and inconsistent) effects on risk for atopic dermatitis/eczema across RCTs, consistent with observational studies[e]
Allergies	Pregnant women: Supplementation with any n-3 FA or	3 RCTs 4 observational studies	Low	RCTs: No significant effect on the risk for food allergy at

Outcome	Intervention/Exposure	Study Design[a]	Strength of Evidence[b]	Conclusion[c]
	exposures as assessed by biomarkers	(including 3 biomarker studies)		12 months OR 0.54 (95% CI 0.05, 6.2); Observational studies: no consistent association of biomarkers and risk for allergy
Allergies	Breastfeeding women or infants: Supplementation of mothers or infants through formula fortification with any n-3 FA or exposure as assessed by biomarkers	3 RCTs 2 observational studies	Low	RCTs: No significant effect on the risk for food or dust mite allergy and no association of breastmilk or infant biomarkers and risk for allergies across observational studies[e]
Asthma and other respiratory illnesses	Pregnant women: Supplementation with any n-3 FA	6 RCTs	Moderate	RCTs: No significant effect on the risk for asthma and other respiratory illnesses Meta-analysis of 3 RCTs OR 0.95 95% CI 0.77, 1.16
Asthma and other respiratory illnesses	Breastfeeding women or infants: Supplementation of mothers or infants through formula fortification with any n-3 FA	3 RCTs	Moderate	RCTs: No significant effect on the risk for asthma and other respiratory illnesses[e]
Asthma and other respiratory illnesses	Pregnant women or infants: Any n-3 FA exposures	10 observational studies	Low	Observational Studies: Inconsistent associations with risk for respiratory illnesses across studies. [e]
Asthma and other respiratory illnesses: Wheeze	Breastfeeding women or infants: Supplementation of mothers or infants through formula fortification with DHA	3 RCTs 5 observational studies 4 biomarkers studies	Low	RCTs: No significant effect on risk for wheeze at 12 months; meta-analysis of 3 RCTs: OR 1.06 (95% CI 0.73,1.54) Observational studies: showed Inconsistent associations with risk for wheeze across studies
Adverse events				
Maternal adverse events Non-serious	Pregnant or breastfeeding women: Supplementation with n-3 FA in the form of fish oil	9 RCTs	Moderate	RCTs: Increased risk for mild gastrointestinal symptoms but no other consistent non-serious adverse events.[e]
Maternal adverse events	Pregnant or breastfeeding women:	4 RCTs	Moderate	RCTs: No significant

Outcome	Intervention/Exposure	Study Design[a]	Strength of Evidence[b]	Conclusion[c]
serious	Supplementation with n-3 FA in the form of fish oil			difference in risk for serious adverse events.[e]
Infant adverse events non-serious	Healthy term infants or preterm infants: Supplementation with n-3 FA in the form of fish oil alone or added to infant formula	13 RCTs	Moderate	RCTs:Increased risk for mild gastrointestinal symptoms across studies but no other consistent non-serious adverse events.[e]
Infant adverse events serious	Healthy term infants: Supplementation with n-3 FA in the form of fish oil	6 RCTs	Moderate	RCTs:No significant difference in risk for serious adverse events.[e]
Infant adverse events serious	Preterm infants: Supplementation with n-3 FA in the form of fish oil	RCTs	Low	RCTs:No significant difference in risk for serious events associated with preterm birth.[e]

[a]Figures represent numbers of studies considered as evidence in drawing the conclusion;
[b]Strength of evidence (SoE) was assessed using a modification of the GRADE method; the assessments for each domain considered in assigning the overall SoE grade are provided in Appendix G for each outcome; RCT outcomes were compared with observational study outcomes, when available, to contribute to the "consistency" domain; [c]Meta-analysis results are shown for all outcomes for which studies were pooled; remaining conclusions are based on trends across studies;
[d]Any n-3 FA refers to a pooled analysis of studies that employed any or unspecified n-3 FA;
[e]RCTs determined to be too heterogeneous to permit pooling.

AA = arachidonic acid; ALA = alpha linolenic acid; CI = confidence interval; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; IUGR = intrauterine growth retardation; n-3 FA = omega-3 fatty acid; OR odds ratio; RCT = randomized controlled trial; SGA = small for gestational age; VEP = visual evoked potentials; WMD = weighted mean difference

Limitations

Within each category of analysis (by outcome, target of intervention, n-3 FA, and study design), studies we identified for this review (like the studies included in the original review) diverged greatly with respect to the sources, doses, and durations of interventions; definitions or tests used to measure outcomes; and follow-up times. For outcomes such as visual, neurological, and cognitive development, by necessity, the tests used over time (in studies with multiple follow-ups) changed to match maturity level. As a result, it was challenging to identify groups of studies that were sufficiently similar to pool, even with studies from the original report. In addition, many RCTs employed and reported the results of numerous outcome measures, which were often internally inconsistent or showed no apparent pattern over time. The majority of studies did not find statistically significant findings. Although one of the charges for the current report was to include observational studies that were excluded from the original report when sufficient numbers of RCTs reported on similar outcomes, only a small number of observational studies that were excluded from the original report met the inclusion criteria for the current report, and the observational studies identified for the current report seldom assessed outcomes that were similar to those assessed in RCTs.

Overall, both RCTs and observational studies included in this review had numerous quality concerns that increased the risk for bias. Across RCTs, the most common risk-of-bias limitation was a lack of intention-to-treat analyses (54 percent of the included RCTs). Of included RCTs, 36 percent failed to describe allocation concealment sufficiently to determine whether it was adequate (and many studies failed to describe recruitment methods). Blinding of study participants contributed only slightly to potential risk of bias because participants were usually infants or children and outcomes were usually clinically apparent or assessed in a clinical laboratory. Thirty-seven percent of RCTs were at risk of attrition bias due to overall dropout rates greater than 20 percent, although most studies reported similar dropout rates between groups. Although 87 percent of the included RCTs reported similar baseline demographic characteristics between groups, 57 percent did not report baseline n-3 FA intake or status. This omission is a critical concern because baseline n-3 FA status likely affects response to changes in n-3 FA intake.

Across observational studies, the most common risk of bias limitation was the lack of representativeness of the cohorts to the population of interest: 35 percent were judged to be select populations or only somewhat representative. In most cases, these populations were described as having high intakes of fish; in several cases, the populations were at high risk for the outcome of interest or another condition. Another reporting inadequacy related to the ranges and distribution of n-3 FA exposures. Of included observational studies, most of the n-3 FA dietary intake assessments included only dietary sources (not n-3 FA supplements). This issue does not affect the quality of biomarker data; however, so many different n-3 FA biomarkers were investigated across studies, that it was impossible to make comparisons. Another limitation of many of these studies was the inability or failure to control for potentially important confounding factors; this issue is magnified for long-term follow up studies.

Few studies reported adverse events, but among the 20 studies that did report adverse events, 60 percent did not predefine or prespecify adverse events to be queried, and none used a recognized categorization system to prespecify or sort categories or levels of intensity of adverse events reported. Only 35 percent reported an active mode of collection of adverse event information, and of the studies that reported serious adverse events (or lack thereof), most did not define "serious adverse event." Of additional concern, studies of preterm infants often comingled morbidities associated with prematurity (such as bronchopulmonary dysplasia and retinopathy of prematurity) and adverse events that might be associated with the intervention. Only one study that met inclusion criteria considered whether mercury exposure could account for the findings on the effects of fish oil intake, but the findings were equivocal.

The population profiles differed somewhat between RCTs and observational studies. Understandably, a number of the RCTs were conducted in women at risk for premature birth, gestational hypertension, a low birth weight infant, or women with a personal or family history of allergy or asthma. However, most observational studies examining the associations between dietary n-3 FA intake or biomarkers of n-3 FA intake and birth, respiratory, allergy, or developmental outcomes were conducted in generally healthy populations. Most RCTs were also small in size, although most reported doing power calculations. Observational studies that enrolled fewer than 250 were excluded by design.

Study interventions or measured exposures tended to be highly heterogeneous. Studies that labeled themselves as studies of DHA alone often included some amount of EPA as well as n-6 FA (usually AA). Fish oil studies did not always report the oil's concentration of n-3 and n-6 FA in addition to the one of interest. Few studies assessed the effects of EPA alone and only one study assessed the effects of ALA alone. Of most concern was the heterogeneity in the description of the n-3 and n-6 FA contents of infant formulas and the systematic lack of assessment of formula intake (realizing the difficulty of this measurement in human infants). Few trials compared n-3 FA dose, formulation (e.g., ratio of EPA to DHA), or source. No trial compared different n-3 to n-6 FA ratios of supplements or intake. None of the observational studies attempted to determine a threshold effect of any associations between n-3 FA and the outcome of interest. Some observational studies failed to report median or range data of n-3 FA levels within quantiles, confidence intervals (or equivalent) of association hazard ratios, or conducted only linear analyses across a full range of n-3 FA values. In addition, studies varied in the range of n-3 FA status (e.g., intake level) within each study. The applicability of many of the observational studies to the U.S. population may also be limited by the higher baseline intakes of fish and other n-3 FA-containing foods and supplements among the populations in these studies.

Among studies that assessed associations between biomarkers of n-3 FA status and an outcome of interest, so many different n-3 FA biomarkers were investigated, that it was impossible to make comparisons across studies.

As mentioned above, another limitation of many of the studies was the inability or failure to control for potentially confounding factors. Observational studies often corrected for a large number of potential confounders, but many important factors could not be or were not measured; this issue is magnified for long-term follow up studies of cognitive development, where environmental factors were seldom considered. RCTs that reported cognitive outcomes at long-term follow up also rarely controlled for potential confounders, although they did report baseline data on characteristics such as SES and parent education, which were usually statistically similar among placebo and intervention groups.

For the outcomes related to infant and child development (except for growth patterns), tests used to measure most outcomes were numerous and heterogeneous across studies regardless of the study designs, and follow-up times varied widely. As a result, studies for a number of outcomes of interest could not be pooled, either with studies identified for the original report or with newly identified studies. In addition, the multiplicity of measures all but ensured that some outcome measure would produce a significant effect. Understandably, studies of cognitive, neurological, and visual acuity development with multiple follow-up points were required to use age/stage-appropriate outcome measures, but they seldom attempted to account for these changes in outcome measures.

The RCTs and observational studies also differed in a number of ways regarding interventions and exposures, making it difficult to compare outcomes across the two study designs. Of note, the doses of n-3 FA supplements in RCTs were often much higher than the highest intake reported for observational studies. Furthermore, not all observational studies explicitly included n-3 FA supplements in their assessment of intake, and almost none of the RCTs attempted to account for background fish or n-3 FA intake as an effect modifier.

For a very small number of RCTs where no significant differences in outcomes were observed between intervention and placebo treatments, posthoc analysis found an association between a biomarker of n-3 FA and the outcome of interest. This observation would seem to suggest that the apparent lack of effect of the intervention on the outcome of interest might be attributable to the participants having had adequate baseline n-3 FA status. However the number of studies that conducted these follow-up analyses was too small to draw definitive conclusions. Likewise, very few RCTs assessed or reported baseline dietary intakes of n-3 FA or biomarker status.

Finally, due to the significant heterogeneity across studies, the interpretation of overall meta-analysis results is limited. Only a small number of RCTs conducted dose response assessments (usually with poor results). For those reasons, we did not attempt to do dose-response meta-analysis of observational studies and performed only a small number of meta-regressions on dose-response across RCTs.

Future Research Recommendations

The design of future RCTs should attempt to determine whether particular populations or individuals are more likely to benefit from n-3 FA supplements or fortified formulas, e.g., individuals with relatively low baseline intakes of n-3 FA. Therefore, studies need to measure—and match intervention groups according to—baseline n-3 FA biomarker status (although the current report has not clearly revealed the most relevant biomarkers). Researchers need to reach consensus on standardized formulations and on reporting of concentrations for interventions. The results of this review should help guide these decisions.

Studies also need to ascertain whether n-3 FA are more effective in individuals at increased risk for particular conditions (such as low birth weight, preterm birth, gestational hypertension, or, for infants, risk for delayed visual acuity development or atopy).

Some recent evidence suggests that individuals' abilities to benefit from dietary supplementation with n-3 FA (or breastfeeding) is influenced by polymorphisms within the gene encoding FADs2, an enzyme involved in the desaturation of fatty acids to convert precursors to LCPUFAs such as DHA. If these findings are confirmed, future studies may need to perform genetic profiles on potential participants and to exclude those who are genetically incapable of responding to supplementation.

Finally, identifying the most promising and clinically relevant outcome measures will be important to expanding the strength of the evidence base for the effectiveness of supplemental n-3 FA for maternal and childhood outcomes. The findings of large cohort studies are still needed to assess the potential role of n-3 FA status in the risk for conditions such as autism spectrum disorder, learning disabilities, and ADHD; however, it may be necessary first to identify clear intermediate risk factors for these conditions, because the length of follow-up needed for diagnosis of the conditions themselves greatly increases the potential interference of other confounding factors.

Conclusions

Most studies identified for this report examined the effects of fish oil (or other combinations of DHA and EPA) supplements on pregnant or breastfeeding women or the effects of infant formula fortified with DHA plus arachidonic acid. With the exception of small effects on birth weight and length of gestation (confirming the findings of the original report), n-3 FA supplementation or fortification has no consistent evidence of effects on peripartum maternal or infant health outcomes. No effects of n-3 FA were seen on gestational hypertension, peripartum depression, or postnatal growth. Apparent effects of n-3 FA supplementation were inconsistent across assessment methods and followup times for outcomes related to infant visual acuity and cognitive development and prevention of allergy and asthma. No association was seen between n-3 FA exposures and the risk for autism spectrum disorders. Evidence was insufficient to draw conclusions regarding effects of n-3 FA on or associations of n-3 FA exposures with ADHD and learning disabilities. Future RCTs need to assess standardized preparations of n-3 and n-6 FA, using a select group of clinically important outcomes, on populations with baseline n-3 FA intakes typical of those of most western populations.

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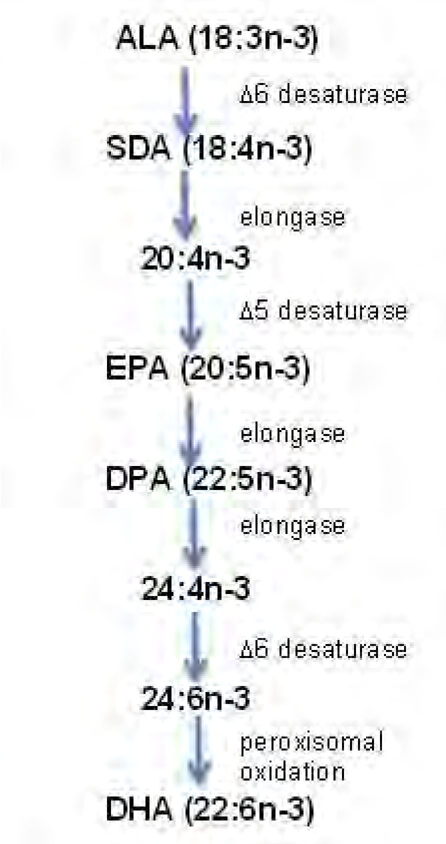
Introduction

The omega-3 fatty acids (n-3 FA) (including alpha-linolenic acid [ALA], stearidonic acid [SDA], eicosapentaenoic acid [EPA], docosapentaenoic acid [DPA], and docosahexaenoic acid [DHA]) are a group of essential long-chain and very-long-chain polyunsaturated fatty acids (LC-PUFA) that are involved in the eicosanoid pathway and are incorporated into cell membranes. Eicosanoids (including prostaglandins, thromboxanes, and leukotrienes) have wide ranges of physiologic effects and play a key role in inflammation regulation. The metabolic pathway of n-3 FA is shown in Figure 1. ALA is the simplest n-3 FA, from which all other n-3 FA are metabolically derived. ALA must come from the diet, as it cannot be made by the body. ALA is found in plant foods, such as leafy green vegetables, nuts, and vegetable oils such as canola, soy, and flaxseed. SDA can be formed from ALA via Δ6-desaturase, the rate-limiting enzyme in the pathway. When SDA enters the metabolic pathway, it is rapidly converted to EPA. EPA can be converted to DPA and vice versa. The rates of conversion from ALA to EPA or DHA are highly variable. Good sources of EPA and DHA in the diet include fin fish, other seafood, other marine sources, and organ meats.

Figure 1. Metabolic pathway of omega-3 fatty acids



ALA = Alpha (α)-linolenic acid; DHA = Docosahexaenoic acid; DPA = Docosapentaenoic acid; EPA = Eicosapentaenoic acid; SDA = Stearidonic acid; n-3 = Omega-3 fatty acids

A role for n-3 FAs in prenatal and postnatal growth and development and risk for certain chronic diseases has been suggested by a variety of evidence from prospective cohort studies and randomized controlled trials (RCTs). In 2002, the Institute of Medicine (IOM) considered the evidence inadequate to establish an estimated average requirement (EAR) for n-3 FAs.[1] Thus, in the absence of sufficient evidence, the IOM set only Adequate Intake values (AIs), based on current population intake in the apparent absence of deficiency symptoms.[a] The IOM set the following AIs for n-3 FA (ALA, whose primary dietary sources are plant foods and algae) for healthy pregnant women and children:

Pregnant women: 1.4 grams (g)/day (d) of ALA
Infants (≤12 months): 0.5 g/d of n-3 FAs
Children (1 to 3 years): 0.7g/d of ALA
Children (4 to 8 years): 0.9 g/d of ALA

In 2004, at the request of the National Institutes of Health's (NIH) Office of Dietary Supplements (ODS), three Evidence-based Practice Centers (EPCs) conducted 11 systematic reviews (SRs) of the evidence for the health effects of n-3 FAs. Included among these SRs was one that encompassed outcomes related to the health of pregnant women and their children.[2] Maternal outcomes included the risk for pregnancy hypertension and preeclampsia. Child health outcomes included risk for preterm birth, intrauterine growth retardation (IUGR) (small-for-gestational age and low birth weight); birth weight, length, and head circumference; neurological development; visual function in the first year of life; and various indices of cognitive development. This review found insufficient evidence to draw definitive conclusions about the effects of n-3 FA on maternal or child outcomes. Since the original review, many new studies and a number of SRs have examined the role of n -3 FAs in these outcomes. In addition, recent studies have suggested a potential role for n-3s in some related outcomes, e.g., the development of attention and working memory.[3]

Scope and Key Questions

Scope of the Review

The NIH ODS has a long history of commissioning AHRQ-based systematic reviews and research methodology reports for nutrient-related topics (http://ods.od.nih.gov/Research/Evidence-Based_Review_Program.aspx). The original 2005 systematic review[2] did not reach strong scientific conclusions for many of the outcomes of interest, most likely related, at least in part, to the fact that some n-3 FA exposures were from fish and other marine sources, some were from dietary supplements, some were indirect (through breast milk), and many studies did not assess biomarkers. In addition, for outcomes of interest for which RCTs were available, observational studies were not considered, whereas for outcomes for which RCTs were unavailable or could not be conducted, the authors relied on observational studies of varying design. Studies of different designs each have their own strengths and weakness that may result in differences in conclusions. For example, observational studies based on self-reported dietary assessments (e.g., food frequency questionnaires) may inaccurately estimate n-3 FA intake; RCTs of specific fish or other n-3 FA-rich food may impose an artificial dietary pattern that might not be applicable to the general population; RCTs of supplements might not fully account for differences in background n-3 FA intake; studies using either study

[a] The use of an AI instead of an EAR indicates the need for more research to determine, with confidence, the mean and distribution of requirements for that nutrient; AIs are based on much less data and more scientific judgment than are EARs.

design may have subtle differences in eligibility criteria, e.g., length of follow-up period, or inclusion of ALA, EPA, and DHA or only EPA and DHA, that significantly impacted the final conclusions.

The current systematic review has four aims: 1) to update the original review on the topic of the effects of n-3 FAs on maternal and child outcomes(Lewin, 2005),[2] 2) to identify the literature for several additional outcomes of interest (see below) not included in the original review; 3) to include prospective observational studies that were excluded from the original report when two or more RCTs were identified for an outcome of interest; and 4) to use this new review to collect additional information that would enhance the usefulness of this report for policy and clinical applications. Therefore, it is of interest to systematically compare results across different exposure/intervention products and study types (e.g., interventional vs. prospective cohort studies), and to account for differences in background n-3 FA intake.

This update includes the addition of seven new outcomes: (maternal) ante- and postnatal depression, and pediatric attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), learning disabilities, atopic dermatitis, allergies, and respiratory disorders, specifically looking at the risk for (or prevention of) these conditions in otherwise healthy individuals and their offspring, rather than the efficacy of n-3 FA in treating affected individuals. The additional outcomes may present several challenges: a limited literature base; the need to rely largely, if not completely, on population-based cohort studies (RCTs are likely to be rare, and case-control studies are inadequate to address these issues); and the need to assess and distinguish the effects of potential maternal and postnatal exposures on postnatal outcomes. Furthermore, there are ongoing concerns in the scientific community regarding systematic biases and random errors in the determination of n-3 FA intakes from dietary and supplement sources, using currently available assessment tools. The limitations of the current methods have been discussed elsewhere.[4, 5] To date, no alternate methods are available. Until "error-free" or "bias-free" methodologies are developed, it is crucial to evaluate the available data with the methodological quality and the limitations in mind. Nutrient biomarkers can provide an objective measure of dietary status. However, the correspondence between intake and biomarker concentration reflects not only recent intake but subsequent metabolism (e.g., elongation, desaturation, metabolism to bioactive compounds). Current biomarkers used to estimate n-3 polyunsaturated fatty acids intakes include ALA, EPA, SDA, and DHA, and are measured in adipose tissue, erythrocytes, plasma, or plasma phospholipids, placenta, and umbilical cord.[6, 7]Adipose tissue FAs are thought to reflect long-term intake, erythrocytes FAs are thought to reflect the previous 120-day intake, and plasma FAs are thought to reflect more immediate intake.[7]

The 2005 review screened 2,049 abstracts, of which 117 articles (describing 89 studies) were included. Of the 89 studies, 63 were RCTs and 26 were observational studies. This current systematic review updated the outcomes included in the previous review and expanded the scope to include additional maternal (risk for perinatal depression) and childhood (risk for ADHD, autism, learning disabilities, allergy, and respiratory conditions) outcomes. Moreover, the current review systematically evaluated possible reasons for inconsistencies between observational and RCT findings by tabulating causality-related study features such as the Bradford Hill criteria.[8]

Key Questions

The Key Questions address both issues of efficacy (i.e., causal relationships from trials) as well as associations (i.e., prospective cohort study results and outcomes or risk factors from

RCTs for which the randomization may not be applicable). Compared with the Key Questions from the 2005 report, they expand the scope of the review to include additional maternal and child outcomes, as noted above and described below (shown in bold face).

Key Question 1: Maternal Exposures

- What is the efficacy of maternal interventions involving—or association of maternal exposures to—n-3 FA (EPA, DHA, EPA+DHA [long-chain n-3 FA], DPA, ALA, SDA or total n-3 FA) on the following:
  - duration of gestation in women with or without a history of preterm birth (less than 37 weeks gestation),
  - incidence of preeclampsia/eclampsia/gestational hypertension in women with or without a history of preeclampsia/ eclampsia/ gestational hypertension
  - Incidence of birth of small-for-gestational age human infants
  - **Incidence of ante- and/or postnatal depression in women with or without a history of major depression or postpartum depression**[*]
- What are the associations of maternal biomarkers of n-3 intake during pregnancy and the outcomes identified above?
- What are the effects of potential confounders or interacting factors (such as other nutrients or use of other supplements, or smoking status)?
- How is the efficacy or association of n-3 FA on the outcomes of interest affected by the ratio of different n-3 FAs, as components of dietary supplements or biomarkers?
- How does the ratio of n-6 FA to n-3 FA intakes or biomarker concentrations affect the efficacy or association of n-3 FA on the outcomes of interest?
- Is there a threshold or dose-response relationship between n-3 FA exposures and the outcomes of interest or adverse events?
- How does the duration of the intervention or exposure influence the effect of n-3 FA on the outcomes of interest?

Key Question 2: Fetal/childhood exposures

- What is the influence of maternal intakes of n-3 fatty acids or the n-3 fatty acid content of maternal breast milk (with or without knowledge of maternal intake of n-3 FA) or n-3 FA-supplemented infant formula or intakes of n-3 FA from sources other than maternal breast milk or supplemented infant formula on the following outcomes in term or preterm human infants?
  - Growth patterns
  - Neurological development
  - Visual function
  - Cognitive development
  - **Autism**
  - **Learning disorders**
  - **ADHD**
  - **Atopic dermatitis**
  - **Allergies**
  - **Respiratory illness**
- What are the associations of the n-3 FA content or the n-6/n-3 FA ratio of maternal or fetal or child biomarkers with each of the outcomes identified above?

Key Question 3: Maternal or childhood adverse events:

- What are the short and long-term risks related to maternal intake of n-3s during pregnancy or breastfeeding on
  - Pregnant women
  - Breastfeeding women
  - Term or preterm human infants at or after birth
- What are the short and long-term risks associated with intakes of n-3s by human infants (as maternal breast milk or infant formula supplemented with n-3 FA)?
- Are adverse events associated with specific sources or doses?

Analytic Frameworks

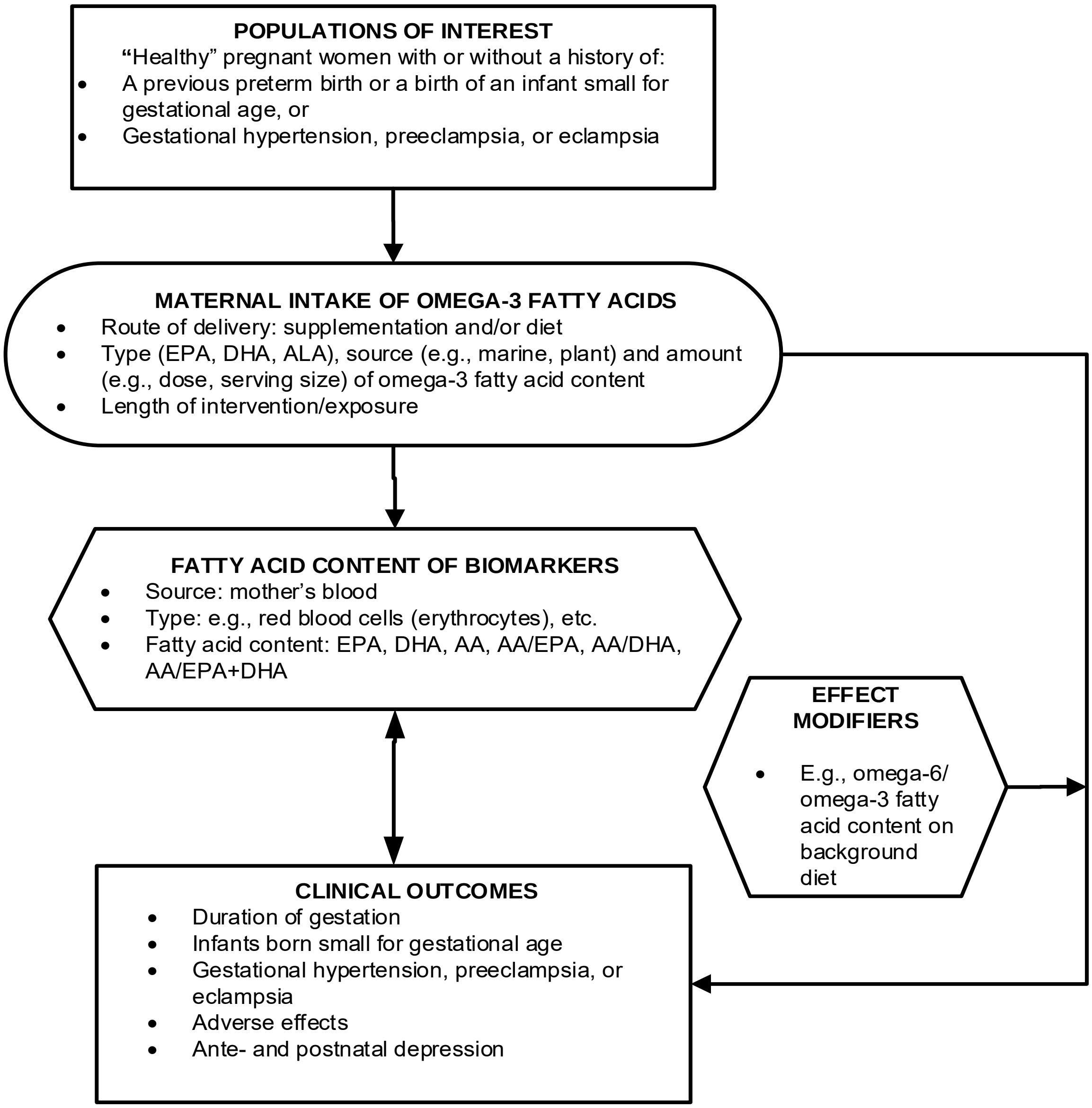
To guide the assessment of studies that examine the association between n-3 FA intake/exposure and the maternal and childhood outcomes of interest, we have created two analytic frameworks (Figures 2 and 3) that map the specific proposed linkages associating the populations of interest, the exposures, modifying factors, and outcomes of interest. The framework graphically presents the key components of the study questions presented above and further described in the Methods section, below.

1. Who are the participants (i.e., what is the population and setting of interest, including the diseases or conditions of interest)?
2. What are the interventions?
3. What are the outcomes of interest (intermediate and health outcomes)?
4. What study designs are of value?

Specifically, this analytic framework depicts the chain of logic that evidence must support to link the intervention (exposure to n-3 FA) to improved health outcomes.

Figure 2. Analytic framework for n-3 fatty acids in maternal health

Populations of interest, Exposure, Outcomes, and Effect modifiers are described. Solid connecting arrows indicate associations and effects reviewed in this report.

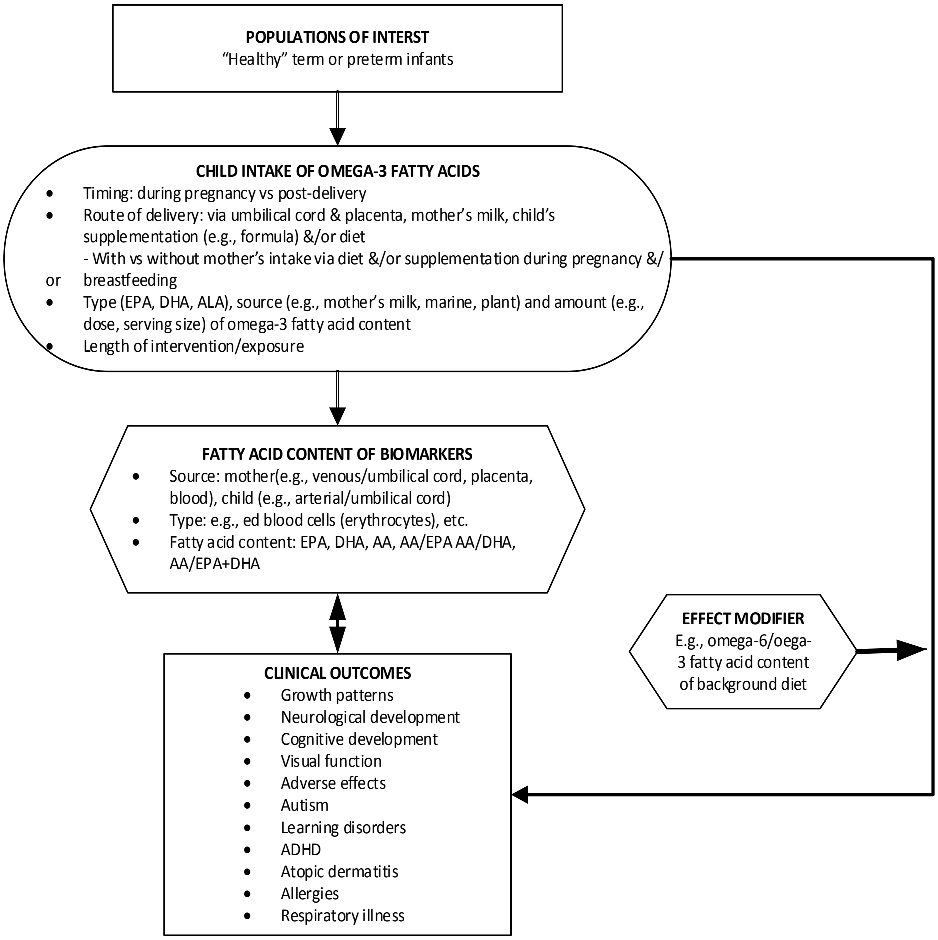


Note: This framework concerns the effect of n-3 FA exposure (as a supplement or from food sources) on maternal health outcomes. Populations of interest, Exposure, Outcomes, and Effect modifiers are described. Solid connecting arrows indicate associations and effects reviewed in this report.

ALA = alpha-linolenic acid, CAD = coronary artery disease, CHF = congestive heart failure, CKD = nondialysis-dependent chronic kidney disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, n-3 FA = omega-3 fatty acid(s); SDA = stearidonic acid.

Figure 3. Analytic framework for n-3 fatty acids in child health

Populations of interest, Exposure Outcomes, Effect modifiers were listed. Solid connecting arrows indicate associations and effects reviewed in this report.



Note: This framework concerns the effect of n-3 FA exposure (as a supplement or from food sources) on infant health outcomes. Populations of interest, Exposure, Outcomes, and Effect modifiers are described. Solid connecting arrows indicate associations and effects reviewed in this report.

ALA = alpha-linolenic acid, CAD = coronary artery disease, CHF = congestive heart failure, CKD = nondialysis-dependent chronic kidney disease, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, SDA = stearidonic acid.

Methods

The present review evaluates the effects ofn-3 FAs (including EPA, DHA, DPA, ALA, SDA, and n-3 biomarkers) on—and the associations between n-3 FA and—maternal and child health outcomes. The Evidence-based Practice Center (EPC) conducted the review of the published scientific literature using established methods as outlined in the Agency for Healthcare Research and Quality (AHRQ)'s Methods Guide for Comparative Effectiveness Reviews.[9]

This review was conducted in parallel with a systematic review of n-3 FA and cardiovascular disease, conducted by another EPC. Several aspects of the reviews are being coordinated, including eligibility criteria regarding interventions and exposures, search strategies, structure of the reviews, and assessments of the studies' risk of bias, strength of the bodies of evidence, and abstraction of study characteristics needed to assess causality.

Topic Refinement and Review Protocol

We convened a Technical Expert Panel (TEP) to help refine the research questions and protocol. The TEP included international experts in n-3 FA research, academic pediatricians, an obstetrician-gynecologist who represents the American Congress of Obstetricians and Gynecologists, and a pediatrician who represents the American Academy of Pediatrics. Also included in the discussions with the TEP were the ODS Director of and a Senior Scientist and the AHRQ Task Order Officer. We discussed the Key Questions, analytic framework, study eligibility criteria, literature searches, and analysis plans. In addition, in separate discussions with the ODS representative and our TOO we considered how and whether to assess the concept of causality, particularly for the observational studies. After discussion of the Bradford Hill criteria and related issues regarding causality,[8] we agreed to provide the study-level data for items that may be pertinent for users of this report to assess causality (this information is included in the Evidence tables in Appendixes C and D).

Furthermore, we had joint discussions with the Brown University EPC—which conducted the parallel report on n-3 FA and cardiovascular disease —and our TOO and the ODS representative to coordinate our protocols and processes. The protocol was entered into the PROSPERO register (registry number CRD42015020638).

Literature Search

Search Strategy

We modified the existing search strategies from the original report (see Appendix A) to include a complete set of terms for the new outcomes of interest based on searches we have conducted on these topics for previous reviews and consultation with colleagues. We conducted literature searches in Medline (Pubmed), Embase, the Cochrane Collection, Web of Science and CAB. For the topics of depression; ADHD; autism; and cognitive, neurological, and visual function development, we searched PsychInfo. We did not search for unpublished (grey) literature; however, a notice was published in the Federal Register requesting unpublished data from manufacturers of omega-3 fatty acid-fortified infant formulae and dietary supplements. Search dates for all topics were January 1, 2000 to August 24, 2015. For the newly added topics, we "reference mined" articles that we identified to determine whether any studies conducted and published prior to 2000 should be obtained and included. Search results were crosschecked with the list of studies included in the original report (as well as the list of prospective cohort studies excluded from the original report that must now be included) to ensure that no studies included in the original report are inadvertently included in the current report as “new” studies.

Appendix A displays the current complete search strategy.

Inclusion and Exclusion Criteria

The current eligibility criteria are mostly similar to the criteria used in the original 2005 review. The populations are expanded to accommodate the expanded outcomes of interest. The interventions and exposures remain the same as those in the original report, with the addition of two n-3 FA (DPA and SDA). Included study designs have been modified slightly.

The Eligibility Criteria are outlined here according to the PICOT framework, with indications of the Key Questions to which they apply.

- **Population(s):**
    - Key Question (KQ) 1(Maternal exposures and outcomes)
        - Healthy pregnant women (for outcomes of birth weight, intrauterine growth restriction/small for gestational age, duration of gestation, risk of pre-eclampsia, eclampsia, or pregnancy hypertension)
        - Pregnant women with a history of pre-eclampsia, eclampsia, or pregnancy hypertension (only for outcome of risk of pre-eclampsia, eclampsia, or pregnancy hypertension)
        - Pregnant women with a history of major depressive disorder or postpartum depression (only for the outcome of risk for peripartum depression)
    - Key Question 2 (In utero and postnatal (through the first year of life) exposures and outcomes)
        - Healthy preterm or full term infants of healthy women/mothers whose n-3 fatty acid exposures were monitored during pregnancy
        - Breastfed infants of healthy mothers whose n-3 fatty acid exposure was monitored and/or who participated in an n-3 fatty acid intervention during breastfeeding beginning at birth
        - Healthy preterm or full term infants with and without family history of respiratory conditions (for outcomes related to atopic dermatitis, allergy, respiratory conditions) of mothers whose n-3 exposures were monitored during pregnancy and/or breastfeeding
        - Healthy children or children with a family history of a respiratory disorder, a cognitive or visual development disorder, autism spectrum disorder, ADHD, or learning disabilities, age 0 to 18 years who participated in an n-3 fatty acid-supplemented infant formula intervention or an n-3 supplementation trial during infancy
    - Key Question 3 (Adverse events associated with n-3 interventions)
        - Healthy pregnant women or pregnant women in the other categories described above
        - Offspring of women enrolled in an n-3 fatty acid intervention during pregnancy
        - Offspring of women whose exposure to n 3 fatty acids was assessed during pregnancy
        - Children whose exposure to n-3 fatty acids (through breast milk, infant

formula, or supplementation) was monitored during the first year of life

- **Interventions/Exposures:**
  - Interventions (KQ1, 2, 3 unless specified):
    - N-3 fatty acid supplements (e.g., EPA, DHA, ALA, singly or in combination;
    - N-3 fatty acid supplemented foods (e.g., eggs) with quantified n-3 content
    - High-dose pharmaceutical grade n-3 fatty acids, e.g., Omacor®, Ropufa®, MaxEPA®, Efamed, Res-Q®, Epagis, Almarin, Coromega, Lovaza®, Vascepa® (icosapent ethyl)
      - Exclude doses of more than 6g/d, except for trials that report adverse events
    - N-3 fatty acid fortified infant formulae (KQ2,3)
      - E.g., Enfamil® Lipil®; Gerber® Good Start DHA & ARA®; Similac® Advance®
      - N-3 fortified follow-up formulae
      - Exclude parenterally administered sources
    - Marine oils, including fish oil, cod liver oil, and menhaden oil with quantified n-3 content
    - Algal or other marine sources of omega-3 fatty acids with quantified n-3 content
  - Exposures (KQ1,2)
    - Dietary n-3 fatty acids from foods if concentrations are quantified in food frequency questionnaires
    - Breast milk n-3 fatty acids (KQ2)
    - Biomarkers (EPA, DHA, ALA, DPA, SDA), including but not limited to the following:
      - Plasma fatty acids
      - Erythrocyte fatty acids
      - Adipocyte fatty acids.

- **Comparators:**
  - Inactive comparators:
    - Placebo (KQ1, 2, 3)
    - Non-fortified infant formula (KQ2)
  - Active comparators
    - Different n-3 sources
    - Different n-3 concentrations (KQ1, 2, 3)
    - Alternative n-3 fortified infant formulae (KQ2)
    - Soy-based infant formula (KQ2)
    - Diet with different level of Vitamin E exposure

- **Outcomes:**
  - Maternal outcomes (KQ1)
    - Blood pressure control
      - Incidence of gestational hypertension
      - Maternal blood pressure

            - Incidence of pre-eclampsia, eclampsia
        - Peripartum depression
            - Incidence of antepartum depression[10]
            - Incidence of postpartum depression, e.g.,
                - Edinburgh Postnatal Depression scale
                - Structured Clinical Interview (SCI)
        - Gestational length
            - Duration of gestation
            - Incidence of preterm birth
        - Birth weight
            - Mean birth weight
            - Incidence of low birth weight/small for gestational age
    - Pediatric Outcomes (KQ2)
        - Neurological/visual/cognitive development
            - Visual development, e.g.,
                - Visual evoked potential acuity
                - Behavioral visual acuity testing
                    - Teller's Acuity Card test and others
                - Electroretinography
            - Cognitive development, e.g.,
                - Bayley's Scale of Infant and Toddler Development Mental Development Index
                - Griffith Mental Developmental Scale
                - Kauffman Assessment Battery for Children
                - Neonatal Behavioral Assessment
                - Wechsler Scales
                - MacArthur Communicative Development Inventory
                - Fagan Test of Infant Intelligence
                - Ages and Stages Questionnaire
                - Stanford-Binet IQ
                    -
            - Neurological development
                - Electroencephalograms (EEGs) as measure of maturity
                - Psychomotor developmental index from Bayley's scales
                - Neurological/movement impairment assessment
                - Active sleep, quiet sleep, sleep-wake transition, wakefulness
                - Nerve conduction test
                - Latency Auditory evoked potential
        - Risk for ADHD
            - Validated evaluation procedures
                - E.g., Wechsler Intelligence Scale for Children,
                - Behavioral rating scales, e.g., Connors, Vanderbilt, and Barkley scales
        - Risk for Autism spectrum disorders

        - Validated evaluation procedures
            - E.g., Modified Checklist of Autism in Toddlers
      - Risk for learning disabilities
        - Validated evaluation procedures
      - Risk for atopic dermatitis
      - Risk for allergies
        - Validated allergy assessment procedures, preferably challenge (skin prick test or validated blood tests accepted)
      - Incidence of respiratory disorders
        - Spirometry in children 5 and over (peak expiratory flow rate [PEFR] and forced expiratory volume in 1 second [FEV_1])
  - Key Question 3: Adverse effects of intervention(s)
      - Incidence of specific adverse events reported in trials by study arm

- **Timing:**
  - Duration of intervention or follow-up
      - Key Question 1,3 (maternal interventions/exposures):
        - Interventions implemented anytime during pregnancy but preferably during the first or second trimester
        - Follow-up duration is anytime during pregnancy (for maternal outcomes of pre/eclampsia or maternal hypertension); term (for outcomes related to birth weight, duration of pregnancy); or within the first 6 months postpartum (for the outcome of postpartum depression)
      - Key Question 2, 3 (infant exposures):
        - Interventions implemented within one month of birth or exposures measured within 1 month of birth
        - Follow-up duration is 0 to 18 years

- **Settings:**
  - Community-dwelling individuals seen by primary care physicians or obstetricians in private or academic medical practices (KQ1, 3)
  - Community dwelling children seen in outpatient health care or educational settings (KQ2, 3)

We limited the study designs of interest to RCTs, prospective cohort studies, and nested case control studies (cross-sectional, retrospective cohort, and case study designs were excluded; studies must have measure of intake/exposure prior to outcome). Only peer-reviewed studies published in English language were included. Unpublished studies were not included.

To focus on studies of the highest relevance and quality, we also excluded observational studies with enrollment sizes of less than 250 unless no other studies were identified for a particular outcome; we also excluded studies that reported exposures only as servings of fish without calculating n-3 FA intakes, study size, exposure duration, or other similar criteria, if the number of studies identified is very large.

Study Selection

The DistillerSR software package was used to manage the search outputs, screening, and data abstraction. Title/abstract screening was conducted in duplicate (after a training session to ensure understanding of the inclusion and exclusion criteria and reasonable inter-rater reliability), using a screening form that lists the inclusion and exclusion criteria and allows selection of reasons for exclusion. All title selections were accepted without reconciliation for further full-text review. Second-level screening of full text articles was conducted by two reviewers and differences reconciled (the project leaders settle disagreements, if needed).

Abstracts for a subset of ten percent of titles selected from the EMBASE search were reviewed; based on the acceptance rate of the abstracts, it was determined that no additional abstracts for publications identified in the EMBASE search would be screened for inclusion.

Reference lists of existing recent SRs on outcomes of interest were reviewed to ascertain that we did not miss relevant studies.

Studies that were excluded at the full-text screening stage are listed in Appendix B with the reasons for exclusion. Publications identified in the searches for this report that were included in the original report were excluded at this stage (for purposes of tracking the literature flow) and are listed in Appendix B, regardless of whether they were subsequently included in analyses in this report.

Data Extraction

Accepted studies underwent single abstraction of study-level data and risk-of-bias assessment in Distiller, with audit by an experienced reviewer. Outcome data were abstracted by a biostatistician and audited by an experienced reviewer. We re-extracted data from studies included in the original report that were included in new pooled analyses as needed.

Data collection forms were designed by the project team in Distiller SR, piloted by the reviewers, further modified, and then the final forms piloted with a random selection of included studies to ensure agreement of interpretation. Studies based on large prospective cohorts were identified in their Distiller records to allow comparison to ensure data were not extracted in duplicate. Study-level data included PICOTs, baseline nutritional status/ biomarkers/other evidence of initial exposure to n-3 fatty acids as well as status of other nutrients that could influence outcomes (e.g., vitamin E), method of exposure assessment and associated margin of error, inclusion/exclusion criteria, study design, comorbidities, other potential effect modifiers, analytic methods, and characteristics necessary to assess risk of bias, including recruitment, blinding, allocation concealment, description of completeness of final dataset, funding source, and other potential conflicts of interest.

Outcome data, including clinical outcomes and intermediate outcomes (concentrations of biomarkers), were abstracted in duplicate in Excel files by the biostatistician and one additional reviewer. At the end of the project, abstracted data will be uploaded to the Systematic Review Data Repository (SRDR) for full public accessibility.

Methodological Quality (Risk of Bias) Assessment of Individual Studies

We assessed the methodological quality of each study based on predefined criteria. Risk of bias among RCTs was assessed using the Cochrane Risk of Bias tool,[11] which evaluates risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential sources of bias. Risk of bias among observational studies was assessed using questions relevant for prospective studies from the Newcastle-Ottawa tools.[12] Both tools were supplemented with nutrition-specific items in consultation with the TEP (e.g., those related to uncertainty of dietary assessment measurements and compliance).[13-15] For pooled analyses with significant effect sizes, we assessed publication bias using the Egger's and Begg's tests. Studies that reported adverse events were also assessed for adverse event assessment and reporting using the McMaster Quality Assessment Scale of harms (McHarm).[16] Any quality issues pertinent to specific outcomes within a study were noted and considered when determining the overall strength of evidence for conclusions related to those outcomes.

Data Synthesis/Analysis

All included studies were summarized narratively and in summary tables that show the important features of the study populations, design, intervention/exposure, outcomes, and results; we built off and improved on the tables used in the original review. Separate summary tables were used to describe studies that report on a particular outcome of interest.

We analyzed the results of studies of different design separately, combining them if appropriate, and we compared and contrasted populations, exposures, and outcomes across study designs, examining any differences in outcomes between interventional and observational studies.

Statistical data were extracted from all trials with an outcome of interest. We considered meta-analyses when there were at least three trials with similar population (e.g., pregnant women, term infants, preterm infants), intervention (e.g., DHA, DHA+EPA, DHA+AA), follow-up time (e.g. birth, 12 months of age), and outcome measure. For trials that had groups with the same intervention but with varying doses, we averaged the outcome across doses for the main analysis. Forest plots were provided for random effects meta-analysis. We used the Hartung-Knapp-Sidik-Jonkman method for our random effects meta-analysis.(Hartung, 1999)[17] (Hartung, 2001)[18] (Sidik, 2006)[19] It has been shown that the error rates from this method are more robust than the previously used DerSimonian and Laird method.[20] Heterogeneity was assessed using the I2 statistic.[21] All statistical analyses were performed in R 3.2.0.[22]

New trial results were added to original meta-analyses, when appropriate, based on similarity of participants, interventions (including doses), and outcomes.[9] When sufficient data were available and clinical heterogeneity was minimal, we conducted dose-response meta-analysis (for observational studies) or meta-regression on doses (for RCTs) to support our qualitative synthesis. When new bodies of observational studies were added, possibility for random-effects multivariate dose-response meta-analysis was also assessed (Shekelle, 2014; Ahmadzai, 2013; Greenland, 1992; Orsini, 2012; Hamling, 2008).[23-27] For meta-analysis of data with clear outliers, sensitivity analyses were conducted, if appropriate to the question.

Summary of Causality-Related Study Features

Appendix I includes data related to possibility causality criteria for all included studies. The list of items in this table was compiled based on discussions between the EPCs and ODS after discussion of the Bradford Hill criteria and other issues related to determining causality.[8] The table lists included studies with their timeframe, country, population category (pregnant, breastfeeding, preterm infant, term infant), baseline n-3 FA intake, n-3 FA source, n-3 FA type, how n-3 FA intake measured, study design (e.g., randomized controlled trial, prospective or retrospective longitudinal cohort, or other design), exposure duration, followup time, outcomes reported, effect sizes and types, difference in n-3 FA intake (between low and high intake groups), and whether outcomes were reported to be primary outcomes (vs. secondary or unspecified). The determination of primary outcomes was based on an explicit statement of the primary outcomes, the outcome used in reported power calculations, or implied by focus of the original article.

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

The strength of evidence was assessed for each outcome and exposure type using the method outlined in the AHRQ Methods Guide[9], in which the body of evidence for each outcome is assessed based on the following dimensions: study limitations (risk of bias), reporting bias, consistency (within and across study designs), and precision, as well as the number of studies by study design. Based on these assessments, we assigned a strength-of-evidence rating (i.e., insufficient, low, moderate, or high level of evidence). The data sources, basic study characteristics, and each strength-of-evidence dimensional rating were summarized in "Summary of Evidence Reviewed" tables detailing our reasoning for arriving at the overall strength of evidence rating (Appendix G). Applicability of studies to the populations and interventions that are the focus of the current review was assessed also, as described below.

Assessing Applicability

The primary basis for assessment of applicability was the similarity of average intake of n-3 fatty acids (as fatty fish or other foods) to that of the U.S. and other healthy western populations at baseline. Studies of healthy pregnant women and healthy infants were also judged to have higher applicability than those enrolling women with a prior history of poor pregnancy outcomes or children with a family history of the conditions of interest. Studies in which the majority of participants were taking n-3 supplements at baseline were also rated as having lower applicability.

Peer Review and Public Commentary

A draft version of this report was reviewed by a panel of expert reviewers, including representatives from the American Academy of Pediatrics and the American College of Obstetrics and Gynecology and the general public. The reviewers included experts in prenatal and postnatal development and in the clinical effects of n-3FA and representatives of dietary supplement trade organizations. These experts were either directly invited by the EPC or offered comments through a public review process. Revisions of the draft were made, where appropriate, based on their comments. The draft and final reports are also reviewed by AHRQ. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Results

This section first describes the results of the literature searches, followed by the key findings, descriptions of the studies that met inclusion criteria, and detailed descriptions of the findings and synthesized outcomes for each of the Key Questions.

Results of Literature Searches

Our searches identified 3,760 titles/abstracts. An additional search of CAB resulted in 480 titles. Twelve references were suggested by experts and 23 references were rescreened from the Ottawa report. This yielded 4,275 titles/abstracts that went out for dual screening, of which 3,617 titles/abstracts were excluded for the following reasons: not human (178), not omega-3 (1,611), not in English (1), treatment study that didn't address prevention/risk (197), study design (including editorials, letters, cross sectional study design, and protocols) (178), population not of interest (653), omega-3 not orally taken (70), no outcomes of interest (101), does not address the KQ (473), only exposure/intervention was total fish intake (33), study only addressed biomarkers and no other outcomes of interest (2), duplicate data (3), non-systematic review background (83), or no abstract was indexed (34).

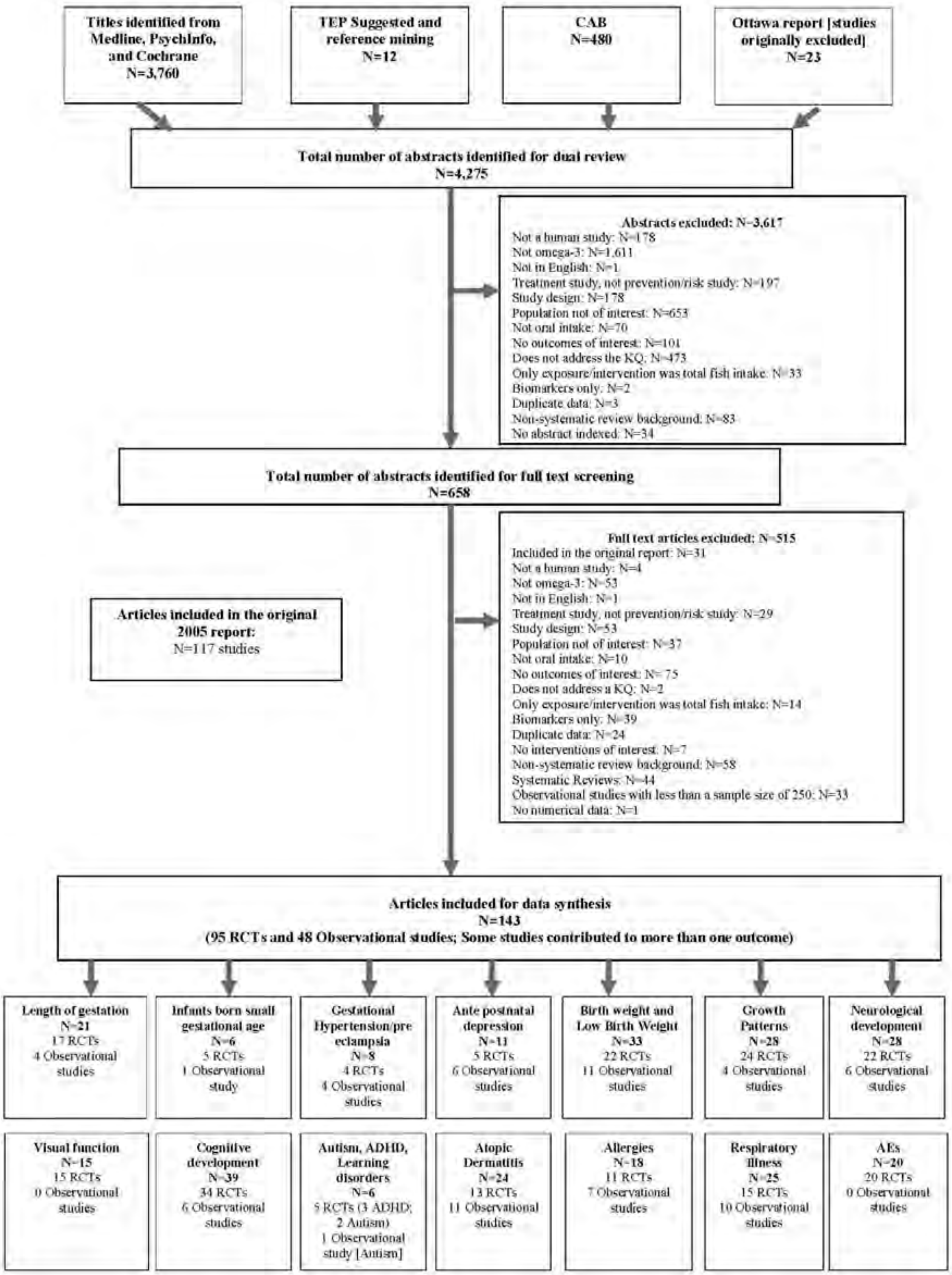
We reviewed 658 full text articles, of which 515 were excluded for the following reasons: study was included in the original report (31: these articles were subsequently included in our analyses but that number was subtracted from the number of new articles included from our searches in the flow; all studies included in the original report, 117, were included in the current report as well, as shown in the flow diagram and in Appendix H), participants were not human (4), not omega-3 (53), not in English (1), treatment study only (29), study design (53), population not of interest (37), not oral intake (10), no outcomes of interest (75), did not address a Key Question (2), fish intake only (14), biomarkers only (39), duplicate data (24), no interventions of interest (7), non-systematic review background (58), systematic review (44), observational studies with less than a sample size of 250 participants (33), and no numerical data (1). A list of references by exclusion reason can be found in Appendix B.

The Federal Register posting did not yield any additional materials to review for possible inclusion.

We include 143 new articles in our report. Ninety-five of the articles are randomized controlled trials (RCTs) and 48 are observational studies.

We break down the included studies by outcomes, which can be found below in the literature flow diagram below (see Figure 4).

Figure 4. Literature flow diagram



AE(s)=Adverse Event(s); KQ=Key Question; RCT(s)=Randomized Controlled Trial(s); SR(s)=Systematic Review(s); TEP = Technical expert panel;

Findings

Key Question 1: Maternal Exposures

- What is the efficacy of maternal interventions involving—or association of maternal exposures to—n-3 FA (EPA, DHA, EPA+DHA [long-chain n-3 FA], DPA, ALA, SDA or total n-3 FA) on the following:
  - duration of gestation in women with or without a history of preterm birth (less than 37 weeks gestation),
  - incidence of preeclampsia/eclampsia/gestational hypertension in women with or without a history of preeclampsia/ eclampsia/gestational hypertension
  - Incidence of birth of small-for-gestational age human infants
  - **Incidence of ante- and/or postnatal depression in women with or without a history of major depression or postpartum depression**
- What are the associations of maternal biomarkers of n-3 intake during pregnancy and the outcomes identified above?
- What are the effects of potential confounders or interacting factors (such as other nutrients or use of other supplements, or smoking status)?
- How is the efficacy or association of n-3 FA on the outcomes of interest affected by the ratio of different n-3 FAs, as components of dietary supplements or biomarkers?
- How does the ratio of n-6 FA to n-3 FA intakes or biomarker concentrations affect the efficacy or association of n-3 FA on the outcomes of interest?
- Is there a threshold or dose-response relationship between n-3 FA exposures and the outcomes of interest or adverse events?
- How does the duration of the intervention or exposure influence the effect of n-3 FA on the outcomes of interest?

Length of Gestation (or Gestational Age) and Preterm Birth

Key Findings and Strength of Evidence for Length of Gestation (or Gestational Age) and Preterm Birth

- Overall meta-analysis combining 12 RCTs showed that algal DHA, DHA-rich fish oil, or fish oil (EPA+DHA) supplementation during pregnancy significantly increased gestational length (Weighted mean difference [WMD] [95% CI] 0.33 [0.04, 0.62] weeks, I^2 = 70.6), but there were no significant effects on the incidence of preterm birth compared with placebo or control.
  - Random-effects meta-regression found no significant linear dose-response relationships between doses of DHA, EPA, or DHA to EPA ratio (beta coefficient [SE]= -0.04 [0.09], P=0.67, n=9) and the effect sizes.
- There is a moderate level of evidence that maternal supplementation with DHA or DHA-enriched fish oil may increase gestational length, and a low level of evidence that maternal supplementation of EPA+DHA fish oils may not have significant effects on infants' gestational length compared with placebo.
  - Pooled analysis of 11 RCTs in healthy pregnant women found a significant increase in gestational length among mothers who received algal DHA or DHA-enriched fish oil supplements (WMD [95% CI]=+0.34 [95% CI 0.02, 0.67] weeks) compared to placebo.
  - Pooled analysis of five RCTs in healthy pregnant women showed that maternal fish oil supplementation (EPA+DHA) had no significant effects on gestational length, while one RCT in at risk pregnant women found that maternal fish oil supplementation significantly increased the infants' mean gestational length compared with placebo.
  - One RCT in healthy pregnant women found no significant effects of various doses of EPA+DHA supplements on gestational length compared to ALA-supplemented controls.
  - Three prospective observational studies were heterogeneous and showed mixed findings on the associations between maternal n-3 FA intake and birth weight.
- There is a low level of evidence that maternal supplementation of n-3 FA (DHA or EPA+DHA) did not have significant effects on the incidence of preterm birth.
  - Pooled analysis of seven RCTs showed no significant effect of DHA or DHA-enriched fish oil in healthy pregnant women on the incidence of preterm birth.
  - Pooled analysis of nine RCTs (in four publications) found no effects of EPA+DHA supplementation in pregnant women who were at risk for preterm birth on the incidence of preterm birth.
  - Three prospective observational studies found no associations between maternal n-3 FA intake and either gestational length or risk of preterm birth.
  - One prospective observational study among pregnant women with at least one prior spontaneous preterm delivery found no significant difference in odds of preterm birth when comparing the lowest quartile of maternal erythrocyte n-3 FA biomarker with the upper three quartiles. Only women in quartile two of erythrocyte n-3 FA levels had a significantly lower risk for preterm birth compared to those in quartile one.

Description of Included Studies

The original report included 15 RCTs (in 10 publications – one publication by Olsen et al.[28] represented the pooled data of six different RCTs) investigating maternal intake of n-3 FA supplementation on infants' gestational length. Of these studies, eleven RCTs compared fish oil capsules (EPA+DHA doses ranging from 0.1 to 5 g/d) with placebo (olive oil and coconut oil), two compared high-DHA eggs (DHA 133-184 mg/d) with regular-DHA eggs (DHA 33-35 mg/d), one compared DHA-rich cod liver oil (1183 mg/d DHA; 803 mg/d EPA; 27.5 mg/d AA) with corn oil (8.3 mg/d DHA), and one compared margarine containing different amount of ALA and LA (ALA group: 2.82 g/d ALA and 9.02 g/d LA; control group: 0.03 g/d ALA and 10.94 g/d LA). Ten of the 15 RCTs did not find a significant effect of maternal n-3 FA supplementation on infants' gestational length. The other five RCTs reported a significant increase in infants' gestational length, comparing maternal n-3 FA supplementation (one study of high-DHA eggs with 133 mg/d DHA and four of fish oil supplementation with EPA+DHA ranging from 2.2. to 5 g/d). Ten of these 15 RCTs also reported incidence of premature delivery outcome. N-3 FA supplementation did not have significant effects on the proportion of premature deliveries in these studies. Random-effects meta-analyses of eight RCTs (in three publications: again, one publication by Olsen et al.[28] represented pooled data from six different RCTs) that compared maternal fish oil supplementation (EPA+DHA) to placebo showed that the odds of premature deliveries did not differ significantly between groups (OR 0.88; 95% CI 0.62, 1.25). Similarly, meta-analysis of two RCTs comparing maternal intake of high-DHA eggs with regular-DHA eggs showed that the odds of premature deliveries did not differ significantly between groups (OR 0.53; 95% CI 0.13, 2.29).

The original report included only one prospective cohort study. This cohort study reported a positive association between plasma triglyceride AA content and gestation length. However, the study did not find a significant association between maternal plasma triglyceride n-3 FA and the length of gestation.

Fifteen new RCTs and four observational studies were identified for the current report (see Table 1). With the exception of one study (Harper, 2010)[29], the remainder were conducted among healthy, pregnant women followed until birth. The one RCT that enrolled pregnant women at risk for preterm labor (defined as a documented history of at least one prior singleton preterm delivery after spontaneous preterm labor or premature rupture of the membranes) was therefore excluded from the meta-analysis. Overall, we found a moderate level of evidence that maternal supplementation of DHA or DHA-rich fish oils may increase gestation length, but the dose-response relationship between DHA doses and effect sizes is still unclear. However, there is a low level of evidence that maternal supplementation of EPA+DHA fish oils may not have any significant effect on infants' gestational length compared with placebo in healthy pregnant women.

Furthermore, there is a low level of evidence that maternal supplementation of any n-3 FA did not have a significant effect on the risk of preterm birth.

Limited evidence from one RCT and one cohort study suggested that effects of n-3 FA on gestation length and risk of preterm birth may be larger in women with a history of spontaneous preterm deliveries.

Randomized Controlled Trials

Fifteen unique RCTs were identified for the current report. Of these, three RCTs (in five publications) compared algal DHA supplements with placebo,[30-34] nine compared DHA-rich fish oil supplementation (DHA:EPA ratio ≥5:1) with controls,[35-43] three compared fish oil (EPA+DHA, DHA:EPA ratio <5:1) with placebo,[29, 42, 44] and one compared five different doses of fish oil supplementation (EPA+DHA 0.1, 0.3, 0.7, 1.4 and 2.8 g/d) with ALA control (ALA 2.2 g/d).[45] Of these, one RCT compared both DHA-rich fish oil supplement and fish oil supplement, with placebo.[42]

All 15 RCTs reported gestation length as an outcome. Among these, seven RCTs also reported the incidence of preterm birth.[29, 31-35, 37, 43] Overall meta-analysis combining 12 RCTs showed that algal DHA, DHA-rich fish oil, or fish oil (EPA+DHA) supplementation during pregnancy significantly increased gestational length compared with placebo or controls (WMD [95% CI] 0.33 [0.04, 0.62] weeks), with high heterogeneity (I^2 = 70.6). (Figure 5) Random-effects meta-regression found no significant linear dose-response relationships between doses of DHA (beta coefficient [SE]= 0.12 [0.26], P=0.66, n=12), EPA (beta coefficient [SE]= -0.04 [0.46], P=0.94, n=11), or the ratio of DHA to EPA (beta coefficient [SE]= -0.04 [0.09], P=0.67, n=9) and the effect sizes (mean differences in gestational length between n-3 FA and placebo groups)

Our update meta-analysis of seven RCTs (two from the original report) did not find a significant effect of algal DHA or DHA-rich fish oil supplementation in healthy pregnant women on the incidence of preterm birth compared with placebo (OR [95% CI 0.87 [0.66, 1.15]), with no heterogeneity (I^2 = 0). Similarly, our update meta-analysis of seven RCTs (two from the original report) did not show a significant effect of fish oil (EPA+DHA) supplementation in pregnant women at risk for preterm birth on the incidence of preterm birth compared with placebo (OR=0.86; 95% CI 0.65, 1.15), with no heterogeneity (I^2 = 0) (Figure 6)

DHA

Four RCTs (in six publications) randomized healthy pregnant women between 8 and 22 weeks of gestation to an algae-oil source of supplemental DHA (0.2 to 0.6 g/d DHA) or placebo (soybean, corn, or olive oil).[30-34] Of these, two RCTs reported the outcome of gestational length in a total of 302 mothers and their infants living in the US[31] and 973 mothers and their infants in Mexico (POSGRAD trial),[32-34] and one RCT reported the outcome of preterm-premature rupture of membranes in a total of 253 pregnant women in Italy.[30] It should be noted that, of the three publications from the POSGRAD trial, the publication by Ramakrishnan (2010) analyzed the largest number of study participants[32] while the other two publications analyzed a subset of the trial participants.[33, 34] Thus, only the results from Ramakrishnan (2010) were included in our meta-analysis. The two RCTs that reported a gestational length outcome both found no significant effect of DHA (0.4 and 0.6 g/d) supplementation on the length of gestation compared with placebo. Furthermore, these two RCTs also showed no significant difference in the incidence of preterm birth between groups.[31-34] The third RCT found a reduced incidence of membrane rupture (0.8% vs. 3.2%, P=0.02) and a longer duration of gestation (data not reported) in the DHA supplementation group (n=129) than in the placebo group (n=126).[30]

Nine RCTs randomized healthy pregnant women between 12 and 24 weeks of gestation to DHA-rich fish oil supplementation or controls.[35-43] Studies were conducted in the US (n=4), Germany (n=2), Australia (n=1), the UK,[43] and the Netherlands (n=1). Of the nine RCTs, three compared DHA cereal-based bars (mean DHA 214-240 and EPA 27-30 mg/d; DHA:EPA ratio = 8) with placebo bars,[38-40] five compared DHA-rich fish oil supplements (DHA 200-1020 and EPA 100-180 mg/d; DHA:EPA ratio = 5-8),[37, 41-43] with controls (vegetable oil, nutritional counseling, vitamins and minerals, high oleic acid sunflower oil, or soy oil), and one is a three-arm RCT that compared DHA-rich fish oil plus soybean oil (DHA 220 and EPA 36 mg/d plus

ALA 32 mg/d), DHA-rich fish oil plus AA (DHA 220 and EPA 36 mg/d plus AA 220 mg/d) with placebo (soybean oil).[36] Five of the nine RCTs with lower DHA doses (0.2-0.60 g/d) did not find significant differences in the mean gestational length between DHA supplementation and placebo in a total of 290 infants,[36, 38, 40, 41] but one found an increase in gestational length (+0.9 [95% CI 0.24, 1.56] weeks) compared DHA cereal-based bars (mean DHA 214-240 and EPA 27-30 mg/d, n=14) with placebo bars (n=15).[39] The other three RCTs with higher DHA doses (0.8-1.02 g/d) all found a significantly higher mean gestational length in infants whose mothers received DHA-rich fish oil supplement compared with those whose mothers received placebo (+0.14 to +1.3 weeks) in a total of 2656 infants.[35, 37, 42] In contrast, two of these three RCTs with higher DHA doses (0.8 and 1.02 g/d) found no significant difference in the incidence of preterm birth between groups (OR 0.75 [95%0.54, 1.04] and OR 0.78 [95% CI 0.17, 3.56].[35, 37]

Meta-analysis of 11 RCTs showed that mean gestational length was significantly higher in infants whose mothers received supplemental algal DHA or DHA-rich fish oil compared with those whose mothers received placebo (WMD [95% CI] 0.34 [0.02, 0.67] weeks), with high heterogeneity ($I^2 = 75.3$) (Figure 5). No evidence of publication bias was seen (Begg's and Egger's p values were 0.542, 0.188, respectively).

However, our update meta-analysis of seven RCTs (two from the original report) found no significant effects of DHA or DHA-rich fish oil supplement on the incidence of preterm birth compared with placebo (OR=0.87; 95% CI 0.66, 1.15), with low heterogeneity ($I^2 = 0$). (Figure 6)

Figure 5. Length of gestation (weeks): DHA versus placebo, DHA + EPA or fish oil versus placebo

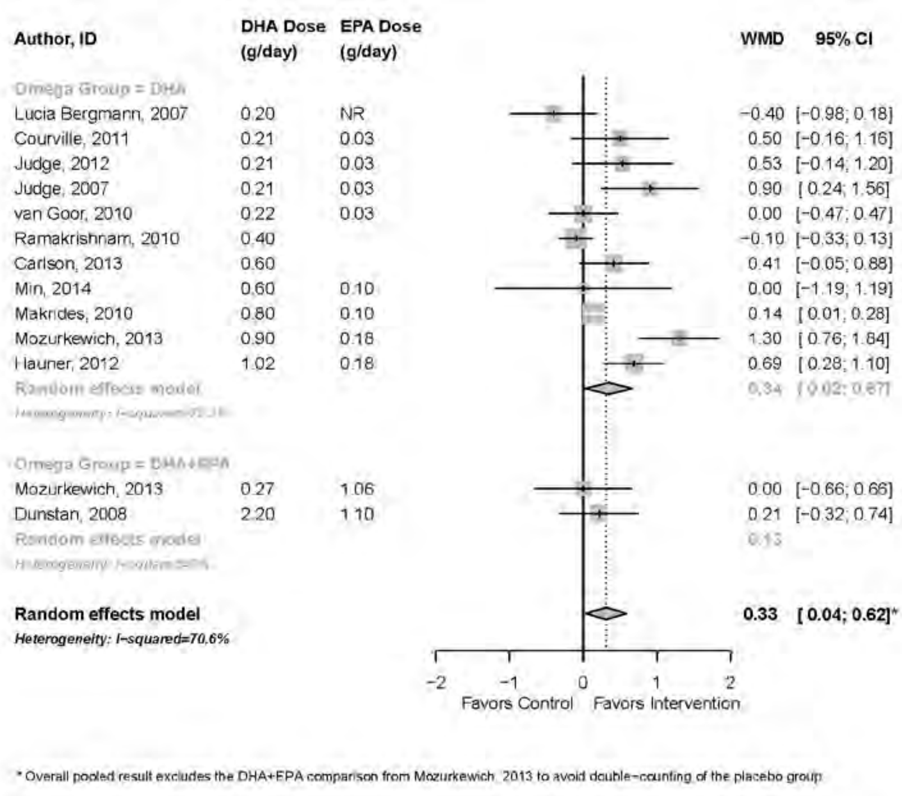
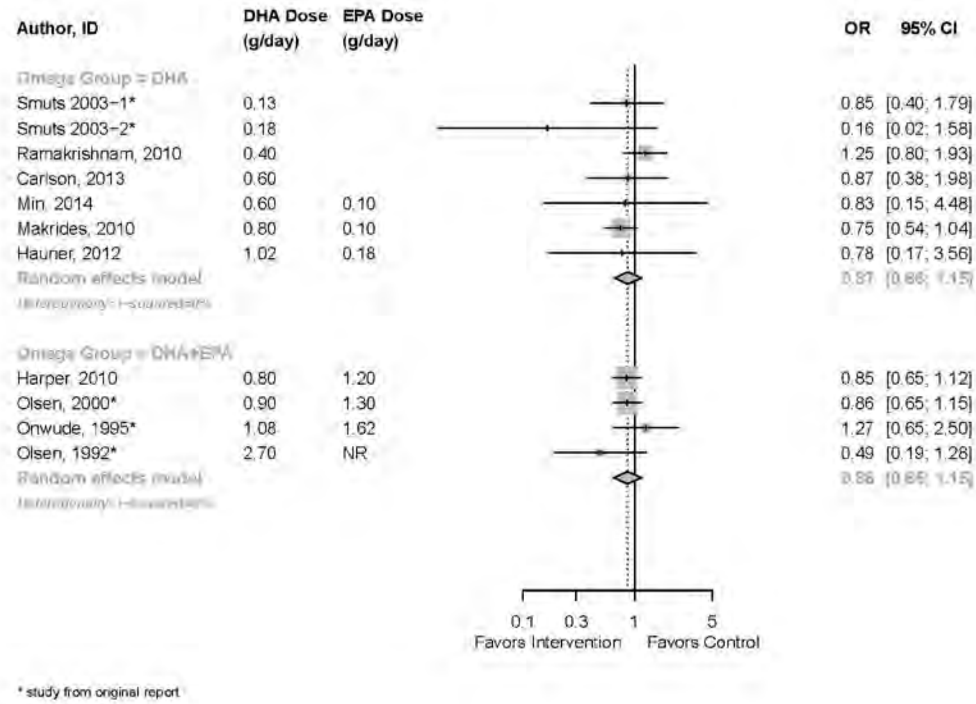


Figure 6. Incidence of premature birth: DHA versus placebo, DHA + EPA or fish oil versus placebo



EPA+DHA

Two RCTs randomized healthy pregnant women between 12 and 20 weeks of gestation, and one RCT randomized at-risk pregnant women between 16 and 22 weeks of gestation to fish oil supplements (EPA+DHA) or placebo (soybean oil, corn oil, olive oil or inert mineral oil).[29, 42, 44] Studies were conducted in the US (n=2) and Australia (n=1). The doses of EPA ranged from 1.06 to 1.20 g/d, and the doses of DHA ranged from 0.27 to 2.2 g/d. The DHA to EPA ratio ranged from 0.25 to 2. The total doses of EPA plus DHA ranged from 1.3 to 3.3 g/d. Two of the three studies did not find a significant effect of maternal fish oil supplementation (EPA+DHA 1.33 and 3.3 g/d) on infants' gestational length compared with placebo in a total of 152 healthy pregnant women,[42, 44] while the third study found that maternal fish oil supplementation (EPA+DHA 2 g/d) significantly increased the infants' mean gestational length (+0.30 [95% CI 0.07, 0.53] weeks, n=852) compared with placebo.[29] However, no significant difference was observed in the incidence of preterm birth between groups in this study (OR 0.85 [95% CI 0.65, 1.12]). It should be noted that this study is the only RCT (out of the 14 RCTs that reported gestation length outcome) enrolled at risk pregnant women with a history of at least one prior singleton preterm delivery.[29]

An insufficient number of RCTs was identified in healthy pregnant women to allow meta-analysis to examine the effect of fish oil supplementation in healthy pregnant women on infants' gestational length. The updated random-effects meta-analysis of nine RCTs (in four publications: one publication by Olsen et al.[28] represented pooled data from six different RCTs) in pregnant women who were at risk for preterm delivery found no significant effects of fish oil supplementation on the incidence of preterm birth compared with placebo (OR [95% CI] 0.86 [0.65, 1.15]), with no heterogeneity (I2 = 0).

EPA+DHA Versus ALA

One RCT compared five differences doses of fish oil supplementation (EPA+DHA 0.1, 0.3, 0.7, 1.4 and 2.8 g/d) with ALA as the control (ALA 2.2 g/d) from week 17–27 of gestation until delivery in a total of 3098 healthy pregnant women with low dietary intake of fish (lowest 20% of fish consumption).[45] There were no significant differences in gestation length between any of the fish oil supplementation groups and the control group. Specifically, the mean differences in gestational length ranged from -0.7 to +0.3 days between the fish oil and ALA control groups.

Observational Studies

Four prospective cohort studies were identified for the current report (see Table 2). Of these, three studies assessed the associations between maternal dietary intake of n-3 FA (from foods or supplements) and infants' gestational length.[46-48] One of the three studies also analyzed the relationship between maternal dietary intake of n-3 FA and risk of preterm birth.[46] The third study examined the relationships between maternal n-3 FA biomarkers and infants' gestational length.[49]

n-3 FA Intake

Three studies assessed the associations between maternal n-3 FA intake from supplements and infants' gestational length.[46, 47] Oken[46] evaluated the association between quartiles of maternal DHA+EPA intake (median 0.27 to 0.38 g/d) at first trimester (median EPA+DHA from 0.02 to 0.36 g/d, n= 1797), second trimester (median EPA+DHA from 0.02 to 0.38 g/d, n=1663), and third trimesters (median EPA+DHA from 0.05 to 0.27 g/d, n=2070) and gestational length. No significant associations were found. This study also compared the risk of preterm birth between the highest and lowest quartiles of maternal DHA+EPA intake, and found no significant association (OR 1.1 [95% CI 0.7, 1.9].[46] Badart-Smook (1997)[47] reported that "No significant correlations were observed between any of the nutrients [including sum of n-3 FA+AA] and birth weight or the length of gestation" (data not shown) in 372 healthy pregnant women at the 22nd week of gestation. Molto-Puigmarti (2014)[48] analyzed the associations between maternal DHA or ALA intake at 34 weeks of pregnancy and gestational length in 2006 healthy pregnant women. This study found that maternal DHA intake (mg/d) was significantly associated with an increase in gestational length (beta coefficient = 0.004 [95% CI 0.001, 0.007], P=0.0016) but maternal ALA intake was not associated with gestational length (beta coefficient = 0.001 [95% CI 0.000, 0.003], P=0.11).

n-3 FA Biomarkers

One study examined the relationships between maternal erythrocyte DHA+EPA biomarkers and risk of preterm birth (<37 weeks of GA) in 852 pregnant women with at least one prior spontaneous preterm delivery.[49] The study showed that the adjusted odds ratio for preterm birth among women in the lowest quartile compared with women in the 3 higher quartiles combined was 1.41 (0.97 – 2.05). When the top 3 quartiles were compared to the lowest quartile (erythrocyte DHA+EPA <3.052 % of total FA), only women in quartile 2 (erythrocyte DHA+EPA 3.052-3.719 % of total FA), but not quartiles 3 (erythrocyte DHA+EPA 3.723-4.426 % of total FA) and quartile 4 (erythrocyte DHA+EPA >4.426 % of total FA), had a statistically significant reduction in the odds of preterm birth compared with those in quartile 1 (adjusted OR 0.59 [95% CI 0.37, 0.94]).

Table 1. RCTs for length of gestation (or gestational age) and preterm birth

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Carlson et al., 2013[31] Study name: NR Study dates: 2006.01-2011.10 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product	Study Population: Healthy pregnant women Pregnant enrolled 350 Pregnant withdrawals 49 Pregnant completers 301 Pregnant age: placebo: 24.8; DHA: 25.3 (placebo 4.7; DHA 4.9) Race of Mother: Black (46%;37%) Non-black (54%; 63%) Baseline biomarker information: RBC-phospholipid-DHA (placebo group 4.3 +- 1.3; 4.3 +- 1.1) Baseline Omega-3 intake: Voluntary DHA intake from supplement (placebo group 15%, DHA group 9%)	Inclusion Criteria: English-speaking, between 8 and 20 wk of gestation, between 16 and 35.99 y of age, and planning to deliver at a hospital in the Kansas City metropolitan area Exclusion Criteria: carrying more than one fetus, had preexisting diabetes mellitus or systolic blood pressure $140 mm Hg at enrollment, or had any serious health condition likely to affect the prenatal or postnatal growth and development of their offspring, including cancer, lupus, hepatitis, HIV/AIDS, or a diagnosed alcohol or chemical dependency. or if the initial screening based on their self-reported weight and height suggested a BMI (in kg/m2 >=40).	Start time: Pregnant 99.6/102.9 day Duration: Pregnant enrollment to birth Arm 1: Placebo Description: half soybean and half coin oil Manufacturer: DSM Nutritional Products) Active ingredients: a-linolenic acid Dose: 3 *capsule 200/day Blinding: both DHA and placebo capsules were orange flavored Arm 2: DHA Description: marine algae-oil source of DHA Manufacturer: DHASCO; DSM Nutritional Products, formerly Martek Biosciences) Dose: 200 mg capsule, 3 times a day DHA: 200mg/capsule * 3	Outcome: gestational age (days) (Primary) Follow-up time: birth Arm 1: Sample size 147; mean 272.8; SD (17) Arm 2: Sample size 154; mean 275.7; SD (11.2) Outcome: incidence of premature birth (Secondary) Follow-up time: birth Arm 1: 13/147 (8.8%) Arm 2: 12/154 (7.8%)
Courville et al., 2011[38] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: US Funding source / conflict:	Study Population: Healthy pregnant women Pregnant enrolled 47 Pregnant withdrawals 0 Pregnant completers 47 Pregnant age: NR (NR) NR Race of Mother: White European (8.5) Black	Inclusion Criteria: Healthy pregnant women, mid-pregnancy (20–24 weeks) Exclusion Criteria: parity .5; history of chronic hypertension; hyperlipidaemia; renal or liver disease; heart disease; thyroid disorder; multiple gestations;	Start time: Pregnant 20-24 wk of gestation Duration: Pregnant until birth Arm 1: Placebo Description: placebo bars (Manufacturer: Nestec Limited (Vevey, Switzerland) Dose: 5 placebo bars per week Blinding: NR Arm 2: DHA-FF Description: DHA cereal-based bars	Outcome: gestational age (weeks) (Unspecified) Follow-up time: birth Arm 1: Sample size 25; mean 39.4; SD (1.2) Arm 2: Sample size 22; mean 39.9; SD (1.1)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Industry, Government	(10.6) Asian (4.3) Minority (Puerto Rican/Latino 66%; African - other 8.5%; Other or mixed ethnicity = 2%) Baseline Omega-3 intake: Dietary DHA intake (mg/d), not including the intervention food, from 24 h dietary recalls: DHA-FF 67+-7 (SD); Placebo 87+-10 (SD), P=0.059	having been pregnant or lactating in the previous 2 years.	Manufacturer: Nestec Limited (Vevey, Switzerland) Dose: 5DHA cereal-based bars per week DHA: 241 mg/d EPA: 30.1 mg/d	
Dunstan et al., 2008[44] Study name: Dunstan Study dates: 2000-2003 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Multiple foundations and Societies Original, same study, or follow-up studies: Dunstan, 2003[50]; Meldrum, 2015[51]	Study Population: Healthy infants Pregnant women with allergies Pregnant enrolled 98 Pregnant completers 83 Infants enrolled 83 Infants withdrawals 11 (7 FO, 4 control) Infants completers 72 Pregnant age: Fish oil: 30.9 Control: 32.6 (Fish oil: 3.7 Control: 3.6) Infant age: Term (mean gestational period 275 days) Race of Mother: NR Baseline biomarker information: Cord blood erythrocyte (as % total fatty acids) 20:4n-6 14.9 (1.4) 17.6 (1.0) ,0.001 20:5n-3 1.3 (0.5) 0.4 (0.3) ,0.001 22:3n-6 2.8 (0.5) 3.9 (0.5) ,0.001	Inclusion Criteria: Healthy term infants of pregnant women enrolled in RCT of gestational supplementation Exclusion Criteria: Women were ineligible for the study if they smoked, had medical problems, a complicated pregnancy, seafood allergy, or if their normal dietary intake exceeded two meals of fish per week. Children were excluded from the study if they were born before 36 weeks' gestation or with major disease (to avoid the confounding effects on immune response) or if cord blood was not collected	Start time: Pregnant 20 weeks gestation Duration: Pregnant to term Arm 1: Control Description: olive oil placebo Blinding: capsules image matched Maternal conditions Current smoker 0% Maternal allergies 100% Arm 2: Fish oil Description: same Manufacturer: Ocean Nutrition, Halifax Nova Scotia Active ingredients: 3-4mg/g vitamin E Viability: none reported Dose: 4 1-gm capsules fish oil per day Maternal conditions DHA: 2.2 EPA: 1.1 Other dose 1: fish oil supplying 2,2g/d DHA and 1.1g/day EPA Current smoker 0% Maternal allergies 100%	Outcome: gestational age (days) (Secondary) Follow-up time: birth Arm 1: Sample size 39; mean 274.5; SD (8) Arm 2: Sample size 33; mean 276.0; SD (8)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	22:4n-6 0.8 (0.2) 1.5 (0.3) ,0.001 22:5n-3 6.3 (0.8) 6.0 (0.5) 0.037 22:6n-3 10.3 (1.1) 7.4 (0.9) ,0.001 Total n-6 PUFAs* 25.0 (1.8) 29.6 (1.1) ,0.001 Total n-3 PUFAs{ 17.9 (1.9) 13.7 (1.3) ,0.001 Total n-3 to n-6{ 0.8 (0.1) 0.5 (0.1) ,0.001			
Harper et al., 2010[29] Study name: NR Study dates: 01. 2005 - 10. 2006 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product Original, same study, or follow-up studies: Klebanoff, 2011[49]	Study Population: At risk for preterm labor Pregnant enrolled 852 Pregnant withdrawals 0 Pregnant completers 852 Pregnant age: n3: 28 placebo 27 n3 23-32; placebo 24-32 Race of Mother: White European (n3: 56.5; placebo 57.7) Black (n3: 34.1; placebo 34.9) Asian (n3: 3, placebo 1.2) Hispanic (n3: 14.7; placebo 13.6) Other race/ethnicity (NR)	Inclusion Criteria: a documented history of at least one prior singleton preterm delivery between 20 0/7 and 36 6/7 weeks of gestation after spontaneous preterm labor or premature rupture of the membranes, and a current singleton pregnancy between 16 and 21 6/7 weeks of gestation Exclusion Criteria: evidence of a major fetal anomaly, intake of a fish oil supplement in excess of 500 mg per week at any time during the preceding month, allergy to fish, anticoagulation therapy, hypertension, White's classification D or higher diabetes, drug or alcohol abuse, seizure disorder, uncontrolled thyroid disease, clotting disorder, current or planned cerclage, or a plan to deliver either elsewhere or before 37	Start time: Pregnant 16-22 week gestation age Duration: Pregnant 36 weeks of gestation Arm 1: placebo Description: inert mineral oil Manufacturer: Eminent Services, Frederick, MD Active ingredients: 10 IU vitamin E per capsule, injections of 17_x0001_-hydroxyprogesterone caproate Dose: four capsules of matching oil containing a minute amount of inert mineral oil Blinding: Boxes containing a woman's entire supply of capsules in blister packs were sequentially numbered according to the predetermined randomization sequence, and on enrollment a woman was assigned the next number in sequence. Study group assignment was not known by study participants, their health care providers, or the research personnel Arm 2: Eminent Services, Frederick, MD Active ingredients: 10 IU vitamin E per capsule, injections of 17_x0001_-hydroxyprogesterone caproate Dose: in 4 capsules total 2000 mg of n3 DHA: 800 mg EPA: 1200 mg	Outcome: gestational age (weeks) (Secondary) Follow-up time: birth Arm 1: Sample size 418; mean 37.4; range Arm 2: Sample size 434; mean 37.7; range Outcome: incidence of premature birth (Primary) Follow-up time: birth Arm 1: 174/418 (41.6%) Arm 2: 164/434 (37.8%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		weeks of gestation		
Hauner et al., 2012[37] Study name: INFAT Study dates: July 14 2006 - may 22 2009 Study design: Trial randomized parallel Location: Germany Funding source / conflict: Industry, Government, Multiple foundations and Societies	Study Population: Healthy pregnant women Pregnant enrolled 208 Pregnant withdrawals 38 Pregnant completers 170 Infants enrolled 188 Infants withdrawals 18 Infants completers 170 Pregnant age: 31.9 (4.9) 18-43 Race of Mother: NR (NR) Baseline biomarker information: Maternal fatty acid profile in RBCs at 15th wk: EPA, DHA, AA, and n-6:n-3 LCPUFA ratio (reported in Table 2 by intervention and control groups). No significant differences between groups. Baseline Omega-3 intake: 7-d dietary records completed by participants at the 15th (baseline) and 32nd wk of gestation but only dietary intake at 32nd we of gestation was reported (in Table 2). At week 32 of gestation, the dietary n-6:n-3 PUFA ratio was .5:1 in the intervention group compared with :1 in the control group, as originally intended.	Inclusion Criteria: healthy pregnant women before the 15th wk of gestation, between 18 and 43 y of age, prepregnancy BMI (in kg/m2) between 18 and 30, willingness to implement the dietary recommendations, sufficient German language skills. Exclusion Criteria: high-risk pregnancy (multiple pregnancy, rhesus incompatibility, hepatitis B infection, or parity .4); hypertension; chronic diseases (e.g., diabetes) or gastrointestinal disorders accompanied by maldigestion, malabsorption, or elevated energy and nutritional requirements (e.g., gluten enteropathy); known metabolic defects (e.g., phenylketonuria); psychiatric diseases; hyperemesis gravidarum; supplementation with n–3 LCPUFAs before randomization; and alcohol abuse and smoking.	Start time: Pregnant 15th wk of gestation Duration: Pregnant to 4 mo postpartum Arm 1: Control Description: brief semistructured counseling on a healthy balanced diet according to the guidelines of the German Nutrition Society and were explicitly asked to refrain from taking fish oil or DHA supplements N-6 N-3: 2.80 +- 1.17 (SD) at 32nd wk of gestation AA: 10.15 +- 3.89 SD) at 32nd wk of gestation Arm 2: Intervention Description: Fish-oil supplement + nutritional counseling (to normalize the consumption of AA Brand name: Marinol D-40 Manufacturer: Lipid Nutrition DHA: 1020 mg EPA: 180 mg N-6 N-3: 1.54 +- 0.63 (SD) at 32nd wk of gestation AA: 8.82 +- 2.84 (SD) at 32nd wk of gestation Other dose 1: Vit E 9 mg	Outcome: gestational age (days) (Secondary) Follow-up time: birth Arm 1: Sample size 96; mean 275.1; SD (11.4) Arm 2: Sample size 92; mean 279.9; SD (8.5)
Judge et al., 2007[39]	Study Population:	Inclusion Criteria: women	Start time: Pregnant 24 weeks gestation	Outcome: gestational age (weeks)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study name: NR Study dates: NR Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Government, None	Healthy pregnant women Pregnant enrolled 29 Pregnant completers 29 Pregnant age: 23.75 years (.4 years) NR Race of Mother: NR (100%)	aged 18 –35 y who were at 20 wk of gestation Exclusion Criteria: Women with a history of drug or alcohol addiction, hypertension, smoking, hyperlipidemia, renal disease, liver disease, diabetes, or psychiatric disorder	Duration: Pregnant until birth Arm 1: placebo Description: cereal based placebo bars Manufacturer: Nestec Active ingredients: 18 g carbohydrates, 1.3 grams protein, 92 calories, 1.7 g fat Viability: NR Dose: 5 bars per week Blinding: NR Arm 2: DHA supplemented cereal bars Manufacturer: Nestec Active ingredients: 18 g carbohydrates, 1.3 grams protein, 92 calories, 1.7 g fat Viability: NR Dose: 5 bars per week. DHA-containing cereal-based bars [1.7 g total fat, 300 mg DHA as low-eicosapentaenoic oil (EPA) fish oil; EPA:DHA 1:8 per bar DHA: mg/d EPA: .75 mg (calculated based on EPA:DHA ratio) EPA-DHA: 1:8	(Secondary) Follow-up time: birth Arm 1: Sample size 15; mean 39.0; SD (1) Arm 2: Sample size 14; mean 39.9; SD (0.8)
Judge et al., 2012[40] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: US Funding source / conflict: Multiple foundations and Societies	Study Population: Healthy pregnant women Pregnant enrolled 48 Pregnant age: Treatment group: 23.93 Placebo: 23.86 (Treatment group: 4.32 Placebo: 4.53) Race of Mother: White European (Treatment: 11.1%, Placebo: 0%) Black (Treatment: 18.5%, Placebo: 4.8%) Asian (Treatment: 3.7%, Placebo: 0%) Hispanic (Treatment: 59.3%, Placebo: 80.9%) NR (Treatment: 7.4%, 3 (14.3%))	Inclusion Criteria: The women were either primiparous or had not been pregnant for the past 2 years. Exclusion Criteria: parity greater than 5, history of chronic hypertension, hyperlipidemia, renal, liver or heart disease, thyroid disorder, multiple gestations or pregnancy induced complications including hypertension, preeclampsia or preterm labor, smoking and psychiatric disorders. Women who were treated during labor with analgesics such as	Start time: Pregnant 24 weeks gestation Duration: Pregnant until delivery Arm 1: Placebo Description: Control group Manufacturer: Nestec, S.A., Switzerland Blinding: The total macronutrient content was the same in both the DHA and placebo bars with respect to carbohydrate, protein and fat, how- ever, the DHA bars contained fish oil (300 mg DHA) and the placebo bars contained corn oil. Arm 2: DHA Description: Intervention group Manufacturer: Nestec, S.A., Switzerland Dose: average of 5 bars weekly DHA: 300 mg EPA-DHA: 8:1 ratio of DHA to EPA	Outcome: gestational age (weeks) (Secondary) Follow-up time: birth Arm 1: Sample size 21; mean 39.19; SD (1.17) Arm 2: Sample size 27; mean 39.72; SD (1.2)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	Baseline biomarker information: Maternal plasma phospholipid (PL) fatty acids (FA): 2.85 +/- .87 % in treatment group and 2.95 +/- .91% in placebo group. Infant RBC PL FA: 7.55 +/- 1.61% in treatment group and 7.07 +/- 1.25% in placebo group.	Stadol (butorphanol tartrate), that may cause infant respiratory distress were also excluded. In addition, infants born preterm and infants with less than 4 h of crib time in the first and second days postpartum were excluded from the analyses.		
Knudsen et al., 2006[45] Study name: Danish National Birth Cohort-Pregnant Women Study dates: 2001- Study design: Trial randomized parallel Location: Denmark Funding source / conflict: Multiple foundations and Societies	Study Population: Healthy pregnant women Pregnant enrolled 3098 Pregnant withdrawals 1033 Pregnant completers 2065 Pregnant age: Group 01: 28.4 years Group 03: 28.7 years Group 07: 28.4 years Group 14: 28.9 years Group 28: 28.8 years Group C18: 28.8 years Group CG: 28.5 years Race of Mother: NR Baseline biomarker information: Level of EPA, DHA, and AA in erythrocyte phospholipids assessed in a subsample of women in the 6 treatment groups Baseline Omega-3 intake: EPA, DHA, EPA+DHA, ALA, AA	Inclusion Criteria: Low dietary intake of fish (lowest 20% of fish consumption), no use of fish oil capsules in pregnancy, gestational age 17-27 weeks. Exclusion Criteria: NR	Start time: Pregnant 17-27 weeks gestation Duration: Pregnant until delivery Arm 1: CG Description: control group (flax oi) Blinding: The women in the control group were allocated to any treatment and were not contacted at all. ALA: 2.2 g/d Arm 2: 01 Description: Treatment Group 1 Brand name: Futura Fish Oil Manufacturer: Dansk Droge A/S, Ishoej, Denmark Active ingredients: 13.4 mg D-alpha-tocopherol per gram Dose: 1 0.5 g three times per week DHA: 22% EPA: 32% Total N-3: 0.1 g per day Arm 3: 03 Description: Treatment group 2 Brand name: Futura Fish Oil Manufacturer: Dansk Droge A/S, Ishoej, Denmark Active ingredients: 13.4 mg D- alpha-tocopherol per gram Dose: 1 0.5 g capsule per day Total N-3: 0.3 g per day Arm 4: 07 Description: Treatment group 3	Outcome: gestational age (days) (Primary) Follow-up time: birth Arm 1: Sample size 748; mean 280.6; SD (11.7) Arm 2: Sample size 229; mean 281.5; SD (12.6) Arm 3: Sample size 224; mean 279.7; SD (12) Arm 4: Sample size 222; mean 280.5; SD (12.6) Arm 5: Sample size 212; mean 280.6; SD (12.6) Arm 6: Sample size 187; mean 279.6; SD (14.8) Arm 7: Sample size 176; mean 280.7; SD (12.8)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			Brand name: Futura Fish Oil Manufacturer: Dansk Droge A/S, Ishoej, Denmark Active ingredients: 13.4 mg D- alpha-tocopherol per gram Dose: 1 1 g capsule per day DHA: 22% EPA: 32% Total N-3: 0.7 g per day Arm 5: 14 Description: Treatment group 4 Brand name: Futura Fish Oil Manufacturer: Dansk Droge A/S, Ishoej, Denmark Active ingredients: 13.4 mg D- alpha-tocopherol per gram Dose: 2 1g capsules per day DHA: 22% EPA: 32% Total N-3: 1.4 g per day Arm 6: 28 Description: Treatment group 5 Brand name: Futura Fish Oil Manufacturer: Dansk Droge A/S, Ishoej, Denmark Active ingredients: 13.4 mg D-alpha-tocopherol per gram Dose: 4 g per day DHA: 22% EPA: 32% Total N-3: 2.8g per day Arm 7: c18 Description: Treatment group 6 - flax oil Brand name: Prima FlaxTM Manufacturer: Bioriginal Food & Science Corp., Saskatoon, Canada Dose: 4 1-g capsules of flax oil ALA: 2.2g per day	
Lucia Bergmann et al., 2007[41] Study name: NR Study dates: 2000-2002	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 144 Pregnant withdrawals 51 Pregnant completers 69	Inclusion Criteria: at least 18 years of age and willing to breastfeed for at least three months were enrolled at 21 weeks' gestation during the period October 2000	Start time: Pregnant 21th week Duration: Pregnant 37th week Arm 1: Vitamins and minerals Manufacturer: Nestle´ (Vevey, Switzerland)	Outcome: gestational age (weeks) (Unspecified) Follow-up time: birth Arm 1: Sample size 74; mean 39.5; SD (1.38) Arm 3: Sample size 43; mean 39.1; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study design: Trial randomized parallel Location: Germany Funding source / conflict: NR Original, same study, or follow-up studies: Lucia, 2007[52]	Pregnant age: 31 (DHA 4.69; control 4.89) Infant age: DHA 39.1; control 39.5 weeks (DHA 1.64; control 1.38) Race of Mother: White European (100) Baseline biomarker information: DHA % of all identified fatty acid in RBC: Vitamin: 5.76 +-2.45 (47); DHA: Prebiotic:5.94+-2.37(48) DHA: DHA: 5.69+-2.40(47) ARA Vitamin: 14.01+-4.04(47) ARA Prebiotic 14.82+-3.60(48) ARA DHA: 14.18+-4.32(47) EPA Vitamin: 0.72+-0.32(47) EPA Prebiotic: 0.78+-0.38(48) EPA DHA: 0.79+-0.41(47)	to August 2002 Exclusion Criteria: increased risk of premature delivery or multiple pregnancy, allergy to cow milk protein, lactose intolerance, diabetes, smoking, consumption of alcohol ()20 g/week), or participation in another study. Infants excluded if they were premature at birth (<37 week gestation, or had any major malformations or hospitalized for more than one week.	Arm 2: Prebiotic Description: basic supplement plus the prebiotic, fructooligosaccharide (FOS) (4.5 g) Manufacturer: Nestle´ (Vevey, Switzerland) Active ingredients: fructooligosaccharide (FOS) (4.5 g) Arm 3: DHA Description: basic supplement with FOS and DHA (200 mg) Manufacturer: Nestle´ (Vevey, Switzerland) Dose: 200 mg DHA prepared from fish oil (assuming that some EPA but dose was not reported) DHA: 200 mg EPA: NR	(1.64)
Makrides et al., 2010[35] Study name: DOMInO Study dates: 2005-2008 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Manufacturer supplied product Original, same study, or follow-up studies:	Study Population: Healthy pregnant women Pregnant enrolled 2399 Pregnant withdrawals 1 Infants enrolled 605 Infants withdrawals 32 Infants completers 726 Pregnant age: 28.9 (DHA5.7___ control5.6) Race of Mother: NR (NR)	Inclusion Criteria: with singleton pregnancies at less than 21 weeks' gestation were approached by study research assistants while attending routine antenatal appointments Exclusion Criteria: already taking a prenatal supplement with DHA, their fetus had a known major abnormality, they had a bleeding disorder in which tuna oil was contraindicated, were taking anticoagulant	Start time: Pregnant < 21 week's gestation Duration: NR Arm 1: vegetable oil capsules Description: a blend of 3 nongenetically modified oils (rapeseed, sunflower, and palm) in equal proportions Manufacturer: Efamol, Surrey, England. Dose: 3* 500mg capsule / day Blinding: All capsules were similar in size, shape, and color Arm 2: DHA Description: DHA-rich fish oil concentrate Manufacturer: ; Incromega 500 TG, Croda Chemicals, East Yorkshire, England Dose: 500mg capsule *3/day	Outcome: gestational age (days) (Secondary) Follow-up time: birth Arm 1: Sample size 1202; median 281.0; IQR Arm 2: Sample size 1197; median 282.0; IQR Outcome: incidence of premature birth (Secondary) Follow-up time: birth Arm 1: 88/1202 (7.34%) Arm 2: 67/1197 (5.6%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Smithers, 2011[53]; Palmer, 2012[54]; Zhou, 2012[55]; Palmer, 2013[56]; Makrides, 2014 [57]		therapy, had a documented history of drug or alcohol abuse, were participating in another fatty acid trial, were unable to give written informed consent, or if English was not the main language spoken at home	DHA: 800mg EPA: 100mg	
Min et al., 2014[43] Study name: NR Study dates: Jan 2008 - Dec 2011 Study design: Trial randomized parallel Location: UK Funding source / conflict: Industry, Government, Multiple foundations and Societies, Manufacturer supplied product Original, same study, or follow-up studies: none	Study Population: Healthy pregnant women, Pregnant women with type 2 diabetes Pregnant enrolled 85 Pregnant completers 59 Pregnant age: 29 18-44 Infant age: 11.0-12.1 weeks gestation 6.0-15.9 weeks gestation Race of Mother: White European (22.3%) Black (28.2%) Asian (40.0%) Other race/ethnicity (9.4%)	Inclusion Criteria: Pregnant women of 17–45 years old with singleton pregnancies with either pre-existing Type 2 diabetes or without any known medical condition (uncomplicated pregnancy group) Exclusion Criteria: Women planning to receive tocolytic or corticosteroid therapy. Note that pregnant women with pre-existing Type 2 diabetes were excluded from this systematic review.	Start time: Pregnant average: 9.9-12.1 weeks gestation (range: 4.3-15.9 weeks gestation) Duration: Pregnant until delivery; average: 26.5 weeks for placebo arm; 28.4 weeks for the fish oil arm Arm 1: Placebo, healthy women Description: high oleic acid sunflower oil Manufacturer: Equazen/Vifor Pharma Ltd. Active ingredients: oleic acid, 82.6%; vitamin E (d- a tocopherol) NR% Dose: 2x 750 mg capsules/day Blinding: identical oblong soft gelatin capsule Maternal conditions Current smoker 0% Arm 2: Fish oil, healthy women Description: HA-enriched fish oil Brand name: Mumomega Manufacturer: Equazen/Vifor Pharma Ltd. Active ingredients: vitamin E (d- a tocopherol) NR% Dose: 2 750 mg capsules/day Maternal conditions DHA: 43.7% (600 mg/d) EPA: 7.5% (estimated to be 103 mg/d) Current smoker 13.3% Arm 3: Placebo, diabetic women Description: high oleic acid sunflower oil Manufacturer: Equazen/Vifor Pharma Ltd. Active ingredients: oleic acid, 82.6%; vitamin E (d- a tocopherol) NR% Dose: 2 750 mg capsules/day Maternal conditions	Outcome: gestational age birth (weeks) (Secondary) Follow-up time: birth Arm 1: Sample size 27; median 39.3; range Arm 2: Sample size 32; median 39.3; range Outcome: preterm birth (Secondary) Follow-up time: birth Arm 1: 3/27 (11.1%) Arm 2: 3/32 (9.4%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			Current smoker 0% Other maternal conditions 1arm_3_maternal_conditions_other1 Other maternal conditions 10 Type 2 diabetes: 100% Arm 4: Fish oil, diabetic women Description: HA-enriched fish oil Brand name: Mumomega Manufacturer: Equazen/Vifor Pharma Ltd. Active ingredients: vitamin E (d- a tocopherol) NR% Dose: 2 750 mg capsules/day Blinding: identical oblong soft gelatin capsule Maternal conditions DHA: 43.7% EPA: 7.5% Current smoker 4.9% Other maternal conditions 1arm_4_maternal_conditions_other1 Other maternal conditions 10 Type 2 diabetes: 100%	
Mozurkewich et al., 2013[42] Study name: NR Study dates: Oct 2008 - May 2011 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product	Study Population: Healthy pregnant women Pregnant enrolled 126 Pregnant withdrawals 8 Pregnant completers 118 Pregnant age: EPA 29.9; DHA 30.6; placebo 30.4 (EPA 5.0; DHA 4.5; placebo 5.9) Race of Mother: White European (85%; 76%; 83%) Black (10%; 11%; 5%) Asian (3%; 3%; 2%) Hispanic (0%; 11%; 7%) Inuit Eskimo (0%; 0%; 2%) Pacific Islander (NR) Baseline biomarker information: EPA group: EPA 0.29+-0.18; DHA 4.24+-2.30; total n3 FA: 22.10+-3.72 DHA group: EPA 0.31+-0.24; DHA	Inclusion Criteria: past history of depression, an EPDS score 9-19 (at risk for depression or mildly depressed), singleton gestation, a maternal age of 18 years or older, and a gestational age of 12-20 weeks Exclusion Criteria: had a history of a bleeding disorder, thrombophilia requiring anticoagulation, multiple gestation, bipolar disorder, current major depressive disorder, current substance abuse, lifetime substance dependence, or schizophrenia. Women were also ineligible if they were currently taking omega-3 fatty acid supplements or antidepressant	Start time: Pregnant 12-20 week gestation Duration: Pregnant assuming till birth Arm 1: Control/Placebo Description: 98% soy oil and 1% each of lemon and fish oil Manufacturer: Nordic Naturals Corporation in Watsonville, CA Viability: centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose: 2 large and 4 small placebo capsules Blinding: The placebos were formulated to be identical in appearance to both the EPA- and DHA-rich supplements Arm 2: EPA-rich fish oil Description: an approximate 4:1 ratio of EPA to DHA (1060 mg EPA plus 274 mg DHA) Brand name: ProEPAXtra, Nordic Naturals Viability: centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose: 2 large EPA capsule and 4 small placebo DHA: 274 mg EPA: 1060 mg	Outcome: gestational age (weeks) (Secondary) Follow-up time: birth Arm 1: Sample size 41; mean 39.1; SD (1.5) Arm 2: Sample size 39; mean 39.1; SD (1.5) Arm 3: Sample size 38; mean 40.4; SD (0.9)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	4.66+-2.29; total n3 FA 36.41+-9.71 placebo: EPA .34+-0.22; DHA 3.85+-1.77; omega3 fa 322.86+-5.02	medications or eating more than 2 fish meals per week.	Arm 3: DHA-rich fish oil Description: DHA and EPA in an approximate 4:1 ratio o (900 mg DHA plus 180 mg EPA) Brand name: ProDHA, Nordic Naturals Viability: centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose: 2 large placebo oil and 4 small DHA rich DHA: 900 mg EPA: 180 mg	
Pietrantoni et al., 2014[30] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: Italy Funding source / conflict: Government	Study Population: Healthy pregnant women Pregnant enrolled 300 Pregnant completers 255 Pregnant age: DHA 30.86 +-4.18/placebo group 29.92+-4.8 Race of Mother: NR (NR)	Inclusion Criteria: caucasians 22 to 35 yrs, 8 week gestational age, single pregnancy, BMI between 18.5 and 25.0kg/m2, habitual fish consumption (twice a week at least), high school or university degree, average socioeconomic status, absence of uterine abnormalities (fibroids, cervical incompetence, uterine malformations etc.) Exclusion Criteria: smoking, substance abuse including alcohol, allergy to fish or derivates, diabetes, hypertension, metabolic, cardiovascular, renal, psychiatric, neurologic, thrombophilic, thyroid or autoimmune diseases, previous pregnancy complications (miscarriage, preterm or operative delivery), previous uterine surgery, recurrent genito-urinary infections	Start time: Pregnant 8th weeks Duration: Pregnant 8th week to delivery Arm 1: Placebo Description: Olive oil Arm 2: DHA group Description: DHA capsule Dose: 2* 100mg capsule DHA: 100mg * 2 capsule	Outcome: preterm-premature rupture of membranes (Unspecified) Follow-up time: birth Arm 1: 4/126 (3.2%) Arm 2: 1/129 (0.8%)
Ramakrishnan et al.,	Study Population:	Inclusion Criteria: 18-35	Start time: Pregnant at study entry	Outcome: gestational age (weeks)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
2010[32] Study name: POSGRAD Study dates: Feb 2005 - Feb 2007 Study design: Trial randomized parallel Location: Mexico Funding source / conflict: Government, March of Dimes Original, same study, or follow-up studies: Stein, 2012[33]; Imhoff-Kunsch, 2011[58]; Escamilla-Nunez, 2014[59]; Gonzalez-Casanova, 2015[60]; Ramakrishnan, 2015[61]; Stein, 2011[34]	Healthy pregnant women Pregnant enrolled 1,094 Pregnant withdrawals 67 Pregnant completers 973 (for birth weight) Pregnant age: 26.2 (controls) 26.3 (DHA) (4.6 (controls) 4.8 (DHA)) Race of Mother: Hispanic (NR) Baseline Omega-3 intake: mg/day for all: LA: 17,846 in controls, 17,645 in DHA AA: 137 in controls, 140 in DHA ALA: 1,488 in controls, 1,477 in DHA EPA: 18 in controls, 18 in DHA: 54 in controls, 56 in DHA	yrs. of age, in gestation weeks 18-22, planned to deliver at the IMSS General Hospital in Cuernavaca, exclusively or predominantly breastfeed for at least 3 months, liver in the area for at least 2 years after delivery. Exclusion Criteria: high-risk pregnancy; lipid metabolism or absorption disorders, regular intake of fish oil or DHA supplements; chronic use of certain medications (e.g., medications for epilepsy).	Duration: Pregnant mid pregnancy (18-22 weeks gestation) until delivery Arm 1: Controls Description: Placebo containing olive oil Manufacturer: Martek Biosciences Dose: 1 capsule, twice a day Blinding: Identical tablets Arm 2: DHA Description: Intervention Manufacturer: Martek Biosciences Dose: 1 capsule twice a day DHA: 400 mg/d, 200 mg/dl derived from algal source	(Primary) Follow-up time: birth Arm 1: Sample size 486; mean 39.1; SD (1.7) Arm 2: Sample size 487; mean 39.0; SD (1.9) Outcome: incidence of premature birth (Secondary) Follow-up time: birth Arm 1: 40/486 (8.3%) Arm 2: 49/487 (10.1%)
Stein et al., 2011[34] Study name: POSGRAD Study dates: 02. 2005-02.2007 Study design: Trial randomized parallel Location: Mexico Funding source / conflict: Government, Multiple foundations and Societies Original, same study, or follow-up studies: Stein, 2012[33]; Imhoff-Kunsch, 2011[58]; Escamilla-Nunez,	Study Population: Healthy infants Pregnant enrolled 1094 Pregnant completers 973 Pregnant age: placebo 26.3; DHA 26.4 (placebo 4.6; DHA 4.9) Infant age: 39.1 (placebo 1.6; DHA 1.8) Race of Mother: NR	Inclusion Criteria: women were 18–35 y, were in gestation wk 18–22, and planned to deliver at the IMSS General Hospital in Cuernavaca, exclusively or predominantly breast-feed for at least 3 mo, and to live in the area for at least 2 y after delivery Exclusion Criteria: NR	Start time: Pregnant 18-22 Gestational week Infants birth Duration: Pregnant birth Arm 1: Placebo Description: Olive oil Manufacturer: Martek Biosciences Dose: 2 capsules olive oil Blinding: Similar in appearance and taste to DHA capsules Arm 2: DHA Description: algal DHA capsules Manufacturer: Martek Biosciences Dose: 2 capsules * 200mg DHA: 400 mg	Outcome: gestational age (weeks) (Primary) Follow-up time: birth Arm 1: Sample size 368; mean 39.1; SD (1.6) Arm 2: Sample size 369; mean 39.1; SD (1.8) Outcome: incidence of premature birth (Secondary) Follow-up time: birth Arm 1: 30/368 (8.2%) Arm 2: 33/369 (8.9%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
2014[59]; Gonzalez-Casanova, 2015[60]; Ramakrishnan, 2015[61]; Ramakrishnan, 2011[32]				
Stein et al., 2012[33] Study name: POSGRAD Study dates: Feb 2005-Feb 2007 Study design: Trial randomized parallel Location: NR Funding source / conflict: Government Original, same study, or follow-up studies: Ramakrishnan, 2010[32]; Imhoff-Kunsch, 2011[58]; Escamilla-Nunez, 2014[59]; Gonzalez-Casanova, 2015[60]; Ramakrishnan, 2015[61]	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 1094 Pregnant withdrawals 63 Pregnant completers 900 Pregnant age: 26.3 (4.6-4.8) Infant age: 39.1 (1.7-1.8) Race of Mother: NR (NR)	Inclusion Criteria: Singleton live births without congenital anomalies Exclusion Criteria: 3364: high risk pregnancy, (history and prevalence of pregnancy complications, including abruption placentae, preeclampsia, pregnancy-induced hypertension, any serious bleeding episode in the current pregnancy, and physician referral); lipid metabolism or absorption disorders, regular intake of fish oil or DHA supplement, or chronic use of certain medication(e.g. epilepsy medications)	Start time: Pregnant 18-22 wk Duration: Pregnant to birth Arm 1: Placebo Description: A mixture of corn and soy oil Manufacturer: Martek Biosciences Blinding: "Participants and members of the study team were unaware of the treatment scheme throughout the intervention period of the study" Arm 2: DHA Description: DHA 400 mg/d Manufacturer: Martek Biosciences Dose: 2 capsule per day DHA: 2*200mg	duplicate data of Ramakrishnan, 2011[32] Outcome: (Primary)
van Goor et al., 2010[36] Study name: Groningen LCPUFA study Study dates: Enrollment from December 2004 until December 2006 Study design: Trial randomized parallel Location: Netherlands Funding source / conflict: Industry, Government	Study Population: Healthy pregnant women Breast-feeding women Pregnant enrolled 183 Pregnant completers 125 Infants completers 119 Pregnant age: 32 years (5 years) Infant age: 14 to 20 weeks gestation Race of Mother: NR	Inclusion Criteria: healthy women with a first or second low-risk singleton pregnancy Exclusion Criteria: women with vegetarian or vegan diets and women with diabetes mellitus	Start time: Pregnant 14 to 20 weeks gestation Infants 14 to 20 weeks gestation Duration: Pregnant until 3 months after delivery Infants until 3 months of age Arm 1: placebo Description: soybean oil capsule Manufacturer: Wuhan Alking Bioengineering Active ingredients: standard dose vitamins and minerals Dose: 2 capsules Maternal conditions ALA: 60 mg DHA: 0 EPA: 0	Outcome: gestational age birth (weeks) (Secondary) Follow-up time: birth Arm 1: Sample size 36; mean 40.2; SD (1) Arm 2: Sample size 42; mean 40.2; SD (1.1) Arm 3: Sample size 41; mean 40.2; SD (1.1)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study follow-up: 12 weeks Original, same study, or follow-up studies: Bouwstra, 2003[62]; Bouwstra, 2005[63]; de Jong, 2010[64]; de Jong, 2012[65]; van Goor, 2011[66]	(100)		AA: 0 Other dose 1: LA 535 mg Current smoker 2% Arm 2: DHA group Description: DHA fish oil capsule Manufacturer: Wuhan Alking Bioengineering Active ingredients: standard dose vitamins and minerals Dose: 2 capsules Maternal conditions ALA: 32 mg DHA: 220 mg EPA: 34 mg AA: 15 mg Other dose 2: LA 274 mg Current smoker 2% Arm 3: DHA + AA group Description: DHA + AA capsule Brand name: Marinol D40 Manufacturer: Lipid Nutrition B.V., Wormerveer, The Netherlands Active ingredients: standard dose vitamins and minerals Dose: 2 capsules Maternal conditions ALA: 7 mg DHA: 220 mg EPA: 36 mg AA: 220 mg Other dose 2: LA 46 mg Current smoker 3%	

AA = arachidonic acid; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FF = functional food; FOS = fructooligosaccharide; INFAT = impact of nutritional fatty acids during pregnancy and lactation on early adipose tissue developmentLCPUFA = long chian polyunsaturated fatty acid; mg = milligram; n-3 FA = omega-3 fatty acid; n-6 FA = omega-6 fatty acid; NR = not reported; OR = odds ratio; RBC = red blood cell; RCT = randomized controlled trial; SD = standard deviation

Table 2. Observational studies for length of gestation (or gestational age) and preterm birth

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Badart-Smook, et al., 1997[47] Outcome domain: Duration Gestation Study dates: NR Study design: Observational prospective Location: Netherlands Funding source / conflict: NR	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 610 Pregnant withdrawals 240 Pregnant completers 370 Pregnant age: 29 (4) Race of Mother: White European (100)	Inclusion Criteria: White race, intention to give birth to the baby in one of the three hospitals involved in the study Exclusion Criteria: Women with diastolic blood pressure of 90mm or higher, women suffering from any metabolic, cardiovascular, neurological, or renal disorder	Adjustments: Maternal(pregnancy) body weight, height, age, smoking habits, education, parity, and sex of the infant were included in each multiple regression model as possible confounding factors; except for the regression equation with gestational age as a dependent variable, gestational age at birth was also added as a confounder
Klebanoff, et al., 2011[49] Outcome domain: Duration Gestation Study dates: Jan 2005- Oct 2006 Study design: Observational prospective Location: US Funding source / conflict: Government Original, same study, or follow-up studies: Harper, 2010[29]	Study Population: Healthy pregnant women Pregnant enrolled 852 Pregnant completers 852 Pregnant age: <1/month, 27.1 (5.6) 0.5-3 per week, 28.0 (5.6) >3 per week, 27.3 (5.7) (<1/month, 27.1 (5.6) 0.5-3 per week, 28.0 (5.6) >3 per week, 27.3 (5.7)) Race of Mother: NR	Inclusion Criteria: at least one prior singleton preterm delivery between 20 0/7 and 36 6/7 weeks of gestation after spontaneous preterm labor or premature rupture of the membranes, and a current singleton pregnancy between 16 and 21 6/7 weeks of gestation Exclusion Criteria: evidence of a major fetal anomaly, intake of a fish oil supplement in excess of 500 mg per week at any time during the preceding month, allergy to fish, anticoagulation therapy, hypertension, White's classification D or higher diabetes, drug or alcohol abuse, seizure disorder, uncontrolled thyroid disease, clotting disorder, current or planned cerclage, or a plan to deliver either elsewhere or before 37 weeks of gestation	Adjustments: Study center, number of previous preterm births, gestation of earliest prior spontaneous preterm birth, receipt of omega-3 versus placebo supplement, smoking, age, education, body mass index and ethnicity
Molto-Puigmarti, et al., 2014[48] Outcome domain: Duration Gestation Study name: KOALA Birth Cohort Study Study dates: 2000-2002 Study design: Observational prospective Location: Netherlands Funding source / conflict: Multiple foundations and Societies	Study Population: Healthy pregnant women Pregnant enrolled 2669 Pregnant completers 1516 Infants enrolled 2669 Infants completers 1515 Pregnant age: years (.7yrs) Race of Mother: NR (100)	Inclusion Criteria: nr, Described in Ref 37 Exclusion Criteria: nr	Adjustments: Adjusted for child gender, study recruitment group, maternal education, parity, maternal smoking status during pregnancy, maternal alcohol use in pregnancy, and maternal age at delivery
Oken, et al., 2004[46]	Study Population: Healthy infants Healthy	Inclusion Criteria: delivered a live infant, and	Adjustments: Enrollment site,

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Outcome domain: Duration Gestation Study name: Project Viva Study dates: 1999-2002 Study design: Observational prospective Location: US Funding source / conflict: Government, Multiple foundations and Societies	pregnant women Pregnant enrolled 2109 Pregnant completers 2109 Pregnant age: 14-<20, 3% 20-<25, 6% 25-<30, 21% 30-<35, 42% 35=<40, 23% >=40, 4% (14-44) Race of Mother: White European (66) Black (16) Asian (6) Hispanic (7) Other race/ethnicity (4)	completed at least one dietary questionnaire Exclusion Criteria: taking cod liver or fish oil supplement	infant sex, and maternal age, height, intrapartum weight gain, prepregnancy BMI, race/ethnicity, smoking during pregnancy, education, and gravidity

Gestational Hypertension and Preeclampsia

Because a number of studies identified for this report combined the outcomes of gestational hypertension (GHTN), preeclampsia (PE), and eclampsia, we report them together.

Key Findings and Strength of Evidence for Risk for Gestational Hypertension/Preeclampsia

- Pooled analysis of three RCTs found no effect of fish oil intake during pregnancy on the risk for gestational hypertension or preeclampsia among women at increased risk for poor pregnancy outcomes.
- Pooled analysis of three RCTs (n=2,875) assessing the effects of DHA alone or DHA-enriched fish oil on the risk for GHTN/PE among women not at increased risk showed no effects.
- One study that assessed the effects of EPA alone on women not at risk showed no effect.
- No studies of ALA supplementation were found.
- Four prospective observational studies that assessed the association between n-3 intake and risk for GHTN or PE showed no consistent associations. Of two studies that assessed the association of biomarkers for n-3 intake with risk for GHTN/PE, one showed no association, whereas one study showed an association between plasma levels and reduced risk for GHTN.

Description of Included Studies

Randomized Controlled Trials

The original report identified 8 RCTs that assessed the effects of supplementation of pregnant women with n-3s on the outcomes of GHTN and/or PE. Pooling the outcomes of two trials on the effects of fish oil on the risk for GHTN among women at increased risk for GHTN or other high-risk pregnancy outcomes (N=582) revealed a non-statistically significant increase in the risk for GHTN among n-3 supplemented women (OR 1.07 [0.75, 1.51]).

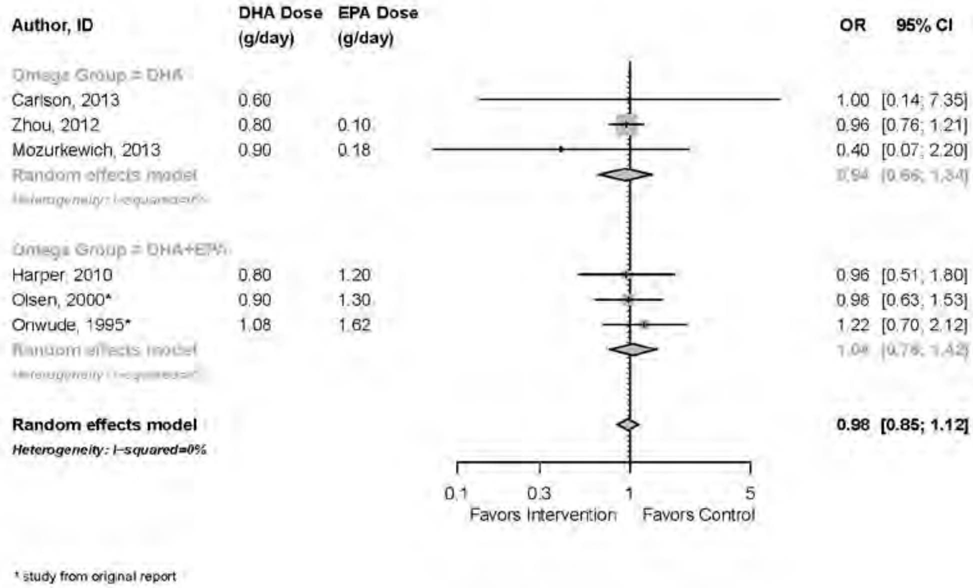
Four RCTs identified for the current report assessed the effects of n-3s on risk for GHTN and/or PE (see Table 3).[29, 31, 42, 55] Three of these RCTs enrolled women with no prior risk of poor pregnancy outcomes (N=2,875) (although one of the studies enrolled women at increased risk for peripartum depression).[31, 42, 55] The fourth RCT, by Harper and colleagues (2012), enrolled 852 women with a history of recurrent preterm birth.[29]

Marine Oil Versus Placebo

Population At Risk For Poor Pregnancy Outcomes.

Meta-analysis of the two RCTs from the original report, which compared the effects of marine oil versus placebo on at-risk populations, and the newly identified RCT by Harper and colleagues, which compared the effects of a mixture of EPA and DHA derived from fish with that of mineral oil among an at-risk population,[29] yielded an insignificant summary effect size for risk of GHTN or preeclampsia (OR [95% CI]=1.04 [0.76 , 1.42], $I^{2=}$ 0%) (see Figure 7).

Figure 7. Pregnancy induced hypertension/preeclampsia: DHA + EPA versus placebo, DHA versus placebo



The latter study also administered intra-muscular alpha-medroxyprogesterone caproate (the primary outcome of interest was prevention of preterm birth) and the fish oil capsules contained vitamin E as a preservative.

The study by Harper and colleagues conducted a subgroup analysis to determine whether the outcomes were affected by fish intake. No differences in outcomes were observed between women who consumed no fish or less than one serving of fish per month and those who consumed more fish.[29]

Population Not At Risk For Poor Pregnancy Outcomes

No studies were identified that assessed the effects of marine oil compared with placebo on the risk for GHTN or PE among women not at risk for poor pregnancy outcomes.

DHA Versus Placebo

Population At risk For Poor Pregnancy Outcomes

We identified no studies that compared the effect of supplements containing only DHA to that of placebo on the risk for GHTN or PE among women at increased risk for poor pregnancy outcomes.

Populations Not At Risk For Poor Pregnancy Outcomes

We identified three RCTs that compared the effect of supplements containing only DHA (600 to 900 mg/day) to that of placebo on the risk for GHTN or PE among women not at increased risk for poor pregnancy outcomes. The DOMInO trial enrolled 2,399 pregnant Australian women (less than 21 weeks gestation) to receive 800 mg/day DHA-enriched fish oil or vegetable oil placebo and followed throughout the second half of pregnancy to assess risk for gestational diabetes and PE as primary outcomes. No differences were seen in the risk for PE (adjusted or unadjusted for clinic and parity).[55] The Mothers, Omega-3, and Mental Health Study enrolled 126 pregnant U.S. women at risk for depression and randomly assigned them to receive

DHA-enriched fish oil (900 mg DHA:180 mg EPA/day), EPA-enriched fish oil (1,060 mg EPA: 274mg DHA), or soy bean oil placebo from early gestation through term. No differences were seen among groups in risk for development of GHTN or PE.[42] Finally, Carlson and coworkers randomized 350 pregnant U.S. women at less than 21 weeks gestation to receive 600mg/day DHA from marine algal oil or soybean and corn oil through term. No differences were seen between groups in the secondary outcome PE.[31]

Meta-analysis of the three RCTs yielded an insignificant summary effect size for DHA supplementation and risk of GHTN or preeclampsia (OR [95% CI]=0.94[0.66, 1.34], I^2=0%)(Figure 7).

EPA Versus Placebo

Only one RCT was identified that compared the effects of EPA supplementation with that of placebo on the risk for GHTN or PE. This study, described above, found no significant difference between EPA-enriched fish oil, DHA-enriched fish oil, and placebo and the risk for developing GHTN or PE.[42]

ALA Versus Placebo

We identified no studies that assessed the effects of ALA supplementation on risk for GHTN or PE.

Observational Studies

Five prospective studies evaluated the association between some measure of n-3 FA exposure and risk for GHTN or PE (see Table 4).[67-70] All enrolled populations of healthy pregnant women, usually at their first prenatal visit. One study was a nested case-control from a large RCT that assessed the association between dietary intakes of n-3 FA and maternal biomarkers and risk for GHTN.[67] The remainder were prospective cohort studies that assessed the association between dietary intakes of n-3 FA and risk for GHTN or PE.[68-70] (Table 4) Publications dated from 1995 to 2007.

n-3 FA Intake

Four studies evaluated the association between-3 FA intake and risk for GHTN and/or PE.[67-70]

A 1995 study assessed the association of n-3 FA intakes with risk for GHTN among a cohort of 208 healthy pregnant women in the Netherlands who enrolled in a RCT at less than 16 weeks gestation (52 of 208 women developed GHTN).[67] Intake of n-3 FA was established based on use of FFQ (and dietary history as a double check). No differences were observed in total n-3 FA intake between women who subsequently developed GHTN and those who did not, prior to delivery. However postpartum levels of serum DHA were significantly higher in women with GHTN than in women without GHTN after correction for gestational age.

A 2001 study of 3,133 healthy Norwegian women who completed a validated FFQ found a slight but significant increase in the risk for PE associated with increasing intakes of n-3 FA and n-6 FA, adjusted for age, smoking status, BMI, systolic blood pressure, and parity.[68] Further adjustment for energy intake resulted in these trends no longer being significant.

A 2006 study followed 488 healthy Icelandic women: 30 developed GHTN and 19 developed PE. Analysis of responses to a semi-quantitative food and lifestyle questionnaire showed that women who consumed cod liver oil early in pregnancy were almost 5 times as likely to develop GHTN or PE than women who did not (adjusted OR 4.7, [1.8, 12.6] p=0.002) (findings were adjusted for weight gain during pregnancy, BMI, weight gain, smoking, parity, and diastolic and systolic blood pressure early in pregnancy). Cod liver oil is a source of vitamins A, D, and E as well as n-3 FA. A slight U-shaped association was seen between daily intakes of n-3FA and risk for GHTN or PE or GHTN alone (p=0.008).[70]

Project Viva, a U.S. study, followed 1,718 pregnant women, 59 of whom developed PE (3%) and 119 who developed GHTN (7%). Multivariate logistic regression analysis of a modified validated semi-quantitative FFQ showed a slightly *decreased* risk for PE with higher intakes of DHA + EPA (adjusted OR 0.84 [0.69, 1.03] per 100 mg per day) and DHA+EPA: AA (adjusted OR 0.82 [0.66, 1.01]) but not for GHTN (adjusted for maternal age [<20, 20–40, 40+ years], prepregnancy body mass index (continuous), first-trimester systolic blood pressure [continuous],race/ethnicity (black, Hispanic, white, other), education [college graduate, < college graduate], and parity [0, 1+]; intakes were adjusted for total energy intake. No association was seen for intakes of ALA.[69]

n-3 FA Biomarkers

One of the studies described above assessed the association between biomarkers for n-3s and the risk for GHTN.[67] No significant differences were found at any point during pregnancy in any of the maternal plasma phospholipid n-3 FA or n-6 FA between women who developed GHTN and those who did not. However postnatal plasma phospholipids of women with GHTN showed lower levels of ALA and LA than did those of women with normal pregnancies.

A second study identified for this report assessed the association between maternal third trimester plasma total n-3 PUFAs and the risk for GHTN.[71] The Growing UP in Singapore Towards healthy Outcomes (GUSTO) study recruited a cohort of pregnant Chinese, Malay, and Indian women residing in Singapore. A total of 28 women out of 722 for whom data were available developed GHTN and/or preeclampsia (women with a history of pre-pregnancy HTN were excluded from this analysis). A 1 percent increase in plasma total and long-chain n-3 FA was significantly inversely associated with the risk for GHTN (adjusted OR 0.76, [0.60, 0.97] and 0.77 [0.60, 0.98], respectively). The authors adjusted for age, ethnicity, education, exercise, alcohol intake, smoking status, BMI and height at the 26^{th}-28^{th} week of gestation, gestational diabetes, heart rate, and fish oil supplementation.

Observational study subgroup analyses

None of the studies reported subgroup analyses.

Table 3. RCTs for gestational hypertension preeclampsia eclampsia

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Carlson et al., 2013[31] Study name: NR Study dates: 2006.01-2011.10 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product	Study Population: Healthy pregnant women Pregnant enrolled 350 Pregnant withdrawals 49 Pregnant completers 301 Pregnant age: placebo: 24.8; DHA: 25.3 (placebo 4.7; DHA 4.9) Race of Mother: Black (46%;37%) Non-black (54%; 63%) Baseline biomarker information: RBC-phospholipid-DHA (placebo group 4.3 +- 1.3; 4.3 +- 1.1) Baseline Omega-3 intake: Voluntary DHA intake from supplement (placebo group 15%, DHA group 9%)	Inclusion Criteria: English-speaking, between 8 and 20 wk of gestation, between 16 and 35.99 y of age, and planning to deliver at a hospital in the Kansas City metropolitan area Exclusion Criteria: carrying more than one fetus, had preexisting diabetes mellitus or systolic blood pressure $140 mm Hg at enrollment, or had any serious health condition likely to affect the prenatal or postnatal growth and development of their offspring, including cancer, lupus, hepatitis, HIV/AIDS, or a diagnosed alcohol or chemical dependency. or if the initial screening based on their self-reported weight and height suggested a BMI (in kg/m2 >=40).	Start time: Pregnant 99.6/102.9 day Duration: Pregnant enrollment to birth Arm 1: Placebo Description: half soybean and half coin oil Manufacturer: DSM Nutritional Products) Active ingredients: a-linolenic acid Dose: 3 *capsule 200/day Blinding: both DHA and placebo capsules were orange flavored Arm 2: DHA Description: marine algae-oil source of DHA Manufacturer: DHASCO; DSM Nutritional Products, formerly Martek Biosciences) Dose: 200 mg capsule, 3 times a day DHA: 200mg/capsule * 3	Outcome: preeclampsia (Secondary) Follow-up time: during pregnancy Arm 1: 2/147 (1.3%) Arm 2: 2/154 (1.3%)
Harper et al., 2010[29] Study name: NR Study dates: 01. 2005 - 10. 2006 Study design: Trial randomized parallel Location: US	Study Population: At risk for preterm labor Pregnant enrolled 852 Pregnant withdrawals 0 Pregnant completers 852 Pregnant age: n3: 28 placebo 27 n3 23-32; placebo 24-32 Race of Mother: White	Inclusion Criteria: a documented history of at least one prior singleton preterm delivery between 20 0/7 and 36 6/7 weeks of gestation after spontaneous preterm labor or premature rupture of the membranes, and a current singleton pregnancy between 16	Start time: Pregnant 16-22 week gestation age Duration: Pregnant 36 weeks of gestation Arm 1: placebo Description: inert mineral oil Manufacturer: Eminent Services, Frederick, MD Active ingredients: 10 IU vitamin E per capsule, injections of 17_x0001_-hydroxyprogesterone caproate Dose: four capsules of matching oil containing a minute amount of inert mineral oil	Outcome: preeclampsia or gestational hypertension (Secondary) Follow-up time: during pregnancy Arm 1: 20/418 (4.8%) Arm 2: 20/434 (4.6%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Funding source / conflict: Government, Manufacturer supplied product Original, same study, or follow-up studies: Klebanoff, 2011[49]	European (n3: 56.5; placebo 57.7) Black (n3: 34.1; placebo 34.9) Asian (n3: 3, placebo 1.2) Hispanic (n3: 14.7; placebo 13.6) Other race/ethnicity (NR)	and 21 6/7 weeks of gestation Exclusion Criteria: evidence of a major fetal anomaly, intake of a fish oil supplement in excess of 500 mg per week at any time during the preceding month, allergy to fish, anticoagulation therapy, hypertension, White's classification D or higher diabetes, drug or alcohol abuse, seizure disorder, uncontrolled thyroid disease, clotting disorder, current or planned cerclage, or a plan to deliver either elsewhere or before 37 weeks of gestation	Blinding: Boxes containing a woman's entire supply of capsules in blister packs were sequentially numbered according to the predetermined randomization sequence, and on enrollment a woman was assigned the next number in sequence. Study group assignment was not known by study participants, their health care providers, or the research personnel Arm 2: Eminent Services, Frederick, MD Active ingredients: 10 IU vitamin E per capsule, injections of 17_x0001_-hydroxyprogesterone caproate Dose: in 4 capsules total 2000 mg of n3 DHA: 800 mg EPA: 1200 mg	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Mozurkewich et al., 2013[42] Study name: NR Study dates: Oct 2008 - May 2011 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product	Study Population: Healthy pregnant women Pregnant enrolled 126 Pregnant withdrawals 8 Pregnant completers 118 Pregnant age: EPA 29.9; DHA 30.6; placebo 30.4 (EPA 5.0; DHA 4.5; placebo 5.9) Race of Mother: White European (85%; 76%; 83%) Black (10%; 11%; 5%) Asian (3%; 3%; 2%) Hispanic (0%; 11%; 7%) Inuit Eskimo (0%; 0%; 2%) Pacific Islander (NR) Baseline biomarker information: EPA group: EPA 0.29+-0.18; DHA 4.24+-2.30; total n3 FA: 22.10+-3.72 DHA group: EPA 0.31+-0.24; DHA 4.66+-2.29; total n3 FA 36.41+-9.71 placebo: EPA .34+-0.22; DHA 3.85+-1.77; omega3 FA 322.86+-5.02	Inclusion Criteria: past history of depression, an EPDS score 9-19 (at risk for depression or mildly depressed), singleton gestation, a maternal age of 18 years or older, and a gestational age of 12-20 weeks Exclusion Criteria: had a history of a bleeding disorder, thrombophilia requiring anticoagulation, multiple gestation, bipolar disorder, current major depressive disorder, current substance abuse, lifetime substance dependence, or schizophrenia. Women were also ineligible if they were currently taking omega-3 fatty acid supplements or antidepressant medications or eating more than 2 fish meals per week.	Start time: Pregnant 12-20 week gestation Duration: Pregnant assuming till birth Arm 1: Control/Placebo Description: 98% soy oil and 1% each of lemon and fish oil Manufacturer: Nordic Naturals Corporation in Watsonville, CA Viability: centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose: 2 large and 4 small placebo capsules Blinding: The placebos were formulated to be identical in appearance to both the EPA- and DHA-rich supplements Arm 2: EPA-rich fish oil Description: an approximate 4:1 ratio of EPA to DHA (1060 mg EPA plus 274 mg DHA) Brand name: ProEPAXtra, Nordic Naturals Viability: centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose: 2 large EPA capsule and 4 small placebo DHA: 274 mg EPA: 1060 mg Arm 3: DHA-rich fish oil Description: DHA and EPA in an approximate 4:1 ratio o (900 mg DHA plus 180 mg EPA) Brand name: ProDHA, Nordic Naturals Viability: centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose: 2 large placebo oil and 4 small DHA rich DHA: 900 mg EPA: 180 mg	Outcome: gestational hypertension or preeclampsia (Secondary) Follow-up time: during pregnancy Arm 1: 5/41 (12.0%) Arm 2: 8/39 (21.0%) Arm 3: 2/38 (5.0%)
Zhou et al., 2012[55] Study name: DOMInO Study dates: 10. 2005 - 01. 2008 Study design: Trial randomized parallel	Study Population: Healthy pregnant women Pregnant enrolled 2399 Race of Mother: White European (88%;88%) Asian (7%;8%) Inuit Eskimo (2%;1%) Other	Inclusion Criteria: NR Exclusion Criteria: If already taking a dietary supplement containing DHA, their fetus had a known major abnormality, they had a bleeding disorder for	Start time: Pregnant medium gestational age 19 weeks Duration: Pregnant birth Arm 1: control Description: 500-mg vegetable oil capsules Dose: 3*500mg 3 nongenetically modified oils (rapeseed, sunflower, and palm) in equal	Outcome: preeclampsia (Secondary) Follow-up time: during pregnancy Arm 1: 58/1202 (4.85%) Arm 2: 60/1197 (4.97%) Outcome: pregnancy induced hypertension (Secondary) Follow-up time: during pregnancy Arm 1: 107/1202 (8.88%) Arm 2: 98/1197 (8.18%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Location: Australia Funding source / conflict: Government, Multiple foundations and Societies, Manufacturer supplied product Original, same study, or follow-up studies: Makrides, 2010[35]; Smithers, 2011[53]; Palmer, 2012[54]; Palmer, 2013[56]; Makrides, 2014 [57]	race/ethnicity (NR)	which fish oil was contraindicated, they were receiving anticoagulant therapy, they had a documented history of drug or alcohol abuse, they were participating in another fatty acid trial, or English was not the main language spoken at home	proportions Blinding: All capsules were similar in size, shape, and color Arm 2: DHA Description: DHA-rich fish oil Manufacturer: Incromega 500 TG; Croda Chemicals Dose: 3*500mg capsule DHA: 800 mg EPA: 100 mg	

AA = arachidonic acid; ALA = alpha linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; Hg = mercury; LCPUFA = long chian polyunsaturated fatty acid; mg = milligram; n-3 FA = omega-3 fatty acid; n-6 FA = omega-6 fatty acid; NR = not reported; RBC = red blood cell; RCT = randomized controlled trial; SD = standard deviation

Table 4. Observational studies for gestational hypertension preeclampsia eclampsia

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Clausen, et al., 2001[68] Outcome domain: Gestational HTN and Preeclampsia Study dates: 12/94-8/96 Study design: Observational prospective Location: Norway Funding source / conflict: NR	Study Population: Healthy pregnant women Pregnant enrolled 3,771 Pregnant completers 3,133 Pregnant age: 29.8 (4.5) Race of Mother: White European (100)	Inclusion Criteria: Caucasian women seen at Aker University Hospital for prenatal care and who agreed to undergo ultrasound at their first prenatal visit and who completed a FFQ Exclusion Criteria: Pregestational diabetes, abortion, twin or triplet pregnancies, patients who give birth at other hospitals, missing records, loss to followup	Adjustments: Age, smoking (yes or no), BMI (<=20, 20-25, 25-30, >30), systolic blood pressure (sBP) before 20 weeks' gestation, and nullipara (yes or no)
Lim, et al., 2015[71] Outcome domain: Gestational HTN and Preeclampsia Study dates: 2009-2012 Study design: Observational prospective Location: NR Funding source / conflict: Industry, Government	Study Population: Healthy pregnant women Pregnant enrolled 1162 Pregnant completers 751 Infants completers Pregnant age: 1st tertile 29.9 2nd tertile 30.0 3rd tertile 31.7 _ (1st tertile 5. 2 2nd tertile 5.2, 3rd tertile 4.8) Race of Mother: Asian (100)	Inclusion Criteria: Healthy women in early pregnancy at one of 3 tertiary care hospitals in Singapore Exclusion Criteria: receiving chemotherapy, taking psychotropic drugs, or having type 1 diabetes	Adjustments: Adjusted for age, ethnicity, education, exercise, alcohol intake, smoking status, BMI, and height at the 26th to the 28th week of gestation, gestational diabetes, and heart rate, fish oil supplementation
Oken, et al., 2007[69] Outcome domain: Gestational HTN and Preeclampsia Study name: Project Viva Study dates: Recruitment 1999-2002 Study design: Observational prospective Location: US Funding source / conflict: Government, Multiple foundations and Societies	Study Population: Healthy pregnant women Pregnant enrolled 2,128 Pregnant completers 1,718 Pregnant age: 93% were 20-40 years Race of Mother: White European (72%) Black (12%) Hispanic (6%) Other race/ethnicity (10%)	Inclusion Criteria: 1st trimester pregnant women attending 1st prenatal visit Exclusion Criteria: Post hoc: no live birth, no medical records, failure to complete dietary questionnaires, pre-existing chronic hypertension and no subsequent preeclampsia	Adjustments: Maternal age, prepregnancy BMI, 1st trimester sBP, race/ethnicity, education, parity; nutrients adjusted for total energy intake
Olafsdottir, et al., 2006[70] Outcome domain: Gestational HTN and Preeclampsia	Study Population: Healthy pregnant women Pregnant enrolled 549 Pregnant completers 488 Pregnant age: 28 (5)	Inclusion Criteria: Pregnant women attending first prenatal visit at Center of Prenatal Care in Reykjavik from 1999-2001, who gave birth to full-term babies completed the study.	Adjustments: Weight gain during pregnancy, BMI X weight gain, smoking, parity and diastolic and systolic blood pressure early in

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Study dates: 1999-2001 Study design: Observational prospective Location: NR Funding source / conflict: Government, Multiple foundations and Societies	Race of Mother: White European (NR)	Exclusion Criteria: Essential hypertension, gestational diabetes, miscarriage/stillbirth, twins/triplets, preterm birth, loss of personal data, moved, missing data,	pregnancy

BMI = body mass index; HTN = hypertension; NR = not reported; sBP = systolic blood pressure

Risk for Low Birth Weight

Key Findings and Strength of Evidence for Risk of Low Birth Weight

- There is a low level of evidence that maternal supplementation of DHA during pregnancy may not have significant effects on risk for delivering a low birth weight (LBW) infant.
  - Pooled analysis of 4 RCTs that assessed the effects of DHA alone or DHA-enriched fish oil on the risk of delivering a LBW infant among women not at increased risk showed no significant effects.
  - One RCT that assessed the effect of DHA+EPA on the risk of delivering a LBW infant among women at increased risk showed no significant effects.
  - One prospective observational study that assessed the effect of EPA intake in the third trimester of pregnancy on LBW found a significantly increased risk among women in the first and second tertiles of EPA intake. No associations were seen between tertiles of EPA intake and risk of LBW in the first or second trimesters of pregnancy.

Description of Included Studies

The original report included three RCTs that assessed the effects of maternal n-3 FA intake on the outcome of intrauterine growth retardation (IUGR) and seven RCTs that assessed the effects of maternal n-3 FA intake on the outcome of low birth weight (LBW, defined as less than 2,500 g or as less than 2,000 g). Two RCTs assessed both IUGR and LBW outcomes. For the IUGR outcome, all three RCTs enrolled pregnant women at risk of IUGR, due to a previous history of IUGR, twin pregnancy, or history of premature delivery. Meta-analysis of these three RCTs found no significant effects of DHA+EPA supplementation (doses ranged from 2.2 to 3 g/d) on the incidence of IUGR (birth weight < 3rd and 10th percentile, adjusted for gestational age [GA]) between DHA+EPA supplementation and control groups (OR: 1.14, 95% Confidence Interval [CI] 0.79; 1.64). Of the seven RCTs that assessed LBW outcomes, two compared n-3 FA-enriched eggs (DHA 0.23 g/d) with control eggs and the other five compared fish oil (DHA+EPA) supplements with placebo. Five of the seven RCTs showed that n-3 FA supplementation did not influence the incidence of LBW infants among pregnant women with or without a history of previous IUGR. The other two RCTs each found a lower incidence of LBW infants born to women who received fish oil (DHA+EPA) supplements compared with those who received placebo (-26% and -1.9%).

For the current report, we identified five RCTs (in 9 publications) [29, 31-35, 43, 55, 61] that assessed the effects of maternal n-3 FA intake on risk of LBW or small-for-gestational-age (SGA) (see Table 5). Three of these RCTs also reported the outcome of risk for very low birth weight (VLBW, less than 1500 g).[29, 31, 43] Of the five RCTs, three (in four publications)[29, 34, 55, 61] assessed the effects of maternal n-3 intake on risk of SGA or IUGR. In addition, we identified one observational study[72] that assessed the effects of maternal n-3 FA intake on risk of LBW and two observational studies [46, 73] that examined the association of maternal n-3 FA exposure (dietary intake or plasma concentration) with risk for SGA/IUGR. In all studies, SGA or IUGR were both defined as birth weight for gestational age <10th percentile of a reference standard, and LBW and VLBW were defined as birth weight <2,500 and <1,500 g, respectively. Of the studies identified for the current report, all were conducted among healthy pregnant women, except for one RCT that enrolled women who were identified as being at risk of having an SGA/IUGR outcome due to having at least one prior spontaneous preterm delivery.[29]

Randomized Controlled Trials

Five RCTs (in eight publications) were identified for the current report that assessed the effects of n-3 FA interventions on LBW or VLBW. Three of the publications were from the POSGRAD (Prenatal DHA (Omega-3 fatty acid) Supplements on infant GRowth And Development) trial, [32-34] and two of the publications were from the Docosahexaenoic Acid to Optimise Mother Infant Outcome (DOMInO) trial.[35, 55]

DHA

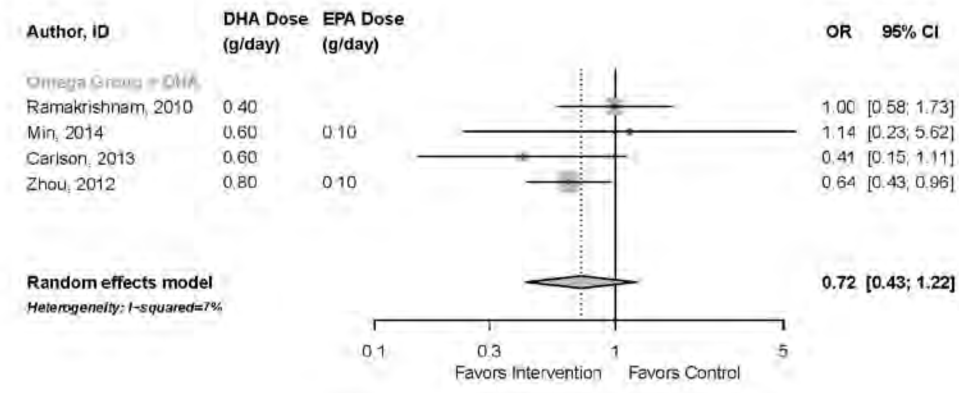
The POSGRAD trial randomized 1,094 pregnant Mexican women (18-22 weeks' gestation) to receive 0.4 g/day DHA or a placebo containing olive oil.[34] Data on birth outcomes were available for 973 women, of whom 487 were randomized to receive DHA and 486 were randomized to receive placebo. Overall, no difference was seen in the percent of women delivering LBW infants (percent LBW, 5.5 percent for DHA vs. 5.6 percent for placebo, p=0.99). However, when stratified by gravidity, the findings showed a trend towards lower percent LBW in the DHA group compared to the placebo group (3.3 percent for DHA vs. 7.4 percent for placebo, p=0.08) among primigravidae women, but no difference among multigravidae women (6.9 percent for DHA vs. 4.4 percent for placebo, p=0.18). The percent of LBW infants was not different in the subset of infants with 18-month follow-up data [34] or the subset on whom measures of auditory or visual evoked potentials were obtained.[33]

The DOMInO trial [35, 55] randomized 2,399 healthy pregnant Australian women (<21 weeks' gestation) to receive a DHA-rich fish oil concentrate containing 0.8 g/day DHA and 0.1 g/day EPA (n=1197) or a vegetable oil placebo (n=1202). Percent LBW differed significantly between the two groups (3.4 percent DHA vs. 5.3 percent placebo, p=0.03).

Two other small RCTs both examined the effects of DHA on the risk for LBW and VLBW in a total of 435 healthy pregnant women. [31, 43] Carlson randomized 350 healthy pregnant women in the US (8-20 weeks' gestation) to receive 0.6 g/day DHA or a placebo containing half soybean and half corn oil. [31] Of the 301 women with birth outcome data, 154 were randomized to DHA and 147 to placebo. The study observed a trend toward lower risk for LBW in the DHA group compared to the placebo group (3.9 percent vs. 9.0 percent, p=0.059). A significant difference was also observed in the percentage of infants born with VLBW between the two groups (0 percent for DHA vs. 3.4 percent for placebo, p=0.026). Min randomized 85 healthy pregnant women in the UK (11-12 weeks' gestation) to receive 0.6 g/day DHA or a placebo containing high oleic acid sunflower oil. [43] Of the 59 women with birth outcome data, 32 were randomized to DHA and 27 to placebo. No significant differences were seen in the risk of LBW (12.5 percent for DHA vs. 11.1 percent for placebo, p>0.05) or VLBW (3.1 percent for DHA vs. 0 percent for placebo, p>0.05).

Our meta-analysis of four trials in healthy pregnant women showed that maternal DHA supplementation had no significant effects on LBW outcome (OR [95% CI]=0.72 [0.43, 1.11], I^2=7%). (Figure 8)

Figure 8. Risk for low birth weight (<2500g) – DHA versus placebo



EPA+DHA

Harper et al (2010)[29] randomized 852 US women who had at least one prior spontaneous preterm delivery to receive marine oils (0.8 g/day DHA plus 1.2 g/day EPA) or a mineral oil placebo. Capsules from both groups also contained 10 IU vitamin E per capsule and all women received weekly injections of 17α-hydroxyprogesterone caproate. Among the 837 liveborn neonates with birth weight data available, 427 were randomized to the n-3 group and 410 were randomized to placebo. This study found no significant difference in the percent of LBW infants between the two groups (22 percent n-3 vs. 27 percent placebo, p>.05). There was also no difference in the percent of VLBW infants between the two groups (6.1 percent n-3 vs. 7.1 percent placebo, p>.05).

Observational Studies

Muthayya (2009) assessed the association between n-3 FA intake in the first, second, and third trimesters of pregnancy and LBW among 675 women (ages 17-40 and <20 weeks of gestation) receiving medical care at St. John's Medical College Hospital in Bangalore, India.[72] Additionally, erythrocyte membrane phospholipid FA status was measured in a random subsample of 150 women in each trimester. No association was observed between tertiles of EPA intake and LBW in the first or second trimesters of pregnancy. In the third trimester (n=419), women in the first and second tertiles of EPA intake had significantly increased risk of LBW compared to the highest tertile after adjusting for confounders (adjusted OR [AOR] 2.75, 95% CI 1.26-6.02 for tertile 1; AOR 2.54, 95% CI1.17-5.50 for tertile 2). No significant association was observed between erythrocyte FA status and risk of LBW in this study.

Table 5. RCTs that assessed risk for low birth weight

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Carlson et al., 2013[31] Study name: NR Study dates: 2006.01-2011.10 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product	Study Population: Healthy pregnant women Pregnant enrolled 350 Pregnant withdrawals 49 Pregnant completers 301 Pregnant age: placebo: 24.8; DHA: 25.3 (placebo 4.7; DHA 4.9) Race of Mother: Black (46%;37%) Non-black (54%; 63%) Baseline biomarker information: RBC-phospholipid-DHA (placebo group 4.3 +- 1.3; 4.3 +- 1.1) Baseline Omega-3 intake: Voluntary DHA intake from supplement (placebo group 15%, DHA group 9%)	Inclusion Criteria: English-speaking, between 8 and 20 wk of gestation, between 16 and 35.99 y of age, and planning to deliver at a hospital in the Kansas City metropolitan area Exclusion Criteria: carrying more than one fetus, had preexisting diabetes mellitus or systolic blood pressure $140 mm Hg at enrollment, or had any serious health condition likely to affect the prenatal or postnatal growth and development of their offspring, including cancer, lupus, hepatitis, HIV/AIDS, or a diagnosed alcohol or chemical dependency. or if the initial screening based on their self-reported weight and height suggested a BMI (in kg/m2 >=40).	Start time: Pregnant 99.6/102.9 day Duration: Pregnant enrollment to birth Arm 1: Placebo Description: half soybean and half coin oil Manufacturer: DSM Nutritional Products) Active ingredients: a-linolenic acid Dose: 3 *capsule 200/day Blinding: both DHA and placebo capsules were orange flavored Arm 2: DHA Description: marine algae-oil source of DHA Manufacturer: DHASCO; DSM Nutritional Products, formerly Martek Biosciences) Dose: 200 mg capsule, 3 times a day DHA: 200mg/capsule * 3	Outcome: birth weight <1500g (Secondary) Follow-up time: birth Arm 1: 5/147 (3.4%) Arm 2: 0/154 (0.0%) Outcome: birth weight <2500g (Secondary) Follow-up time: birth Arm 1: 13/147 (9.0%) Arm 2: 6/154 (3 .9%)
Harper et al., 2010[29] Study name: NR Study dates: 01. 2005 - 10. 2006 Study design: Trial randomized parallel Location: US Funding source / conflict:	Study Population: At risk for preterm labor Pregnant enrolled 852 Pregnant withdrawals 0 Pregnant completers 852 Pregnant age: n3: 28 placebo 27 n3 23-32; placebo 24-32 Race of Mother: White European (n3: 56.5;	Inclusion Criteria: a documented history of at least one prior singleton preterm delivery between 20 0/7 and 36 6/7 weeks of gestation after spontaneous preterm labor or premature rupture of the membranes, and a current singleton pregnancy between 16 and 21 6/7 weeks of	Start time: Pregnant 16-22 week gestation age Duration: Pregnant 36 weeks of gestation Arm 1: placebo Description: inert mineral oil Manufacturer: Eminent Services, Frederick, MD Active ingredients: 10 IU vitamin E per capsule, injections of 17_x0001_-hydroxyprogesterone caproate Dose: four capsules of matching oil containing a minute amount of inert mineral oil Blinding: Boxes containing a woman's entire supply	Outcome: birth weight <1500g (Secondary) Follow-up time: birth Arm 1: 29/410 (7.1%) Arm 2: 26/427 (6.1%) Outcome: birth weight <2500g Follow-up time: birth Arm 1: 112/410 (27.3%) Arm 2: 94/427 (22.0%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Government, Manufacturer supplied product Original, same study, or follow-up studies: Klebanoff, 2011[49]	placebo 57.7) Black (n3: 34.1; placebo 34.9) Asian (n3: 3, placebo 1.2) Hispanic (n3: 14.7; placebo 13.6) Other race/ethnicity (NR)	gestation Exclusion Criteria: evidence of a major fetal anomaly, intake of a fish oil supplement in excess of 500 mg per week at any time during the preceding month, allergy to fish, anticoagulation therapy, hypertension, White's classification D or higher diabetes, drug or alcohol abuse, seizure disorder, uncontrolled thyroid disease, clotting disorder, current or planned cerclage, or a plan to deliver either elsewhere or before 37 weeks of gestation	of capsules in blister packs were sequentially numbered according to the predetermined randomization sequence, and on enrollment a woman was assigned the next number in sequence. Study group assignment was not known by study participants, their health care providers, or the research personnel Arm 2: Eminent Services, Frederick, MD Active ingredients: 10 IU vitamin E per capsule, injections of 17_x0001_-hydroxyprogesterone caproate Dose: in 4 capsules total 2000 mg of n3 DHA: 800 mg EPA: 1200 mg	
Makrides et al., 2010[35] Study name: DOMInO Study dates: 2005-2008 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Manufacturer supplied product Original, same study, or follow-up studies: Smithers, 2011[53]; Palmer, 2012[54]; Zhou, 2012[55]; Palmer, 2013[56]; Makrides, 2014 [57]	Study Population: Healthy pregnant women Pregnant enrolled 2399 Pregnant withdrawals 1 Infants enrolled 605 Infants withdrawals 32 Infants completers 726 Pregnant age: 28.9 (DHA5.7___ control5.6) Race of Mother: NR	Inclusion Criteria: with singleton pregnancies at less than 21 weeks' gestation were approached by study research assistants while attending routine antenatal appointments Exclusion Criteria: already taking a prenatal supplement with DHA, their fetus had a known major abnormality, they had a bleeding disorder in which tuna oil was contraindicated, were taking anticoagulant therapy, had a documented history of drug or alcohol abuse, were participating in another fatty acid trial, were unable to give	Start time: Pregnant < 21 week's gestation Duration: NR Arm 1: vegetable oil capsules Description: a blend of 3 nongenetically modified oils (rapeseed, sunflower, and palm) in equal proportions Manufacturer: Efamol, Surrey, England. Dose: 3* 500mg capsule / day Blinding: All capsules were similar in size, shape, and color Arm 2: DHA Description: DHA-rich fish oil concentrate Manufacturer: ; Incromega 500 TG, Croda Chemicals, East Yorkshire, England Dose: 500mg capsule *3/day DHA: 800mg EPA: 100mg	duplicate data of id 4404

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		written informed consent, or if English was not the main language spoken at home		
Min et al., 2014[43] Study name: NR Study dates: Jan 2008 - Dec 2011 Study design: Trial randomized parallel Location: UK Funding source / conflict: Industry, Government, Multiple foundations and Societies, Manufacturer supplied product Original, same study, or follow-up studies: none	Study Population: Healthy pregnant women, Pregnant women with type 2 diabetes Pregnant enrolled 85 Pregnant completers 59 Pregnant age: 29 18-44 Infant age: 11.0-12.1 weeks gestation 6.0-15.9 weeks gestation Race of Mother: White European (22.3%) Black (28.2%) Asian (40.0%) Other race/ethnicity (9.4%)	Inclusion Criteria: Pregnant women of 17–45 years old with singleton pregnancies with either pre-existing Type 2 diabetes or without any known medical condition (uncomplicated pregnancy group) Exclusion Criteria: Women planning to receive tocolytic or corticosteroid therapy. Note that pregnant women with pre-existing Type 2 diabetes were excluded from this systematic review.	Start time: Pregnant average: 9.9-12.1 weeks gestation (range: 4.3-15.9 weeks gestation) Duration: Pregnant until delivery; average: 26.5 weeks for placebo arm; 28.4 weeks for the fish oil arm Arm 1: Placebo, healthy women Description: high oleic acid sunflower oil Manufacturer: Equazen/Vifor Pharma Ltd. Active ingredients: oleic acid, 82.6%; vitamin E (d- a tocopherol) NR% Dose: 2x 750 mg capsules/day Blinding: identical oblong soft gelatin capsule Maternal conditions Current smoker 0% Arm 2: Fish oil, healthy women Description: HA-enriched fish oil Brand name: Mumomega Manufacturer: Equazen/Vifor Pharma Ltd. Active ingredients: vitamin E (d- a tocopherol) NR% Dose: 2 750 mg capsules/day Maternal conditions DHA: 43.7% (600 mg/d) EPA: 7.5% (estimated to be 103 mg/d) Current smoker 13.3% Arm 3: Placebo, diabetic women Description: high oleic acid sunflower oil Manufacturer: Equazen/Vifor Pharma Ltd. Active ingredients: oleic acid, 82.6%; vitamin E (d- a tocopherol) NR% Dose: 2 750 mg capsules/day Maternal conditions Current smoker 0% Other maternal conditions 1arm_3_maternal_conditions_other1 Other maternal conditions 10 Type 2 diabetes: 100% Arm 4: Fish oil, diabetic women	Outcome: birth weight <1500g (Secondary) Follow-up time: birth Arm 1: 0/27 (0.0%) Arm 2: 1/32 (3.1%) Outcome: birth weight <2500g (Secondary) Follow-up time: birth Arm 1: 3/27 (11.1%) Arm 2: 4/32 (12.5%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			Description: HA-enriched fish oil Brand name: Mumomega Manufacturer: Equazen/Vifor Pharma Ltd. Active ingredients: vitamin E (d- a tocopherol) NR% Dose: 2 750 mg capsules/day Blinding: identical oblong soft gelatin capsule Maternal conditions DHA: 43.7% EPA: 7.5% Current smoker 4.9% Other maternal conditions 1arm_4_maternal_conditions_other1 Other maternal conditions 10 Type 2 diabetes: 10	
Ramakrishnan et al., 2010[32] Study name: POSGRAD Study dates: Feb 2005 - Feb 2007 Study design: Trial randomized parallel Location: Mexico Funding source / conflict: Government, March of Dimes Original, same study, or follow-up studies: Stein, 2012[33]; Imhoff-Kunsch, 2011[58]; Escamilla-Nunez, 2014[59]; Gonzalez-Casanova, 2015[60]; Ramakrishnan, 2015[61]; Stein, 2011[34]	Study Population: Healthy pregnant women Pregnant enrolled 1,094 Pregnant withdrawals 67 Pregnant completers 973 (for birth weight) Pregnant age: 26.2 (controls) 26.3 (DHA) (4.6 (controls) 4.8 (DHA)) Race of Mother: Hispanic (NR) Baseline Omega-3 intake: mg/day for all: LA: 17,846 in controls, 17,645 in DHA AA: 137 in controls, 140 in DHA ALA: 1,488 in controls, 1,477 in DHA EPA: 18 in controls, 18 in DHA DHA: 54 in controls, 56 in DHA	Inclusion Criteria: 18-35 yrs. of age, in gestation weeks 18-22, planned to deliver at the IMSS General Hospital in Cuernavaca, exclusively or predominantly breastfeed for at least 3 months, liver in the area for at least 2 years after delivery. Exclusion Criteria: high-risk pregnancy; lipid metabolism or absorption disorders, regular intake of fish oil or DHA supplements; chronic use of certain medications (e.g., medications for epilepsy).	Start time: Pregnant at study entry Duration: Pregnant mid pregnancy (18-22 weeks gestation) until delivery Arm 1: Controls Description: Placebo containing olive oil Manufacturer: Martek Biosciences Dose: 1 capsule, twice a day Blinding: Identical tablets Arm 2: DHA Description: Intervention Manufacturer: Martek Biosciences Dose: 1 capsule twice a day DHA: 400 mg/d, 200 mg/dl derived from algal source	Outcome: birth weight <2500g (Secondary) Follow-up time: birth Arm 1: 27/486 (5.6%) Arm 2: 27/487 (5.5%)
Stein et al., 2011[34] Study name: POSGRAD Study dates: 02. 2005-02.2007	Study Population: Healthy infants Pregnant enrolled 1094 Pregnant completers 973 Pregnant age: placebo	Inclusion Criteria: women were 18–35 y, were in gestation wk 18–22, and planned to deliver at the IMSS General Hospital in Cuernavaca, exclusively or predominantly breast-	Start time: Pregnant 18-22 Gestational week Infants birth Duration: Pregnant birth Arm 1: Placebo Description: Olive oil	Outcome: birth weight <2500g (Secondary) Follow-up time: birth Arm 1: 20/370 (5.4%) Arm 2: 16/369 (4.3%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study design: Trial randomized parallel Location: Mexico Funding source / conflict: Government, Multiple foundations and Societies Original, same study, or follow-up studies: Stein, 2012[33]; Imhoff-Kunsch, 2011[58]; Escamilla-Nunez, 2014[59]; Gonzalez-Casanova, 2015[60]; Ramakrishnan, 2015[61]; Ramakrishnan, 2011[32]	26.3; DHA 26.4 (placebo 4.6; DHA 4.9) Infant age: 39.1 (placebo 1.6; DHA 1.8) Race of Mother: NR	feed for at least 3 mo, and to live in the area for at least 2 y after delivery Exclusion Criteria: NR	Manufacturer: Martek Biosciences Dose: 2 capsules olive oil Blinding: Similar in appearance and taste to DHA capsules Arm 2: DHA Description: algal DHA capsules Manufacturer: Martek Biosciences Dose: 2 capsules * 200mg DHA: 400 mg	
Stein et al., 2012[33] Study name: POSGRAD Study dates: Feb 2005-Feb 2007 Study design: Trial randomized parallel Location: NR Funding source / conflict: Government Original, same study, or follow-up studies: Ramakrishnan, 2010[32]; Imhoff-Kunsch, 2011[58]; Escamilla-Nunez, 2014[59]; Gonzalez-Casanova, 2015[60]; Ramakrishnan, 2015[61]	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 1094 Pregnant withdrawals 63 Pregnant completers 900 Pregnant age: 26.3 (4.6-4.8) Infant age: 39.1 (1.7-1.8) Race of Mother: NR (NR)	Inclusion Criteria: Singleton live births without congenital anomalies Exclusion Criteria: 3364: high risk pregnancy, (history and prevalence of pregnancy complications, including abruption placentae, preeclampsia, pregnancy-induced hypertension, any serious bleeding episode in the current pregnancy, and physician referral); lipid metabolism or absorption disorders, regular intake of fish oil or DHA supplement, or chronic use of certain medication(e.g. epilepsy medications)	Start time: Pregnant 18-22 wk Duration: Pregnant to birth Arm 1: Placebo Description: A mixture of corn and soy oil Manufacturer: Martek Biosciences Blinding: "Participants and members of the study team were unaware of the treatment scheme throughout the intervention period of the study" Arm 2: DHA Description: DHA 400 mg/d Manufacturer: Martek Biosciences Dose: 2 capsule per day DHA: 2*200mg	Outcome: birth weight <2500g (Primary) Follow-up time: birth Arm 1: 24/452 (5.3%) Arm 2: 17/448 (3.8%)
Zhou et al., 2012[55] Study name: DOMInO	Study Population: Healthy pregnant women	Inclusion Criteria: NR Exclusion Criteria: If	Start time: Pregnant medium gestational age 19 weeks	Outcome: birth weight <2500g (Secondary) Follow-up time: birth Arm 1: 63/1202 (5.27%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study dates: 10. 2005 - 01. 2008 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies, Manufacturer supplied product Original, same study, or follow-up studies: Makrides, 2010[35]; Smithers, 2011[53]; Palmer, 2012[54]; Palmer, 2013[56]; Makrides, 2014 [57]	Pregnant enrolled 2399 Race of Mother: White European (88%;88%) Asian (7%;8%) Inuit Eskimo (2%;1%) Other race/ethnicity (NR)	already taking a dietary supplement containing DHA, their fetus had a known major abnormality, they had a bleeding disorder for which fish oil was contraindicated, they were receiving anticoagulant therapy, they had a documented history of drug or alcohol abuse, they were participating in another fatty acid trial, or English was not the main language spoken at home	Duration: Pregnant birth Arm 1: control Description: 500-mg vegetable oil capsules Dose: 3*500mg 3 nongenetically modified oils (rapeseed, sunflower, and palm) in equal proportions Blinding: All capsules were similar in size, shape, and color Arm 2: DHA Description: DHA-rich fish oil Manufacturer: Incromega 500 TG; Croda Chemicals Dose: 3*500mg capsule DHA: 800 mg EPA: 100 mg	Arm 2: 41/1197 (3.41%)

DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; mg = milligram; n-3 FA = omega-3 fatty acid;; NR = not reported; OR = odds ratio; RBC = red blood cell; RCT = randomized controlled trial; UK = United Kingdom

Small for Gestational Age (SGA)/Intrauterine Growth Retardation (IUGR)

Key Findings and Strength of Evidence for Risk for SGA/IUGR

- There is a low level of evidence that maternal EPA+DHA supplementation may not have significant effects on risk for SGA/IUGR among women at increased risk for preterm delivery.
  - Two RCTs in our update found no effect of DHA alone or DHA-enriched fish oil on SGA/IUGR outcomes in healthy pregnant women.
  - Pooled analyses of four RCTs that assessed the effects of fish oil supplementation (DHA+EPA) on SGA/IUGR among women at increased risk for preterm delivery found no significant effects.
  - One prospective observational study found no association between intake of DHA+EPA intake and SGA outcome.
  - One observational study among multiparous pregnant women found a two-fold increase in risk of SGA among women in the lowest quintile of plasma EPA concentration in early pregnancy compared to those in the middle quintile. No association was seen between plasma DHA concentrations in early pregnancy and risk of SGA.

Description of Included Studies

Randomized Controlled Trials

Three RCTs (in four publications) were identified for the current report that examined the effects of maternal n-3 supplementation on SGA/IUGR outcomes: one from the POSGRAD trial,[34, 61] one from the DOMInO trial, [35, 55] and the third by Harper et al.[29] Details of these three studies have been described above (see Table 6). Overall, our update meta-analysis of six RCTs (three from the original report) showed that n-3 supplementation did not have significant effects on SGA/IUGR (OR=0.98; 95% CI 0.85, 1.13; $I^2 = 0$).

DHA

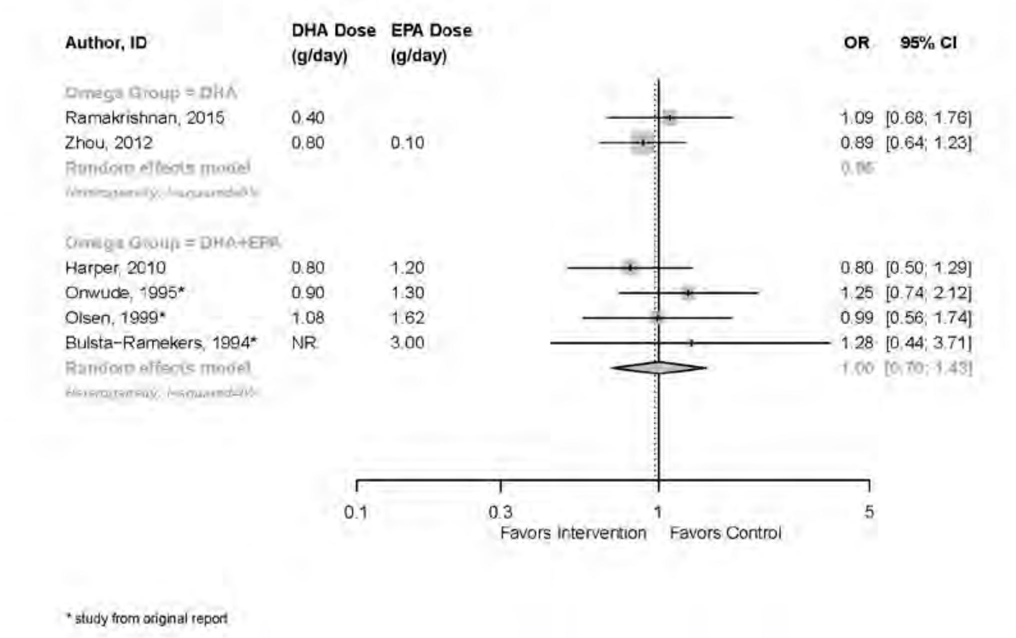
In the POSGRAD trial, Ramakrishnan (2015) reported SGA/IUGR outcomes on the subset of infants who were followed up at 18 months. Among these, 365 pregnant women were randomized to receive 400 mg/day DHA, and 365 received placebo.[34, 61] The authors reported no significant difference in percent of infants born with IUGR between the two groups (9.9 percent DHA vs. 10.7 percent placebo, p=0.91).

Zhou (2012) reported SGA/IUGR outcomes among women enrolled in the DOMInO trial.[55] They found no difference in percent of infants born SGA between the two groups (6.1 percent DHA-enriched fish oil vs. 6.8 percent placebo, p=0.49).

EPA+DHA

In the US study by Harper (2010),[29] no significant difference was observed in infants born SGA between the progesterone group and the progesterone plus marine oils group. Random effects meta-analysis of the four RCTs enrolling women at risk of SGA/IUGR (this study plus the three from the original report) found no significant effects of DHA+EPA supplementation (doses ranged from 2.0 to 3 g/d) on the incidence of SGA/IUGR compared with placebo (OR [95% CI]=1.00, CI[0.70, 1.43], I^2=0%) (Figure 9).

Figure 9. Risk for small for gestational age: DHA + EPA or DHA versus placebo



Observational Studies

Two prospective studies evaluated the association between some measure of maternal n-3 FA exposure and risk of SGA (see Table 7). One[46] measured dietary n-3 FA intake and the other[73] measured concentrations of DHA and EPA in the plasma.

n-3 FA Intake

Oken et al.[46] evaluated the association between maternal n-3 FA intake and risk of having an SGA birth among 2,109 women enrolled in Project Viva, a prospective, observational cohort study of gestational diet, pregnancy outcomes, and offspring health in the US (Massachusetts). The investigators reported no association between quartiles of DHA+EPA intake and risk of having an SGA birth outcome.

n-3 FA Biomarkers

Smits[73] evaluated the role of plasma DHA and EPA concentrations in the relationship between interpregnancy interval and adverse pregnancy outcome in a subsample (n=1,659) of the Amsterdam Born Children and their Development (ABCD) cohort, a population-based cohort study of multiparous pregnant women in the Netherlands. Women in the lowest quintile of EPA concentration (<0.33 mg/L) in early pregnancy had a two-fold increased risk (OR=2.09, 95% CI1.32-3.30) of having an SGA birth compared to those in the middle quintile (0.46 -0.58 mg/L). Concentrations of DHA in early pregnancy showed no association with risk of SGA.

Table 6. RCTs for infants born small gestational age and intrauterine growth retardation

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Harper et al., 2010[29] Study name: NR Study dates: 01. 2005 - 10. 2006 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product Original, same study, or follow-up studies: Klebanoff, 2011[49]	Study Population: At risk for preterm labor Pregnant enrolled 852 Pregnant withdrawals 0 Pregnant completers 852 Pregnant age: n3: 28 placebo 27 n3 23-32; placebo 24-32 Race of Mother: White European (n3: 56.5; placebo 57.7) Black (n3: 34.1; placebo 34.9) Asian (n3: 3, placebo 1.2) Hispanic (n3: 14.7; placebo 13.6) Other race/ethnicity (NR)	Inclusion Criteria: a documented history of at least one prior singleton preterm delivery between 20 0/7 and 36 6/7 weeks of gestation after spontaneous preterm labor or premature rupture of the membranes, and a current singleton pregnancy between 16 and 21 6/7 weeks of gestation Exclusion Criteria: evidence of a major fetal anomaly, intake of a fish oil supplement in excess of 500 mg per week at any time during the preceding month, allergy to fish, anticoagulation therapy, hypertension, White's classification D or higher diabetes, drug or alcohol abuse, seizure disorder, uncontrolled thyroid disease, clotting disorder, current or planned cerclage, or a plan to deliver either elsewhere or before 37 weeks of gestation	Start time: Pregnant 16-22 week gestation age Duration: Pregnant 36 weeks of gestation Arm 1: placebo Description: inert mineral oil Manufacturer: Eminent Services, Frederick, MD Active ingredients: 10 IU vitamin E per capsule, injections of 17_x0001_-hydroxyprogesterone caproate Dose: four capsules of matching oil containing a minute amount of inert mineral oil Blinding: Boxes containing a woman's entire supply of capsules in blister packs were sequentially numbered according to the predetermined randomization sequence, and on enrollment a woman was assigned the next number in sequence. Study group assignment was not known by study participants, their health care providers, or the research personnel Arm 2: Eminent Services, Frederick, MD Active ingredients: 10 IU vitamin E per capsule, injections of 17_x0001_-hydroxyprogesterone caproate Dose: in 4 capsules total 2000 mg of n3 DHA: 800 mg EPA: 1200 mg	Outcome: SGA less than 10th percentile (Secondary) Follow-up time: birth Arm 1: 41/410 (10.0%) Arm 2: 35/427 (8.2%)
Hauner et al., 2012[37] Study name: INFAT Study dates: July 14 2006 - may 22 2009 Study design: Trial randomized parallel	Study Population: Healthy pregnant women Pregnant enrolled 208 Pregnant withdrawals 38	Inclusion Criteria: healthy pregnant women before the 15th wk of gestation, between 18 and 43 y of age, prepregnancy BMI (in kg/m2) between 18 and 30, willingness to implement the dietary recommendations, sufficient German	Start time: Pregnant 15th wk of gestation Duration: Pregnant to 4 mo postpartum Arm 1: Control Description: brief semi structured counseling on a healthy balanced diet according to the guidelines of the German Nutrition Society and were explicitly asked to refrain from taking fish oil or DHA supplements	Outcome: incidence of premature birth (Secondary) Follow-up time: birth Arm 1: 4/96 (4.2%) Arm 2: 3/92 (3.3%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Location: Germany Funding source / conflict: Industry, Government, Multiple foundations and Societies	Pregnant completers 170 Infants enrolled 188 Infants withdrawals 18 Infants completers 170 Pregnant age: 31.9 (4.9) 18-43 Race of Mother: NR (NR) Baseline biomarker information: Maternal fatty acid profile in RBCs at 15th wk: EPA, DHA, AA, and n-6:n-3 LCUFA ratio (reported in Table 2 by intervention and control groups). No significant differences between groups. Baseline Omega-3 intake: 7-d dietary records completed by participants at the 15th (baseline) and 32nd wk of gestation but only dietary intake at 32nd we of gestation	language skills. Exclusion Criteria: high-risk pregnancy (multiple pregnancy, rhesus incompatibility, hepatitis B infection, or parity .4); hypertension; chronic diseases (e.g., diabetes) or gastrointestinal disorders accompanied by maldigestion, malabsorption, or elevated energy and nutritional requirements (e.g., gluten enteropathy); known metabolic defects (e.g., phenylketonuria); psychiatric diseases; hyperemesis gravidarum; supplementation with n–3 LCPUFAs before randomization; and alcohol abuse and smoking.	N-6 N-3: 2.80 +- 1.17 (SD) at 32nd wk of gestation AA: 10.15 +- 3.89 SD) at 32nd wk of gestation Arm 2: Intervention Description: Fish-oil supplement + nutritional counseling (to normalize the consumption of AA Brand name: Marinol D-40 Manufacturer: Lipid Nutrition DHA: 1020 mg EPA: 180 mg N-6 N-3: 1.54 +- 0.63 (SD) at 32nd wk of gestation AA: 8.82 +- 2.84 (SD) at 32nd wk of gestation Other dose 1: Vit E 9 mg	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	was reported (in Table 2). At week 32 of gestation, the dietary n-6:n-3 PUFA ratio was .5:1 in the intervention group compared with :1 in the control group, as originally intended.			
Ramakrishnan et al., 2015[61] Study name: POSGRAD Study dates: 2005-2009 Study design: Trial randomized parallel Location: Mexico Funding source / conflict: Government, None, March of Dimes Study follow-up: 18 months Original, same study, or follow-up studies: Ramakrishnan, 2010[32]; Stein, 2012[33]; Imhoff-Kunsch, 2011[58]; Escamilla-Nunez, 2014[59]; Gonzalez-Casanova, 2015[60]; Ramakrishnan, 2015[61]	Study Population: Healthy pregnant women Pregnant enrolled 1094 Pregnant completers 968 Infants enrolled 973 Infants completers 730 Pregnant age: Placebo: 26.3 Intervention: 26.5 (Placebo: 4.6 Intervention: 4.9) Infant age: Placebo: 20.5 weeks gestation Intervention: 20.6 weeks gestation (Placebo: 2.1 weeks Intervention: 2.0 weeks)	Inclusion Criteria: Women who were in gestation week 18–22, age 18–35 years, planned to deliver at the IMSS General Hospital and to remain in the area for the next 2 years, and planned predominant breastfeeding for at least 3 months Exclusion Criteria: High risk pregnancy, had any lipid metabolism/absorption conditions, regularly took DHA or fish oil supplements, or used certain chronic medications (such as antiepileptic drugs)	Start time: Pregnant 18-22 weeks gestation Duration: Pregnant 18-22 weeks gestation until delivery Arm 1: Control Description: Corn and soy oils with no added antioxidants Dose: 2 capsules/day Blinding: Similar in appearance and taste to the DHA capsules Arm 2: Intervention Description: Algal-sourced DHA capsule Manufacturer: Martek Biosciences Dose: 2 capsules/day DHA: 200 mg * 2 = 400 mg/d	Outcome: IUGR (Secondary) Follow-up time: birth Arm 1: 36/365 (9.9%) Arm 2: 39/365 (10.7%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	Race of Mother: NR (NR) Baseline Omega-3 intake: From original study ref 3364 mg/day for all: LA: 17,846 in controls, 17,645 in DHA AA: 137 in controls, 140 in DHA ALA: 1,488 in controls, 1,477 in DHA EPA: 18 in controls, 18 in DHA DHA: 54 in controls, 56 in DHA			
Stein et al., 2011[34] Study name: POSGRAD Study dates: 02. 2005- 02.2007 Study design: Trial randomized parallel Location: Mexico Funding source / conflict: Government, Multiple foundations and Societies Original, same study, or follow-up studies: Stein, 2012[33]; Imhoff-Kunsch, 2011[58]; Escamilla-Nunez, 2014[59]; Gonzalez-Casanova, 2015[60]; Ramakrishnan, 2015[61]; Ramakrishnan, 2011[32]	Study Population: Healthy infants Pregnant enrolled 1094 Pregnant completers 973 Pregnant age: placebo 26.3; DHA 26.4 (placebo 4.6; DHA 4.9) Infant age: 39.1 (placebo 1.6; DHA 1.8) Race of Mother: NR	Inclusion Criteria: women were 18–35 y, were in gestation wk 18–22, and planned to deliver at the IMSS General Hospital in Cuernavaca, exclusively or predominantly breast-feed for at least 3 mo, and to live in the area for at least 2 y after delivery Exclusion Criteria: NR	Start time: Pregnant 18-22 Gestational week Infants birth Duration: Pregnant birth Arm 1: Placebo Description: Olive oil Manufacturer: Martek Biosciences Dose: 2 capsules olive oil Blinding: Similar in appearance and taste to DHA capsules Arm 2: DHA Description: algal DHA capsules Manufacturer: Martek Biosciences Dose: 2 capsules * 200mg DHA: 400 mg	Outcome: IUGR (intrauterine growth retardation); birth weight for gestational age < 10th percentile (Secondary) Follow-up time: birth Arm 1: 38/368 (10.3%) Arm 2: 39/369 (10.6%)
Zhou et al., 2012[55]	Study Population:	Inclusion Criteria: NR	Start time: Pregnant medium gestational age 19 weeks	Outcome: SGA for weight (Secondary) Follow-up time: birth

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study name: DOMInO Study dates: 10. 2005 - 01. 2008 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies, Manufacturer supplied product Original, same study, or follow-up studies: Makrides, 2010[35]; Smithers, 2011[53]; Palmer, 2012[54]; Palmer, 2013[56]; Makrides, 2014[57]	Healthy pregnant women Pregnant enrolled 2399 Race of Mother: White European (88%;88%) Asian (7%;8%) Inuit Eskimo (2%;1%) Other race/ethnicity (NR)	Exclusion Criteria: If already taking a dietary supplement containing DHA, their fetus had a known major abnormality, they had a bleeding disorder for which fish oil was contraindicated, they were receiving anticoagulant therapy, they had a documented history of drug or alcohol abuse, they were participating in another fatty acid trial, or English was not the main language spoken at home	Duration: Pregnant birth Arm 1: control Description: 500-mg vegetable oil capsules Dose: 3*500mg 3 nongenetically modified oils (rapeseed, sunflower, and palm) in equal proportions Blinding: All capsules were similar in size, shape, and color Arm 2: DHA Description: DHA-rich fish oil Manufacturer: Incromega 500 TG; Croda Chemicals Dose: 3*500mg capsule DHA: 800 mg EPA: 100 mg	Arm 1: 82/1202 (6.83%) Arm 2: 73/1197 (6.13%)

Table 7. Observational studies for infants born small gestational age

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Smits, et al., 2013[73] Outcome domain: SGA Study name: Amsterdam Born Children and their Development (ABCD) Study dates: Jan 2003- Mar 2004 Study design: Observational prospective Location: Netherlands Funding source / conflict: None	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 1659 Pregnant completers 1659 Infants enrolled 1659 Infants completers 1659 Pregnant age: <25 y, 5.7% 25-34 y, 61.2% >=35 y, 33.1% Infant age: 40.0 weeks (1.2) Race of Mother: White European (88.4)	Inclusion Criteria: NR Exclusion Criteria: primiparous women or delivered preterm	Adjustments: Potential confounding factors were evaluated but none of them was significant confounding defined as changing the odds ratio by 10%

Birth Weight

Key Findings and Strength of Evidence for Birth Weight

- Overall meta-analysis of 16 RCTs showed that n-3 FA supplementation in healthy pregnant women significantly increased birth weight compared with placebo or other controls (WMD [95% CI] 74.80 [12.42, 137.17] grams). No evidence of publication bias was seen (Begg's and Egger's p values were 0.368 and 0.245, respectively)
    - Random-effects meta-regression found no significant linear dose-response relationships between doses of DHA, EPA, or DHA to EPA ratio and the effect sizes.
    - No significant difference was seen in the pooled effect sizes between DHA and EPA+DHA supplementation subgroups (P=0.52).
- There is a moderate level of evidence that maternal supplementation of DHA or DHA-rich fish oils may increase birth weight.
    - Pooled analysis of 12 RCTs showed significantly higher birth weights among infants whose mothers received algal DHA or DHA-enriched fish oil than among infants of mothers who received a placebo (WMD [95% CI]=90.12 [2.62, 177.62] grams).
    - Pooled analysis of five RCTs found no significant effect of maternal EPA+DHA supplementation on infant birth weight.
    - One RCT that assessed the effects of ALA on infant birth weight showed no effects.
    - Three prospective observational studies showed that maternal n-3 FA biomarker levels were significantly and positively associated with infant birth weight, whereas the one other study did not find an association between maternal quartile of erythrocyte EPA+DHA and infants' birth weight.
- There is a low level of evidence that supplementation of EPA+DHA may not have significant effects on infants' birth weight compared with placebo.
    - Pooled analysis of five RCTs showed that fish oil or fish supplementation among healthy pregnant women did not have a significant effect on birth weight compared with placebo or control.
    - Two prospective observational studies showed no association between maternal n-3 FA intake from supplements and infant birth weight.
    - Four prospective observational studies that assessed the effects of maternal dietary n-3 FA intake on infant birth weight showed inconsistent results. Two studies found no association between dietary n-3 FA intake and infant birth weight. A third study found that infants born to mothers in the lowest quartile of DHA+EPA intake had significantly higher birth weights than infants born to mothers in the highest quartile of DHA+EPA intake. This association held true for DHA+EPA intake measured in all three trimesters of pregnancy. The fourth study found that both maternal DHA and ALA intake were significantly and positively associated with birth weight.

Description of Included Studies

The original report included 12 RCTs (in nine publications) that compared mean birth weight values (in grams) between maternal n-3 FA supplemented and control groups. Of these studies, pregnant women received DHA-enriched eggs (DHA 0.23 g/d) in two RCTs, fish oil supplements (EPA+DHA doses ranged from 0.23 to 5 g/d) in nine RCTs, and dietary supplementation with margarine delivering ALA (2.82 g/d) and linoleic acids (9.02 g/d) in one RCT. The between-group difference in the mean birth weight was not significant in eight of the 12 studies, was significantly higher in the n-3 FA supplementation groups compared with controls in three studies (1 DHA-enriched eggs, 1 fish oil supplementation, and 1 dietary supplementation with ALA and linoleic acids), and was significantly lower in the fish oil supplementation (EPA+DHA 2.2 g/d) than in the control group (olive oil) in one study. Only one prospective cohort study was included in the original report. This cohort study found that the maternal plasma triglyceride AA, but not phospholipid or cholesteryl ester AA, was positively related to infant birth weight and length ($p<0.01$). No other correlations were found between maternal plasma n-3 or n-6 FA and these variables.

Eighteen new RCTs and ten observational studies were identified for the current report. All, except for one study [29] were conducted among healthy pregnant women and followed up until birth. The one RCT that enrolled pregnant women at risk for preterm labor (defined as a documented history of at least one prior singleton preterm delivery after spontaneous preterm labor or premature rupture of the membranes) was therefore excluded from the meta-analysis. Overall we found a moderate level of evidence that maternal supplementation of DHA or DHA-rich fish oils may increase birth weight but the dose-response relationship between DHA dose and the effect size is still unclear. This finding is consistent with findings from the observational studies, which found that higher maternal blood DHA concentrations were associated with higher birth weight.

Randomized Controlled Trials

Eighteen unique RCTs were identified for the current report (see Table 8). Of these, four RCTs (in six publications) compared algal DHA supplements with placebo controls,[31-34, 74, 75], eight (in nine publications) compared DHA-rich fish oil supplementation (DHA:EPA ratio ≥5:1) with placebo controls,[35, 37-42, 55, 66] five compared fish oil supplements (EPA+DHA, DHA:EPA ratio <5:1) with placebo,[29, 42, 44, 76, 77] one compared a salmon-rich diet with no dietary salmon (EPA+DHA, DHA:EPA ratio <5:1),[78] and one compared black current seed oil (ALA 0.42 g/d; 0.09 SDA g/d) with placebo.[79] One RCT compared both DHA-rich fish oil supplement and more balanced (EPA/DHA) fish oil supplement with placebo.[42] Overall, meta-analysis combining 16 RCTs showed that n-3 FA supplementation in healthy pregnant women significantly increased birth weight compared with placebo or controls (WMD [95% CI] 74.8 [12.42, 137.17] grams), with moderate heterogeneity ($I^2 = 49.5$). (Figure 10) Random-effects meta-regression found no significant linear dose-response relationships between doses of DHA (beta coefficient [SE]= 32.86 [61.32], P=0.60, n=16), EPA (beta coefficient [SE]= -39.64 [51.55], P=0.46, n=15), or DHA to EPA ratio (beta coefficient [SE]= 12.0 [13.3], P=0.39, n=11) and the effect sizes (mean differences in birth weight between n-3 FA and placebo groups).

DHA

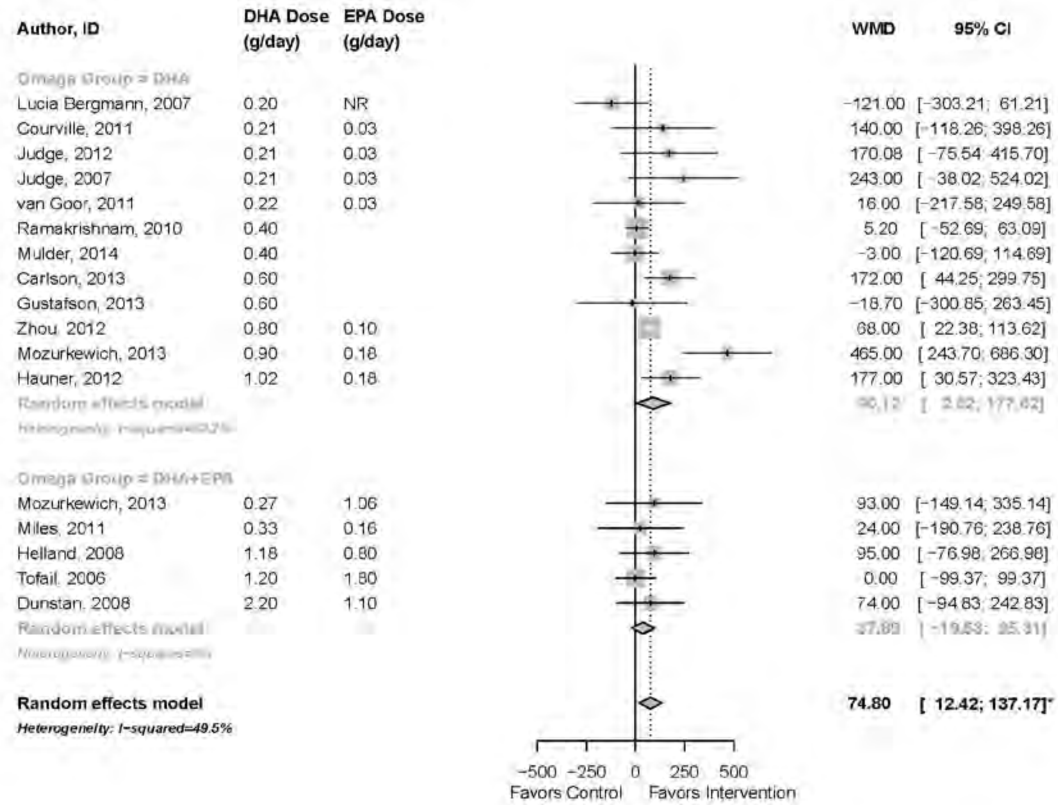
Four RCTs (in six publications) randomized healthy pregnant women between 12 and 20 weeks of gestation to DHA supplements from algae oil (0.4 or 0.6 g/d DHA) or placebo (soybean, corn, or olive oil).[31-34, 74] Two RCTs analyzed the birth weight outcome in a total of

353 mothers and their infants living in the US,[31, 74] one analyzed 200 mothers and their infants in Canada,[75] and one analyzed 973 mothers and their infants in Mexico (POSGRAD trial).[32-34] It should be noted that, of the three publications from the POSGRAD trial, the Ramakrishnan (2010) publication analyzed the largest number of study participants,[32] while the other two publications analyzed a subset of the trial participants.[33, 34] Thus, only results from Ramakrishnan (2010) were included in our meta-analysis. Overall, only one of the four RCTs found a significantly higher mean birth weight (+172 grams, P=0.004) in infants whose mothers received DHA (0.6 g/d) supplementation (n=154) than those whose mothers received placebo (n=147).[31] The other three RCTs (DHA 0.4 and 0.6 g/d) did not find significant differences in mean birth weight between DHA supplementation and placebo groups.[32-34, 74]

Eight RCTs randomized healthy pregnant women between 12 and 24 weeks of gestation to DHA-rich fish oil supplementation or controls. Studies were conducted in the US (n=4), Germany (n=2), Australia (n=1), and the Netherlands (n=1). Of the eight RCTs, three compared DHA-containing cereal-based bars (mean DHA 0.214-0.240 and EPA 0.027-0.030 g/d; DHA:EPA ratio = 8) with placebo bars;[38-40] four (in five publications) compared DHA-rich fish oil supplements (DHA 0.200-1.020 and EPA 0.100-0.180 g/d; DHA:EPA ratio = 5-8), [37, 41, 42] with controls (vegetable oil, nutritional counseling, vitamins and minerals, or soy oil), and one three-arm RCT compared DHA-rich fish oil plus soybean oil (DHA 0.220 and EPA 0.036 g/d plus ALA 0.032 g/d), DHA-rich fish oil plus AA (DHA 0.220 and EPA 0.036 g/d plus AA 0.220 g/d) with placebo (soybean oil).[66] Five of the eight RCTs with lower DHA doses (0.2-0.22 g/d) did not find significant differences in the mean birth weight between DHA supplementation and placebo in a total of 316 infants,[38-41, 66] whereas the other three RCTs (in four publications) with higher DHA doses (0.8-1.02 g/d) all found a significantly higher mean birth weight in infants whose mothers received DHA-rich fish oil supplement compared with those whose mothers received placebo (+68 to +465 grams) among a total of 2,656 infants.[35, 37, 42, 55] The three-arm RCT also did not find a significant difference in the mean birth weight between DHA-rich fish oil plus AA (DHA 0.220 and EPA 0.036 g/d plus AA 0.220 g/d, n=39) and placebo (soybean oil, n=34).[66]

Our random-effects meta-analysis of 12 RCTs showed that the mean birth weight was significantly higher in infants whose mothers received algal DHA or DHA-rich fish oil supplement than in those whose mothers received placebo (WMD [95% CI]=90.12 [2.62 177.62] grams high heterogeneity (I^2 = 63.2). (Figure 10)

Figure 10. Birth weight (g): DHA versus Placebo, DHA + EPA versus placebo



* Overall pooled result excludes the DHA+EPA comparison from Mozurkewich, 2013 to avoid double−counting of the placebo group.

EPA+DHA

Four RCTs randomized healthy pregnant women between 12 and 25 weeks of gestation to fish oil supplements (EPA+DHA) or placebo (soybean oil, corn oil, olive oil or inert mineral oil).[42, 44, 76, 77] In addition, one other single-blind trial randomized healthy pregnant women at week 20 of gestation to oily fish (farmed salmon) or no oily fish added to their habitual diet.[78] Studies were conducted in the US (n=2), U.K. (n=1), Norway (n=1), and Bangladesh (n=1). The doses of EPA ranged from 0.16 to 1.8 g/d, and the doses of DHA ranged from 0.27 to 2.2 g/d. The DHA to EPA ratio ranged from 0.26 to 2. The total doses of EPA plus DHA ranged from 0.49 to 3.3 g/d. None of these studies found a significant difference in mean birth weight between groups.

Our random-effects meta-analysis of five RCTs showed that maternal fish oil or fish supplementation (EPA+DHA doses ranged from 0.49 to 3.3 g/d) did not have a significant effect on birth weight compared with placebo or control (WMD [95% CI]=37.89 [-19.53, 95.31] grams; no heterogeneity [I^2 = 0%]).

One additional RCT that enrolled 852 pregnant US women at risk for preterm labor (defined as a documented history of at least one prior singleton preterm delivery after spontaneous preterm labor or premature rupture of membranes) also did not find a significant effect of fish oil supplementation (EPA+DHA 2 g/d) on birth weight (Figure 10).[29]

ALA

One RCT randomized healthy pregnant women (<16 weeks of gestation) to either black current seed oil (ALA 0.42 g/d; SDA 0.09 g/d) or placebo (olive oil). The results did not show a significant difference in birth weight between groups in a total of 241 infants.[79]

Observational Studies

Ten prospective cohort studies that assessed the association between n-3 FA intakes or status and birth weight were identified for the current report (see Table 9). Of these, six studies assessed the associations between maternal dietary intake of n-3 FA (from foods or supplements) and birth weight.[46, 47, 80-82] The other four studies examined the relationships between maternal n-3 FA biomarkers and birth weight.[73, 83, 84]

n-3 FA Intake

Two studies assessed the associations between maternal n-3 FA intake from supplements and birth weight.[81, 82] The Norwegian Mother and Child Cohort Study (MoBa), which enrolled a nation-wide pregnancy cohort, did not find significant associations between maternal supplementary n-3 FA intake (g/d) at 28 weeks of gestation and infants' birth weight (n=61,387). In contrast, a small cohort study in Iceland found that infants born to mothers who reported taking liquid cod liver oil in first trimester had higher birth weight (132 [95% CI 18, 246] grams) than did those born to mothers who did not take liquid cod liver oil in first trimester (n=350)

Four studies assessed the associations between maternal dietary n-3 FA intake and birth weight.[46-48, 80] Two of the four studies, enrolling a total of 1816 mother-infant pairs, did not find a significant association between maternal dietary n-3 FA intake and birth weight.[47, 80] The third study, by Oken et al.,[46] evaluated the association between quartiles of maternal DHA+EPA intake (median 0.02 g/d) and birth weight: They found that infants born to mothers in the lowest quartile of DHA+EPA intake had higher birth weight than those born to mothers in the highest quartile of DHA+EPA intake (median 0.27 to 0.38 g/d) during the first (94 [95%CI 23, 166] grams, n=1797), second (50 [95%CI -19, 119] grams, n=1663), and third (90 [95%CI 33, 147] grams, n=2070) trimesters. The fourth study, by Molto-Puigmarti,[48] found that maternal DHA intake (mg/d) was significantly associated with birth weight in a fully adjusted model (beta coefficient=0.16; 95% CI 0.008, 0.313, n=2606). Similarly, a significant association was observed between maternal ALA intake (mg/d) and birth weight (beta coefficient=0.106; 95% CI 0.026, 0.186, n=2606).

n-3 FA Biomarkers

Four prospective cohort studies examined the relationships between maternal n-3 FA biomarkers and birth weight.[73, 83-85] Three studies assessed blood DHA measures (one red blood cell [RBC]; two plasma phospholipids). All three studies found that higher maternal blood DHA concentrations were associated with higher birth weight in a total of 2,491 mother-and-infant pairs. One study each also assessed RBC total n-3 FA[83], RBC EPA+DHA (% total FA),[85] and plasma EPA.[73] Similar findings were reported for the associations between plasma EPA or RBC total n-3 FA concentrations and birth weight, but no associations was found between RBC EPA+DHA concentrations and birth weight. Individual study findings are described below.

The INFAT study,[83] conducted in Germany, enrolled healthy pregnant women at the 14th week of gestation and examined the associations between maternal RBC DHA and total n-3 FA at 32 weeks of gestation and birth weight. They found that per unit increase in percent maternal RBC DHA or percent total n-3 FA of total FA was significantly associated with an average of 24 (95% CI 0.42, 48) and 20 (95% CI 2.78, 38) grams increase in birth weight (n=187).

Dirix (2009)[84] enrolled healthy pregnant women less than 16 weeks of gestation and measured their plasma DHA (%, w/w plasma phospholipids) at 16, 22, and 32 weeks of gestation. This study found that per unit increase in maternal plasma DHA content (%, w/w plasma phospholipids) at 16 weeks of gestation was significantly associated with an average of 52 (95% CI 20, 84) grams increase in infants' birth weight (n=665). Per unit increase in maternal plasma DHA content (%, w/w plasma phospholipids) at 22 weeks (n=623) and 32 weeks (n=644) of gestation were marginally associated with an average of 31 (95% CI -4.3, 67) and 33 (95% CI -5.7, 72) grams increase in infants' birth weight, respectively.

Smits et al.[73] analyzed the associations between plasma DHA and EPA concentrations and infants' birth weight in a subsample (n=1,659) of the Amsterdam Born Children and their Development (ABCD) cohort, a population-based cohort study of multiparous pregnant women in the Netherlands. Infants born to mothers in the lowest quintile of EPA concentration (<0.33 mg/L) or DHA concentration (<3.74 mg/L) in early pregnancy had significantly lower birth weight (-182.5 [39 SE] or -118.2 [39 SE] grams, respectively) compared with those born to mothers in the middle quintile (EPA 0.46 -0.58 mg/L or DHA 4.35 -4.86 mg/L).

Mohanty (2015)[85] analyzed a subset of 534 (60%) healthy pregnant women at 16 weeks gestation who participated in the Omega study and were randomly selected for the analysis of erythrocyte membrane EPA and DHA. Their analysis did not find an association between maternal quartile of erythrocyte EPA + DHA (ranging from 2.28 to 9.55 percent of total fatty acids) and infants' birth weight after adjusting for potential confounders.

Table 8. RCTs for birth weight

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Carlson et al., 2013[31] Study name: NR Study dates: 2006.01-2011.10 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product	Study Population: Healthy pregnant women Pregnant enrolled 350 Pregnant withdrawals 49 Pregnant completers 301 Pregnant age: placebo: 24.8; DHA: 25.3 (placebo 4.7; DHA 4.9) Race of Mother: Black (46%;37%) Non-black (54%; 63%) Baseline biomarker information: RBC-phospholipid-DHA (placebo group 4.3 +- 1.3; 4.3 +- 1.1) Baseline Omega-3 intake: Voluntary DHA intake from supplement (placebo group 15%, DHA group 9%)	Inclusion Criteria: English-speaking, between 8 and 20 wk of gestation, between 16 and 35.99 y of age, and planning to deliver at a hospital in the Kansas City metropolitan area Exclusion Criteria: carrying more than one fetus, had preexisting diabetes mellitus or systolic blood pressure $140 mm Hg at enrollment, or had any serious health condition likely to affect the prenatal or postnatal growth and development of their offspring, including cancer, lupus, hepatitis, HIV/AIDS, or a diagnosed alcohol or chemical dependency. or if the initial screening based on their self-reported weight and height suggested a BMI (in kg/m2 >=40).	Start time: Pregnant 99.6/102.9 day Duration: Pregnant enrollment to birth Arm 1: Placebo Description: half soybean and half coin oil Manufacturer: DSM Nutritional Products) Active ingredients: a-linolenic acid Dose: 3 *capsule 200/day Blinding: both DHA and placebo capsules were orange flavored Arm 2: DHA Description: marine algae-oil source of DHA Manufacturer: DHASCO; DSM Nutritional Products, formerly Martek Biosciences) Dose: 200 mg capsule, 3 times a day DHA: 200mg/capsule * 3	Outcome: birth weight (g) (Primary) Follow-up time: birth Arm 1: Sample size 147; mean 3187.0; SD (602) Arm 2: Sample size 154; mean 3359.0; SD (524)
Courville et al., 2011[38] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: US Funding source / conflict:	Study Population: Healthy pregnant women Pregnant enrolled 47 Pregnant withdrawals 0 Pregnant completers 47 Pregnant age: NR (NR) NR Race of Mother: White European (8.5) Black	Inclusion Criteria: Healthy pregnant women, mid-pregnancy (20–24 weeks) Exclusion Criteria: parity .5; history of chronic hypertension; hyperlipidaemia; renal or liver disease; heart disease; thyroid disorder; multiple gestations;	Start time: Pregnant 20-24 wk of gestation Duration: Pregnant until birth Arm 1: Placebo Description: placebo bars (Manufacturer: Nestec Limited (Vevey, Switzerland) Dose: 5 placebo bars per week Blinding: NR Arm 2: DHA-FF Description: DHA cereal-based bars	Outcome: birth weight (kg) (Unspecified) Follow-up time: birth Arm 1: Sample size 25; mean 3.19; SD (0.44) Arm 2: Sample size 22; mean 3.33; SD (0.46)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Industry, Government	(10.6) Asian (4.3) Minority (Puerto Rican/Latino 66%; African - other 8.5%; Other or mixed ethnicity = 2%) Baseline Omega-3 intake: Dietary DHA intake (mg/d), not including the intervention food, from 24 h dietary recalls: DHA-FF 67+-7 (SD); Placebo 87+-10 (SD), P=0.059	having been pregnant or lactating in the previous 2 years.	Manufacturer: Nestec Limited (Vevey, Switzerland) Dose: 5DHA cereal-based bars per week DHA: 241 mg/d EPA: 30.1 mg/d	
Dunstan et al., 2008[44] Study name: Dunstan Study dates: 2000-2003 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Multiple foundations and Societies Original, same study, or follow-up studies: Dunstan, 2003[50]; Meldrum, 2015[51]	Study Population: Healthy infants Pregnant women with allergies Pregnant enrolled 98 Pregnant completers 83 Infants enrolled 83 Infants withdrawals 11 (7 FO, 4 control) Infants completers 72 Pregnant age: Fish oil: 30.9 Control: 32.6 (Fish oil: 3.7 Control: 3.6) Infant age: Term (mean gestational period 275 days) Race of Mother: NR (NR) Baseline biomarker information: Cord blood erythrocyte (as % total fatty acids) 20:4n-6 14.9 (1.4) 17.6 (1.0) ,0.001 20:5n-3 1.3 (0.5) 0.4 (0.3) ,0.001 22:3n-6 2.8 (0.5) 3.9 (0.5) ,0.001	Inclusion Criteria: Healthy term infants of pregnant women enrolled in RCT of gestational supplementation Exclusion Criteria: Women were ineligible for the study if they smoked, had medical problems, a complicated pregnancy, seafood allergy, or if their normal dietary intake exceeded two meals of fish per week. Children were excluded from the study if they were born before 36 weeks' gestation or with major disease (to avoid the confounding effects on immune response) or if cord blood was not collected	Start time: Pregnant 20 weeks gestation Duration: Pregnant to term Arm 1: Control Description: olive oil placebo Blinding: capsules image matched Maternal conditions Current smoker 0% Maternal allergies 100% Arm 2: Fish oil Description: same Manufacturer: Ocean Nutrition, Halifax Nova Scotia Active ingredients: 3-4mg/g vitamin E Viability: none reported Dose: 4 1-gm capsules fish oil per day Maternal conditions DHA: 2.2 EPA: 1.1 Other dose 1: fish oil supplying 2,2g/d DHA and 1.1g/day EPA Current smoker 0% Maternal allergies 100%	Outcome: birth weight (g) (Secondary) Follow-up time: birth Arm 1: Sample size 39; mean 3434.0; SD (377) Arm 2: Sample size 33; mean 3508.0; SD (353)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	22:4n-6 0.8 (0.2) 1.5 (0.3) ,0.001 22:5n-3 6.3 (0.8) 6.0 (0.5) 0.037 22:6n-3 10.3 (1.1) 7.4 (0.9) ,0.001 Total n-6 PUFAs* 25.0 (1.8) 29.6 (1.1) ,0.001 Total n-3 PUFAs{ 17.9 (1.9) 13.7 (1.3) ,0.001 Total n-3 to n-6{ 0.8 (0.1) 0.5 (0.1) ,0.001			
van Goor et al., 2011[66] Study name: Groningen LCPUFA study Study dates: 2004-2009 Study design: Trial randomized parallel Location: Netherlands Funding source / conflict: Industry Study follow-up: 18 months Original, same study, or follow-up studies: Bouwstra, 2003[62]; Bouwstra, 2005[63]; de Jong, 2010[64]; de Jong, 2012[65]; van Goor, 2010[36]	Study Population: Healthy infants Pregnant enrolled 119 Infants enrolled 119 Infants completers 114 Pregnant age: Placebo: 32.7 DHA: 32.5 DHA+AA: 32.9 (Placebo: 5.1 DHA: 4.4 DHA+AA: 4.8) Infant age: 18 months Race of Mother: NR (100)	Inclusion Criteria: women with a first or second low-risk singleton pregnancy, between the 14th and 20th weeks of pregnancy Exclusion Criteria: women with vegetarian or vegan diets; women with diabetes mellitus; birth complications	Start time: Pregnant 14th-20th week pregnancy Lactating 3 months after delivery Mothers 3 months after delivery Infants NR Duration: Pregnant NR Lactating 33-39 weeks Mothers 33-39 weeks Infants NR Arm 1: placebo Description: Soy bean oil Brand name: none Arm 2: DHA Description: DHA plus soy bean oil Brand name: Marinol D40 Manufacturer: Lipid Nutrition B.V., Wormerveer, The Netherlands; AA: Dose: 1 capsule DHA and 1 capsule soy bean oil once a day ALA: 32 mg/d DHA: 220 mg/d EPA: 34 mg/d Arm 3: DHA+AA Description: DHA plus AA Brand name: AA: no brand name Manufacturer: Wuhan Alking Bioengeneering Co. Ltd., Wuhan, China Dose: 2 capsules once a day ALA: 7 mg/d DHA: 220 mg/d EPA: 36 mg/d AA: 220 mg per capsule	Outcome: birth weight (g) (Unspecified) Follow-up time: birth Arm 1: Sample size 34; mean 3576.0; SD (551) Arm 2: Sample size 41; mean 3592.0; SD (465) Arm 3: Sample size 39; mean 3652.0; SD (377)
Gustafson et al., 2013[74]	Study Population:	Inclusion Criteria:	Start time: Pregnant 12-20 week gestation Infants	Outcome: birth weight (g) (Secondary)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study name: NR Study dates: May 2009 - July 2011 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product	Healthy infants Healthy pregnant women Pregnant enrolled 67 Pregnant withdrawals 12 Pregnant completers 52 Infants enrolled 44 Infants completers 41 Pregnant age: placebo 25.6+; DHA 25.5 (placebo 4.8; DHA 4.3) Race of Mother: White European (46.3) Black (37.3) Asian (3) Hispanic (13.4) Baseline biomarker information: plasma DHA (wt% TFA) placebo group: 3.91 (3.15-4.21); DHA group: 3.94(3.39-4.72) RBC DHA (wt% TFA) placebo group 4.30(3.99-5.03); DHA group 4.50 (3.73-5.44)	between 16–35.9 years of age and carrying a singleton pregnancy between the 12th and 20th week of gestation Exclusion Criteria: any serious health condition likely to affect the growth and development of the fetus or health of the mother including cancer, lupus, hepatitis, diabetes mellitus (Type1, Type 2 or gestational) or HIV/AIDS at baseline or fetal cardiac structural or conduction defects. Women who self-reported illicit drug use or alcohol use during pregnancy and those with hypertension or BMI Z40 were excluded. Women who were taking more than 200 mg/day DHA in prenatal vitamins or over the counter supplements were excluded from participation	birth Duration: Pregnant till birth Arm 1: Placebo Description: g 50% soy and 50% corn oil Manufacturer: Martek Biosciences, now DSM Nutritional Products Dose: 3 capsule a day each 500 mg Blinding: Only members of the investigational pharmacy knew the subject allocation. Participants and all members of the investigational team were blinded to the intervention assignment. Participants were allocated to either group based on the simple randomization procedure using random numbers generated by SAS. All capsules were the same color, size, weight and the oils were orange-flavored to prevent investigator or subject bias. Arm 2: algal oil as a source of DHA (200 mg of DHA per capsule for a total of 600 mg DHA/day) Dose: 3 capsule of 200mg DHA total 600 mg DHA: 200 mg * 3	Follow-up time: birth Arm 1: Sample size 24; mean 3435.5; SD (404.8) Arm 2: Sample size 22; mean 3416.8; SD (552.9)
Harper et al., 2010[29] Study name: NR Study dates: 01. 2005 - 10. 2006 Study design: Trial randomized parallel Location: US Funding source / conflict: Government,	Study Population: At risk for preterm labor Pregnant enrolled 852 Pregnant withdrawals 0 Pregnant completers 852 Pregnant age: n3: 28 placebo 27 n3 23-32; placebo 24-32 Race of Mother: White European (n3: 56.5; placebo 57.7) Black (n3:	Inclusion Criteria: a documented history of at least one prior singleton preterm delivery between 20 0/7 and 36 6/7 weeks of gestation after spontaneous preterm labor or premature rupture of the membranes, and a current singleton pregnancy between 16 and 21 6/7 weeks of gestation	Start time: Pregnant 16-22 week gestation age Duration: Pregnant 36 weeks of gestation Arm 1: placebo Description: inert mineral oil Manufacturer: Eminent Services, Frederick, MD Active ingredients: 10 IU vitamin E per capsule, injections of 17_x0001_-hydroxyprogesterone caproate Dose: four capsules of matching oil containing a minute amount of inert mineral oil Blinding: Boxes containing a woman's entire supply of capsules in blister packs were sequentially	Outcome: birth weight (g) (Secondary) Follow-up time: birth Arm 1: Sample size 418; median 2923.0; IQR Arm 2: Sample size 434; median 2990.0; IQR

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Manufacturer supplied product Original, same study, or follow-up studies: Klebanoff, 2011[49]	34.1; placebo 34.9) Asian (n3: 3, placebo 1.2) Hispanic (n3: 14.7; placebo 13.6) Other race/ethnicity (NR)	Exclusion Criteria: evidence of a major fetal anomaly, intake of a fish oil supplement in excess of 500 mg per week at any time during the preceding month, allergy to fish, anticoagulation therapy, hypertension, White's classification D or higher diabetes, drug or alcohol abuse, seizure disorder, uncontrolled thyroid disease, clotting disorder, current or planned cerclage, or a plan to deliver either elsewhere or before 37 weeks of gestation	numbered according to the predetermined randomization sequence, and on enrollment a woman was assigned the next number in sequence. Study group assignment was not known by study participants, their health care providers, or the research personnel Arm 2: Eminent Services, Frederick, MD Active ingredients: 10 IU vitamin E per capsule, injections of 17_x0001_-hydroxyprogesterone caproate Dose: in 4 capsules total 2000 mg of n3 DHA: 800 mg EPA: 1200 mg	
Hauner et al., 2012[37] Study name: INFAT Study dates: July 14 2006 - may 22 2009 Study design: Trial randomized parallel Location: Germany Funding source / conflict: Industry, Government, Multiple foundations and Societies	Study Population: Healthy pregnant women Pregnant enrolled 208 Pregnant withdrawals 38 Pregnant completers 170 Infants enrolled 188 Infants withdrawals 18 Infants completers 170 Pregnant age: 31.9 (4.9) 18-43 Race of Mother: NR (NR) Baseline biomarker information: Maternal fatty acid profile in RBCs at 15th wk: EPA, DHA, AA, and n-6:n-3 LCUFA ratio (reported in Table 2 by intervention and control groups). No significant differences	Inclusion Criteria: healthy pregnant women before the 15th wk of gestation, between 18 and 43 y of age, prepregnancy BMI (in kg/m2) between 18 and 30, willingness to implement the dietary recommendations, sufficient German language skills. Exclusion Criteria: high-risk pregnancy (multiple pregnancy, rhesus incompatibility, hepatitis B infection, or parity .4); hypertension; chronic diseases (e.g., diabetes) or gastrointestinal disorders accompanied by maldigestion, malabsorption, or elevated energy and nutritional requirements	Start time: Pregnant 15th wk of gestation Duration: Pregnant to 4 mo postpartum Arm 1: Control Description: brief semistructured counseling on a healthy balanced diet according to the guidelines of the German Nutrition Society and were explicitly asked to refrain from taking fish oil or DHA supplements N-6 N-3: 2.80 +- 1.17 (SD) at 32nd wk of gestation AA: 10.15 +- 3.89 SD) at 32nd wk of gestation Arm 2: Intervention Description: Fish-oil supplement + nutritional counseling (to normalize the consumption of AA Brand name: Marinol D-40 Manufacturer: Lipid Nutrition DHA: 1020 mg EPA: 180 mg N-6 N-3: 1.54 +- 0.63 (SD) at 32nd wk of gestation AA: 8.82 +- 2.84 (SD) at 32nd wk of gestation Other dose 1: Vit E 9 mg	Outcome: birth weight (g) (Secondary) Follow-up time: birth Arm 1: Sample size 96; mean 3357.0; SD (557) Arm 2: Sample size 92; mean 3534.0; SD (465)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	between groups. Baseline Omega-3 intake: 7-d dietary records completed by participants at the 15th (baseline) and 32nd wk of gestation but only dietary intake at 32nd we of gestation was reported (in Table 2). At week 32 of gestation, the dietary n-6:n-3 PUFA ratio was .5:1 in the intervention group compared with :1 in the control group, as originally intended.	(e.g., gluten enteropathy); known metabolic defects (e.g., phenylketonuria); psychiatric diseases; hyperemesis gravidarum; supplementation with n–3 LCPUFAs before randomization; and alcohol abuse and smoking.		
Helland et al., 2008[76] Study name: NR Study dates: 1994-2003 Study design: Trial randomized parallel Location: Norway Funding source / conflict: Industry, Government, Multiple foundations and Societies Study follow-up: 7 years Original, same study, or follow-up studies: Helland, 2001[86] and Helland, 2003[87] and which are both included in the original report	Study Population: Healthy infants Healthy pregnant women Breast-feeding women Infants enrolled 262 Infants completers 143 Pregnant age: cod oil 28.6 n=175 corn oil 27.6 n=166 (cod oil 3.4; corn oil 3.2) Race of Mother: NR (100) Baseline biomarker information: from id 10331 cod(n148) corn (n137) n-3 cod: 73.7 (30.0) corn 52.0 (14.9)*** 20:5n-3 cod: 10.8 (7.6) corn: 2.5 (1.8)*** 22:5n-3 cod: 5.0 (2.6) corn: 2.9 (1.3)*** 22:6n-3 cod: 55.8 (20.6) corn: 45.3 (12.8)***	Inclusion Criteria: Healthy nulliparous or primiparous women, aged 19-35 with single pregnancies Exclusion Criteria: Unhealthy neonates	Start time: Pregnant week 18 of pregnancy Duration: NR Arm 1: Cod oil Manufacturer: NR Active ingredients: Vit 1: 117 ug/mL, Vit D3: 1 ug/mL, vit E: 1.4 mg/mL Viability: frozen at _x0003_ 70 ° C under nitrogen. Before storage, the samples were sonicated and ethylenediaminetetraacetic acid and butylated hydroxytoluene were added to a final concentration of 1.85 mg/mL and 75 _x0003_ g/mL, respectively DHA: 1183mg/10 mL EPA: 803 mg/10mL Total N-3: 2494 mg/10mL Arm 2: corn oil Active ingredients: Vit 1: 117 ug/mL, Vit D3: 1 ug/mL, vit E: 1.4 mg/mL Viability: frozen at _x0003_ 70 ° C under nitrogen. Before storage, the samples were sonicated and ethylenediaminetetraacetic acid and butylated hydroxytoluene were added to a final concentration of 1.85 mg/mL and 75 _x0003_ g/mL, respectively ALA: 92 mg/10mL	Outcome: birth weight (g) (Primary) Follow-up time: birth Arm 1: Sample size 61; mean 3518.0; SD (560) Arm 2: Sample size 82; mean 3613.0; SD (458)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	Baseline Omega-3 intake: from 10331 cod n147 corn n159 18:3 n-3: cod: 1.3 (0.5) corn: 1.2 (0.5) 20:5 n-3 cod: 0.2 (0.2) corn:0.2 (0.2) 22:5 n-3 cod: 0.05 (0.03) corn: 0.05 (0.03) 22:6 n-3 cod: 0.3 (0.3) corn: 0.3 (0.3)			
Judge et al., 2007[39] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Government, None	Study Population: Healthy pregnant women Pregnant enrolled 29 Pregnant completers 29 Pregnant age: 23.75 years (.4 years) NR Race of Mother: NR (100%)	Inclusion Criteria: women aged 18 –35 y who were at 20 wk of gestation Exclusion Criteria: Women with a history of drug or alcohol addiction, hypertension, smoking, hyperlipidemia, renal disease, liver disease, diabetes, or psychiatric disorder	Start time: Pregnant 24 weeks gestation Duration: Pregnant until birth Arm 1: placebo Description: cereal based placebo bars Manufacturer: Nestec Active ingredients: 18 g carbohydrates, 1.3 grams protein, 92 calories, 1.7 g fat Viability: NR Dose: 5 bars per week Blinding: NR Arm 2: DHA supplemented cereal bars Manufacturer: Nestec Active ingredients: 18 g carbohydrates, 1.3 grams protein, 92 calories, 1.7 g fat Viability: NR Dose: 5 bars per week. DHA-containing cereal-based bars [1.7 g total fat, 300 mg DHA as low-eicosapentaenoic oil (EPA) fish oil; EPA:DHA 1:8 per bar DHA: mg/d EPA: .75 mg (calculated based on EPA:DHA ratio) EPA-DHA: 1:8	Outcome: birth weight (g) (Secondary) Follow-up time: birth Arm 1: Sample size 15; mean 3222.0; SD (363) Arm 2: Sample size 14; mean 3465.0; SD (406)
Judge et al., 2012[40] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: US	Study Population: Healthy pregnant women Pregnant enrolled 48 Pregnant age: Treatment group: 23.93 Placebo: 23.86 (Treatment group: 4.32 Placebo: 4.53)	Inclusion Criteria: The women were either primiparous or had not been pregnant for the past 2 years. Exclusion Criteria: parity greater than 5, history of chronic hypertension, hyperlipidemia, renal,	Start time: Pregnant 24 weeks gestation Duration: Pregnant until delivery Arm 1: Placebo Description: Control group Manufacturer: Nestec, S.A., Switzerland Blinding: The total macronutrient content was the same in both the DHA and placebo bars with respect to carbohydrate, protein and fat, how- ever, the DHA	Outcome: birth weight (g) (Secondary) Follow-up time: birth Arm 1: Sample size 21; mean 3224.62; SD (431.25) Arm 2: Sample size 27; mean 3394.7; SD (430)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Funding source / conflict: Multiple foundations and Societies	Race of Mother: White European (Treatment: 11.1%, Placebo: 0%) Black (Treatment: 18.5%, Placebo: 4.8%) Asian (Treatment: 3.7%, Placebo: 0%) Hispanic (Treatment: 59.3%, Placebo: 80.9%) NR (Treatment: 7.4%, 3 (14.3%)) Baseline biomarker information: Maternal plasma phospholipid (PL) fatty acids (FA): 2.85 +/- .87 % in treatment group and 2.95 +/- .91% in placebo group. Infant RBC PL FA: 7.55 +/- 1.61% in treatment group and 7.07 +/- 1.25% in placebo group.	liver or heart disease, thyroid disorder, multiple gestations or pregnancy induced complications including hypertension, preeclampsia or preterm labor, smoking and psychiatric disorders. Women who were treated during labor with analgesics such as Stadol (butorphanol tartrate), that may cause infant respiratory distress were also excluded. In addition, infants born preterm and infants with less than 4 h of crib time in the first and second days postpartum were excluded from the analyses.	bars contained fish oil (300 mg DHA) and the placebo bars contained corn oil. Arm 2: DHA Description: Intervention group Manufacturer: Nestec, S.A., Switzerland Dose: average of 5 bars weekly DHA: 300 mg EPA-DHA: 8:1 ratio of DHA to EPA	
Linnamaa et al., 2010[79] Study name: NR Study dates: 2004-2008 Study design: Trial randomized parallel Location: Finland Funding source / conflict: Government, Multiple foundations and Societies	Study Population: Healthy infants Healthy pregnant women Infants enrolled 314 Infants withdrawals 137 Infants completers 177 Mother age: NR (NR) NR Race of Mother: NR (NR)	Inclusion Criteria: All pregnant mothers <16 weeks of gestation Exclusion Criteria: Sick children and those born prematurely who required more intensive care (n=8)	Start time: Pregnant 8th to 16th weeks of pregnancy and then continued Infants when exclusive breastfeeding ended Duration: Pregnant until the end of the exclusive breastfeeding period Infants until 2 years of age Arm 1: Controls Description: Olive oil Manufacturer: Santagata Luigi s.r.l., Genova, Italia Dose: 3 g/day for mothers, 1 mL/day for infants Blinding: NR "double-blind" ALA: 0 DHA: 0 EPA: 0 EPA-DHA: 0 AA: 0 Total N-3: 0 Other dose 1: LA (18:2n-6): 9 weight% of total Arm 2: Intervention Description: Blackcurrant seed oil	Outcome: birth weight (g) (Secondary) Follow-up time: birth Arm 1: Sample size 129; mean 3599.0; SD (468) Arm 2: Sample size 112; mean 3595.0; SD (461)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			Manufacturer: Aromtech Ltd, Tornio, Finland Dose: 3 g/day for mothers, 1 mL/day for infants ALA: 14 weight% of total DHA: 0 EPA: 0 EPA-DHA: 0 AA: 0 Total N-3: 17 weight% of total Other dose 1: SDA: 3 weight% of total	
Lucia Bergmann et al., 2007[41] Study name: NR Study dates: 2000-2002 Study design: Trial randomized parallel Location: Germany Funding source / conflict: NR Original, same study, or follow-up studies: Lucia, 2007[52]	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 144 Pregnant withdrawals 51 Pregnant completers 69 Pregnant age: 31 (DHA 4.69; control 4.89) Infant age: DHA 39.1; control 39.5 weeks (DHA 1.64; control 1.38) Race of Mother: White European (100) Baseline biomarker information: DHA % of all identified fatty acid in RBC: Vitamin: 5.76 +-2.45 (47); DHA: Prebiotic:5.94+-2.37(48) DHA: DHA: 5.69+-2.40(47) ARA Vitamin: 14.01+-4.04(47) ARA Prebiotic 14.82+-3.60(48) ARA DHA: 14.18+-4.32(47) EPA Vitamin: 0.72+-0.32(47) EPA Prebiotic: 0.78+-0.38(48) EPA DHA: 0.79+-0.41(47)	Inclusion Criteria: at least 18 years of age and willing to breastfeed for at least three months were enrolled at 21 weeks' gestation during the period October 2000 to August 2002 Exclusion Criteria: increased risk of premature delivery or multiple pregnancy, allergy to cow milk protein, lactose intolerance, diabetes, smoking, consumption of alcohol (20 g/week), or participation in another study. Infants excluded if they were premature at birth (<37 week gestation, or had any major malformations or hospitalized for more than one week.	Start time: Pregnant 21th week Duration: Pregnant 37th week Arm 1: Vitamins and minerals Manufacturer: Nestle´ (Vevey, Switzerland) Arm 2: Prebiotic Description: basic supplement plus the prebiotic, fructooligosaccharide (FOS) (4.5 g) Manufacturer: Nestle´ (Vevey, Switzerland) Active ingredients: fructooligosaccharide (FOS) (4.5 g) Arm 3: DHA Description: basic supplement with FOS and DHA (200 mg) Manufacturer: Nestle´ (Vevey, Switzerland) Dose: 200 mg DHA prepared from fish oil (assuming that some EPA but dose was not reported) DHA: 200 mg EPA: NR	Outcome: birth weight (g) (Unspecified) Follow-up time: birth Arm 1: Sample size 74; mean 3548.0; SD (469.3) Arm 3: Sample size 43; mean 3427.0; SD (493.6)
Makrides et al., 2010[35]	Study Population:	Inclusion Criteria: with	Start time: Pregnant < 21 week's gestation	duplicate data of id 4404

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study name: DOMInO Study dates: 2005-2008 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Manufacturer supplied product Original, same study, or follow-up studies: Smithers, 2011[53]; Palmer, 2012[54]; Zhou, 2012[55]; Palmer, 2013[56]; Makrides, 2014 [57]	Healthy pregnant women Pregnant enrolled 2399 Pregnant withdrawals 1 Infants enrolled 605 Infants withdrawals 32 Infants completers 726 Pregnant age: 28.9 (DHA5.7___ control5.6) Race of Mother: NR (NR)	singleton pregnancies at less than 21 weeks' gestation were approached by study research assistants while attending routine antenatal appointments Exclusion Criteria: already taking a prenatal supplement with DHA, their fetus had a known major abnormality, they had a bleeding disorder in which tuna oil was contraindicated, were taking anticoagulant therapy, had a documented history of drug or alcohol abuse, were participating in another fatty acid trial, were unable to give written informed consent, or if English was not the main language spoken at home	Duration: NR Arm 1: vegetable oil capsules Description: a blend of 3 nongenetically modified oils (rapeseed, sunflower, and palm) in equal proportions Manufacturer: Efamol, Surrey, England. Dose: 3* 500mg capsule / day Blinding: All capsules were similar in size, shape, and color Arm 2: DHA Description: DHA-rich fish oil concentrate Manufacturer: ; Incromega 500 TG, Croda Chemicals, East Yorkshire, England Dose: 500mg capsule *3/day DHA: 800mg EPA: 100mg	Outcome: (Secondary)
Miles et al., 2011[78] Study name: SiPS Study dates: NR Study design: Trial randomized parallel Location: UK Funding source / conflict: Government, Some authors employed by industry (companies that make the supplements) Original, same study, or	Study Population: Healthy pregnant women Pregnant enrolled 123 Pregnant completers 101 Pregnant age: Salmon: 29.5 Control: 28.4 (Salmon 0.5 Control: 0.6) Race of Mother: NR (100%)	Inclusion Criteria: age 18–40 y; ,19 wk gestation; healthy, uncomplicated singleton pregnancy; infant at risk of atopy (one or more first-degree relatives of the baby affected by atopy, asthma, or allergy by self-report); consuming <2 portions of oily fish/mo (excluding canned tuna); not using fish-oil supplements currently or in the previous 3 mo Exclusion Criteria: age	Start time: Pregnant Week 20 Duration: Pregnant Week 20 until Term (delivery) Arm 1: Control Description: No added fish DHA: 16 mg/d in diet EPA: 10 mg/d in diet EPA-DHA: 24 mg/d in diet Arm 2: Salmon Description: 2 portions salmon per week DHA: 326 mg/d EPA: 162 mg/d EPA-DHA: 491 mg/d	Outcome: birth weight (g) (Secondary) Follow-up time: birth Arm 1: Sample size 54; mean 3425.0; SE (82) Arm 2: Sample size 53; mean 3449.0; SE (72)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
follow-up studies: Noakes, 2012[88]		<18 or >40 y; .19 wk gestation; no first-degree relatives of the infant affected by atopy, asthma, or allergy; consuming >2 portions of oily fish/mo (excluding canned tuna); use of fish-oil supplements within previous 3 mo; participation in another research study; known diabetic; or presence of any autoimmune disease, learning disability, terminal illness, or mental health problems		
Mozurkewich et al., 2013[42] Study name: NR Study dates: Oct 2008 - May 2011 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product	Study Population: Healthy pregnant women Pregnant enrolled 126 Pregnant withdrawals 8 Pregnant completers 118 Pregnant age: EPA 29.9; DHA 30.6; placebo 30.4 (EPA 5.0; DHA 4.5; placebo 5.9) Race of Mother: White European (85%; 76%; 83%) Black (10%; 11%; 5%) Asian (3%; 3%; 2%) Hispanic (0%; 11%; 7%) Inuit Eskimo (0%; 0%; 2%) Pacific Islander (NR) Baseline biomarker information: EPA group: EPA 0.29+-0.18; DHA 4.24+-2.30; total n3 FA: 22.10+-3.72 DHA group: EPA 0.31+-0.24; DHA 4.66+-2.29; total n3 FA	Inclusion Criteria: past history of depression, an EPDS score 9-19 (at risk for depression or mildly depressed), singleton gestation, a maternal age of 18 years or older, and a gestational age of 12-20 weeks Exclusion Criteria: had a history of a bleeding disorder, thrombophilia requiring anticoagulation, multiple gestation, bipolar disorder, current major depressive disorder, current substance abuse, lifetime substance dependence, or schizophrenia. Women were also ineligible if they were currently taking omega-3 fatty acid supplements or antidepressant medications or eating	Start time: Pregnant 12-20 week gestation Duration: Pregnant assuming till birth Arm 1: Control/Placebo Description: 98% soy oil and 1% each of lemon and fish oil Manufacturer: Nordic Naturals Corporation in Watsonville, CA Viability: centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose: 2 large and 4 small placebo capsules Blinding: The placebos were formulated to be identical in appearance to both the EPA- and DHA-rich supplements Arm 2: EPA-rich fish oil Description: an approximate 4:1 ratio of EPA to DHA (1060 mg EPA plus 274 mg DHA) Brand name: ProEPAXtra, Nordic Naturals Viability: centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose: 2 large EPA capsule and 4 small placebo DHA: 274 mg EPA: 1060 mg Arm 3: DHA-rich fish oil	Outcome: birth weight (g) (Secondary) Follow-up time: birth Arm 1: Sample size 40; mean 3309.0; SD (555) Arm 2: Sample size 40; mean 3402.0; SD (550) Arm 3: Sample size 38; mean 3774.0; SD (438)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	36.41+-9.71 placebo: EPA .34+-0.22; DHA 3.85+-1.77; omega3 fa 322.86+-5.02	more than 2 fish meals per week.	Description: DHA and EPA in an approximate 4:1 ratio o (900 mg DHA plus 180 mg EPA) Brand name: ProDHA, Nordic Naturals Viability: centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose: 2 large placebo oil and 4 small DHA rich DHA: 900 mg EPA: 180 mg	
Mulder et al., 2014[75] Study name: NR Study dates: 2004 to 2008 Study design: Trial randomized parallel Location: Canada Funding source / conflict: Government Study follow-up: 18 months	Study Population: Healthy pregnant women Pregnant enrolled 271 Pregnant completers 200 Pregnant age: 33 years (4 years) NR Race of Mother: White European (73%) Other race/ethnicity (27%) Baseline biomarker information: maternal RBC Phusphatidylethanolamine DHA: placebo group 6.25 (1.60) g/ 100g DHA group 6.36 (1.62) g/ 100g Baseline Omega-3 intake: median (2.5 to 97.5th percentile range) intake: placebo group 80.0 (0.00-334) mg/day, DHA group 90.0 (6.00-472) mg/d	Inclusion Criteria: at least 16 wk gestation, not taking any lipid or fatty acid supplement, and were expected to deliver one infant at full-term gestation, with no maternal or fetal complications Exclusion Criteria: NR	Start time: Pregnant 16 weeks gestation Duration: Pregnant Until birth Arm 1: placebo Description: corn and soybean oil supplement Manufacturer: Martek Biosciences Blinding: supplements were identical in appearance, contained an orange flavor mask Arm 2: DHA supplement Description: algal oil DHA supplement Manufacturer: Martek Biosciences DHA: 400 mg	Outcome: birth weight (g) (Unspecified) Follow-up time: birth Arm 1: Sample size 111; mean 3497.0; SD (479) Arm 2: Sample size 104; mean 3494.0; SD (400)
Ramakrishnan et al., 2010[32] Study name: POSGRAD Study dates: Feb 2005 - Feb 2007	Study Population: Healthy pregnant women Pregnant enrolled 1,094 Pregnant withdrawals 67 Pregnant completers 973 (for birth weight)	Inclusion Criteria: 18-35 yrs. of age, in gestation weeks 18-22, planned to deliver at the IMSS General Hospital in Cuernavaca, exclusively or predominantly breastfeed for at least 3	Start time: Pregnant at study entry Duration: Pregnant mid pregnancy (18-22 weeks gestation) until delivery Arm 1: Controls Description: Placebo containing olive oil Manufacturer: Martek Biosciences	Outcome: birth weight (g) (Primary) Follow-up time: birth Arm 1: Sample size 486; mean 3202.0; SD (472) Arm 2: Sample size 487; mean 3207.2; SD (449.4)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study design: Trial randomized parallel Location: Mexico Funding source / conflict: Government, March of Dimes Original, same study, or follow-up studies: Stein, 2012[33]; Imhoff-Kunsch, 2011[58]; Escamilla-Nunez, 2014[59]; Gonzalez-Casanova, 2015[60]; Ramakrishnan, 2015[61]; Stein, 2011[34]	Pregnant age: 26.2 (controls) 26.3 (DHA) (4.6 (controls) 4.8 (DHA)) Race of Mother: Hispanic (NR) Baseline Omega-3 intake: mg/day for all: LA: 17,846 in controls, 17,645 in DHA AA: 137 in controls, 140 in DHA ALA: 1,488 in controls, 1,477 in DHA EPA: 18 in controls, 18 in DHA DHA: 54 in controls, 56 in DHA	months, liver in the area for at least 2 years after delivery. Exclusion Criteria: high-risk pregnancy; lipid metabolism or absorption disorders, regular intake of fish oil or DHA supplements; chronic use of certain medications (e.g., medications for epilepsy).	Dose: 1 capsule, twice a day Blinding: Identical tablets Arm 2: DHA Description: Intervention Manufacturer: Martek Biosciences Dose: 1 capsule twice a day DHA: 400 mg/d, 200 mg/dl derived from algal source	
Stein et al., 2011[34] Study name: POSGRAD Study dates: 02. 2005-02.2007 Study design: Trial randomized parallel Location: Mexico Funding source / conflict: Government, Multiple foundations and Societies Original, same study, or follow-up studies: Stein, 2012[33]; Imhoff-Kunsch, 2011[58]; Escamilla-Nunez, 2014[59]; Gonzalez-Casanova, 2015[60]; Ramakrishnan, 2015[61]; Ramakrishnan, 2011[32]	Study Population: Healthy infants Pregnant enrolled 1094 Pregnant completers 973 Pregnant age: placebo 26.3; DHA 26.4 (placebo 4.6; DHA 4.9) Infant age: 39.1 (placebo 1.6; DHA 1.8) Race of Mother: NR	Inclusion Criteria: women were 18–35 y, were in gestation wk 18–22, and planned to deliver at the IMSS General Hospital in Cuernavaca, exclusively or predominantly breast-feed for at least 3 mo, and to live in the area for at least 2 y after delivery Exclusion Criteria: NR	Start time: Pregnant 18-22 Gestational week Infants birth Duration: Pregnant birth Arm 1: Placebo Description: Olive oil Manufacturer: Martek Biosciences Dose: 2 capsules olive oil Blinding: Similar in appearance and taste to DHA capsules Arm 2: DHA Description: algal DHA capsules Manufacturer: Martek Biosciences Dose: 2 capsules * 200mg DHA: 400 mg	Outcome: birth weight (g) (Primary) Follow-up time: birth Arm 1: Sample size 370; mean 3220.0; SD (475) Arm 2: Sample size 369; mean 3242.0; SD (441)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Tofail et al., 2006[77] Study name: NR Study dates: Enrollment January to March 2000 Study design: Trial randomized parallel Location: Bangladesh Funding source / conflict: Government Study follow-up: 10 months	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 400 Pregnant completers 151 Pregnant age: 22.7 years (4.35 years) NR Race of Mother: Asian (100%)	Inclusion Criteria: seems as if all pregnant women at 25 weeks gestation were enrolled, no inclusion criteria specified Exclusion Criteria: NR	Start time: Pregnant 25 weeks gestation Duration: Pregnant until birth Arm 1: placebo Description: soy oil capsule Dose: 4 one gram capsules per day Blinding: capsules were identical in appearance Other dose 1: LNA 0.27 g Other dose 2: linoleic acid 2.25 g Arm 2: DHA supplement Description: fish oil capsules Dose: 4 one gram capsules per day DHA: 1.2 g EPA: 1.8 g	Outcome: birth weight (kg) (Unspecified) Follow-up time: birth Arm 1: Sample size 124; mean 2.7; SD (0.4) Arm 2: Sample size 125; mean 2.7; SD (0.4)
Zhou et al., 2012[55] Study name: DOMInO Study dates: 10. 2005 - 01. 2008 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies, Manufacturer supplied product Original, same study, or follow-up studies: Makrides, 2010[35]; Smithers, 2011[53]; Palmer, 2012[54]; Palmer, 2013[56]; Makrides, 2014 [57]	Study Population: Healthy pregnant women Pregnant enrolled 2399 Race of Mother: White European (88%;88%) Asian (7%;8%) Inuit Eskimo (2%;1%) Other race/ethnicity (NR)	Inclusion Criteria: NR Exclusion Criteria: If already taking a dietary supplement containing DHA, their fetus had a known major abnormality, they had a bleeding disorder for which fish oil was contraindicated, they were receiving anticoagulant therapy, they had a documented history of drug or alcohol abuse, they were participating in another fatty acid trial, or English was not the main language spoken at home	Start time: Pregnant medium gestational age 19 weeks Duration: Pregnant birth Arm 1: control Description: 500-mg vegetable oil capsules Dose: 3*500mg 3 nongenetically modified oils (rapeseed, sunflower, and palm) in equal proportions Blinding: All capsules were similar in size, shape, and color Arm 2: DHA Description: DHA-rich fish oil Manufacturer: Incromega 500 TG; Croda Chemicals Dose: 3*500mg capsule DHA: 800 mg EPA: 100 mg	Outcome: birth weight (g) (Secondary) Follow-up time: birth Arm 1: Sample size 1202; mean 3407.0; SD (576) Arm 2: Sample size 1197; mean 3475.0; SD (564)

Table 9. Observational studies for birth weight

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Badart-Smook, et al., 1997[47] Outcome domain: Birth Weight Study dates: NR Study design: Observational prospective Location: Netherlands Funding source / conflict: NR	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 610 Pregnant withdrawals 240 Pregnant completers 370 Pregnant age: 29 (4) Race of Mother: White European (100)	Inclusion Criteria: White race, intention to give birth to the baby in one of the three hospitals involved in the study Exclusion Criteria: Women with diastolic blood pressure of 90mm or higher, women suffering from any metabolic, cardiovascular, neurological, or renal disorder	Adjustments: Maternal(pregnancy) body weight, height, age, smoking habits, education, parity, and sex of the infant were included in each multiple regression model as possible confounding factors; except for the regression equation with gestational age as a dependent variable, gestational age at birth was also added as a confounder
Brantsaeter, et al., 2012[81] Outcome domain: Birth Weight Study name: Norwegian Mother and Child Cohort Study (MoBa) Study dates: 2002-2009 Study design: Observational prospective Location: Norway Funding source / conflict: Government	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 76218 Pregnant completers 62099 Race of Mother: NR	Inclusion Criteria: first participation for women with multiple participation in MoBa and women with singleton births. Exclusion Criteria: participants with a pregnancy duration <28 weeks or >42 weeks (n=628), if the birth weight of the baby had not been recorded or if the birth weight was, <600 g (n = 35). We also excluded participants who had not given birth to a live baby (n 153). Lastly, we excluded women having improbable energy intakes, i.e. energy intake , >4·5 MJ or .<20 MJ (n 1063)	Adjustments: Adjusted for maternal age, height, pre-pregnant BMI, parity, pregnancy duration, maternal education, smoking status, mother tongue other than Norwegian and total energy intake, and with intakes of seafood/seafood items and supplementary n-3 mutually adjusted
Dirix, et al., 2009[84] Outcome domain: Birth Weight Study name: Maastricht Essential Fatty Acid Birth (MEFAB) Cohort Study dates: 1990-1997 Study design: Observational prospective Location: Netherlands Funding source / conflict: Government	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 1238 Pregnant completers 782 Infants enrolled 1238 Infants completers 782 Pregnant age: 29.0 26.2-31.7 Infant age: 40.1 wk 39.3-41.0 Race of Mother: White European (100)	Inclusion Criteria: gestational age of <16 weeks at study entry, singleton pregnancy, Caucasian race, diastolic blood pressure, 90 mmHg and the absence of any metabolic, cardiovascular, neurological or renal disorder at the time of recruitment Exclusion Criteria: excluded if infants were born preterm (gestational age < 37 weeks,), mothers had diabetes or developed pregnancy-induced hypertension, mothers had reported specific health problems in the past (e.g. diabetes mellitus, hypertension and heart, kidney, liver, gall bladder or thyroid gland disorders, one or both parents were non-Caucasians or values for any of the afore-mentioned exclusion criteria were missing. The mother – infant pairs were also excluded if fatty acid	Adjustments: Infant sex, gestational age, maternal height

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
		analyses were not reported or values were missing for birth weight, birth length and head circumference	
Drouillet, et al., 2009[80] Outcome domain: Birth Weight Study name: EDEN Study dates: February 2003 - September 2003 Study design: Observational prospective Location: NR Funding source / conflict: Industry, Government, Multiple foundations and Societies Original, same study, or follow-up studies: Bernard, 2013[89]	Study Population: Healthy pregnant women Pregnant enrolled 2002 Pregnant completers 1446 Pregnant age: 29.2 (4.8) Race of Mother: NR	Inclusion Criteria: NR Exclusion Criteria: twin pregnancies, known diabetes before pregnancy, not being able to speak and read French, and planned moving away from the region	Adjustments: Centre, mother's age and height, smoking habits, parity, gestational age, newborn's sex, delay between birth and anthropometric measures, and BMI
Mohanty, et al., 2015[85] Outcome domain: Birth Weight Study dates: 1996-2008 Study design: Observational prospective Location: US Funding source / conflict: Government	Study Population: Healthy infants Healthy pregnant women Pregnant completers 534 Race of Mother: White European (88)	Inclusion Criteria: initiated prenatal care at or before 20 weeks gestation, were aged = 18 years, able to speak and read English, planned to carry the pregnancy to term, and to deliver at either of the two hospitals Exclusion Criteria: multi-fetal pregnancies, implausible total energy intake of <500 or >3500 kcal/day, pregnancies complicated by fetal demise (after 20 weeks of gestation), missing labor and delivery information, missing information on fetal growth indices, missing seafood intake information	Adjustments: Adjusted for maternal age (years), non-Hispanic white race, post high-school education, unmarried marital status, pre-pregnancy body mass index (indicator variables: 18.5-24.9, 25-29.9, =30 kg/m2), total energy (kcal/day), current recreational physical activity, current smoking, current alcohol intake, nulliparity, intake of red/processed meats (servings/day), male infant sex.
Molto-Puigmarti, et al., 2014[48] Outcome domain: Birth Weight Study name: KOALA Birth Cohort Study Study dates: 2000-2002 Study design: Observational prospective Location: Netherlands	Study Population: Healthy pregnant women Pregnant enrolled 2669 Pregnant completers 1516 Infants enrolled 2669 Infants completers 1515 Pregnant age: years (.7yrs) Race of Mother: NR (100)	Inclusion Criteria: nr, Described in Ref 37 Exclusion Criteria: nr	Adjustments: Adjusted for child gender, study recruitment group, maternal education, parity, maternal smoking status during pregnancy, maternal alcohol use in pregnancy, and maternal age at delivery

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Funding source / conflict: Multiple foundations and Societies			
Much, et al., 2013[83] Outcome domain: Birth Weight Study name: INFAT Study dates: >2009-<2013 Study design: Observational prospective Location: Germany Funding source / conflict: Industry, Government, Some authors employed by industry (companies that make the supplements), Multiple foundations and Societies, None	Study Population: Healthy infants Breast-feeding women Pregnant enrolled 208 Infants completers 187 Race of Mother: NR (NR)	Inclusion Criteria: Healthy pregnant women at 14th week of gestation Exclusion Criteria: None reported	Adjustments: Pregnancy duration, group, parity, and sex
Muthayya, et al., 2009[72] Outcome domain: Birth Weight Study dates: Jan 2002- Mar 2006 Study design: Observational prospective Location: NR Funding source / conflict: Industry, Government	Study Population: Healthy pregnant women Pregnant enrolled 829 Pregnant completers 676 Pregnant age: group 1, 23 group 2, 23 group 3, 23 total, 24 group 1, 21-26 group 2, 21-27 group 3, 23-29 total: 21-27 Race of Mother: Asian (Indian, 100%)	Inclusion Criteria: pregnant women aged 17–40 years and at <20 weeks of gestation, registered for antenatal screening at the Department of Obstetrics and Gynecology at St John's Medical College Hospital, Exclusion Criteria: Women with multiple pregnancies, those with a clinical diagnosis of chronic illness such as diabetes mellitus, hypertension, heart disease and thyroid disease, those who tested positive for HbSAg/HIV/VDRL infection or who anticipated moving out of the city before delivery were excluded	Adjustments: Adjusted for maternal age, maternal education, parity, maternal weight/maternal weight gain per week and gestational age
Oken, et al., 2004[46] Outcome domain: Birth Weight Study name: Project Viva Study dates: 1999-2002 Study design: Observational prospective Location: US Funding source / conflict: Government, Multiple foundations and Societies	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 2109 Pregnant completers 2109 Pregnant age: 14-<20, 3% 20-<25, 6% 25-<30, 21% 30-<35, 42% 35=<40, 23% >=40, 4% (14-44) Race of Mother: White European (66) Black (16) Asian (6) Hispanic (7) Other race/ethnicity (4)	Inclusion Criteria: delivered a live infant, and completed at least one dietary questionnaire Exclusion Criteria: taking cod liver or fish oil supplement	Adjustments: Enrollment site, infant sex, and maternal age, height, intrapartum weight gain, prepregnancy BMI, race/ethnicity, smoking during pregnancy, education, and gravidity

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Olafsdottir, et al., 2005[82] Outcome domain: Birth Weight Study dates: 1999-2001 Study design: Observational prospective Location: NR Funding source / conflict: Government, Multiple foundations and Societies	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 436 Pregnant completers 436 Pregnant age: No 27.8; Yes 29.6 (no 4.9; yes 4.6) Race of Mother: NR	Inclusion Criteria: absence of pre-eclampsia, hypertension or diabetes mellitus Exclusion Criteria: women whose personal data could not be found or who moved abroad before giving birth (n 8), had a miscarriage or stillbirth (n 17), twins or triplets (n 5), a preterm birth hypertension/pre-eclampsia (n 62) or gestational diabetes mellitus (n=4)	Adjustments: Gender, gestational age, mother's height, BMI, haemoglobin, alcohol consumption in first trimester, parity, smoking during pregnancy, weight gain during pregnancy
Smits, et al., 2013[73] Outcome domain: Birth Weight Study name: Amsterdam Born Children and their Development (ABCD) Study dates: Jan 2003- Mar 2004 Study design: Observational prospective Location: Netherlands Funding source / conflict: None	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 1659 Pregnant completers 1659 Infants enrolled 1659 Infants completers 1659 Pregnant age: <25 y, 5.7% 25-34 y, 61.2% >=35 y, 33.1% Infant age: 40.0 weeks (1.2) Race of Mother: White European (88.4)	Inclusion Criteria: NR Exclusion Criteria: primiparous women or delivered preterm	Adjustments: Potential confounding factors were evaluated but none of them was significant confounding defined as changing the odds ratio by 10%

Antenatal and Postnatal Depression

Key Findings and Strength of Evidence for Antenatal and/or Postnatal Depression Outcome

- Three RCTs that assessed the effects of prenatal supplementation with DHA alone, DHA+AA, or EPA-enriched fish oil found no effects on either antenatal or postnatal depression among healthy pregnant women.
- One small RCT showed that women who received prenatal DHA supplementation had significantly fewer symptoms of postpartum depression compared to the placebo group.
- Two prospective observational studies found no associations between prenatal dietary or supplemental n-3 FA intake and antenatal or postnatal depression.
- Three prospective observational studies found no significant associations between n-3 FA biomarkers and postnatal depression.
- One RCT that assessed the effects of postnatal supplementation with DHA alone found no effects on postnatal depression.

This outcome is an additional outcome of interest that was not included in the original review. A total of five eligible RCTs and six observational studies were identified. Of these 11 studies, four RCTs and all of the observational studies evaluated the effects of prenatal maternal n-3 FA interventions or exposures, while the fifth RCT examined the effects of postnatal maternal n-3 FA interventions. All studies that assessed the effects of n-3 FA on antenatal or postnatal depression were conducted among healthy pregnant or lactating women.

Description of Included Studies

Prenatal Maternal n-3 FA Interventions/Exposures

Randomized Controlled Trials

Four RCTs assessed the effects of prenatal maternal supplementation on the risk for antenatal and/or postnatal depression (See Table 10).[35, 42, 90, 91] While all of the studies compared the effects of DHA (200 to 900 mg/day) to that of placebo, two studies also included a third study arm. One included a third arm with supplements containing DHA+AA [90], and the other included a third arm with supplements containing EPA-rich fish oil. [42] Two studies examined the effects of n-3 FAs on postnatal depression only [35, 91], while the other two RCTs examined the effects on both antenatal and postnatal depression.[42, 90] Three of the four studies found no significant effects of marine oils on ante- or postnatal depression outcomes compared with placebo. Only one small pilot study showed that women who received prenatal DHA supplementation had significantly fewer symptoms of postpartum depression compared to the placebo group.[91]

The DOMInO trial randomized 2,399 pregnant Australian women (<21 week's gestation) to receive fish oil containing 0.80 g/day DHA and 0.10 g/day EPA (n=1197) or vegetable oil placebo (n=1202) and followed women up to six months postpartum to assess for depressive symptoms using the Edinburgh Postnatal Depression Scale (EPDS).[35] The duration of intervention was not reported. No differences were found between the groups in percentage of women reporting high levels of depressive symptoms (EPDS score >12) at either 6 weeks or 6 months postpartum.

Doornbos (2009) enrolled 182 pregnant Dutch women (14-20 weeks gestation) into a three-arm trial (0.220 g/day DHA+ 0.220 g/day AA vs. 0.220 g/day DHA vs. soybean oil placebo)[90]. Sixty three women dropped out prior to 36 weeks gestation, leaving data from 119 women available for analysis. No differences were found in median EPDS scores among the groups at either week 36 of pregnancy or 6 months postpartum.

Mozurkewich (2013) enrolled 126 pregnant women in the US (12-20 weeks gestation) into a three arm trial (0.900 g/d DHA+0.180 g/d EPA vs. 1.060 g/d EPA+274 g/d DHA vs. soy oil placebo). After adjusting for baseline Beck Depression Inventory (BDI) scores, no differences were found in mean BDI score between groups at either 34-36 weeks' gestation or 6-8 weeks postpartum. However, a trend was observed toward significance at 26-28 weeks' gestation (p=0.05).

Judge (2015) enrolled 42 healthy pregnant women in the US at 24 weeks of gestation into a pilot trial comparing the effect of prenatal supplementation of 300 mg/d DHA to that of placebo (corn oil) on postpartum depression. After adjusting for baseline Center for Epidemiological Studies –Depression (CES-D) score, age, dietary DHA outside of intervention, and ethnicity, women who received prenatal DHA supplementation had significantly lower Postpartum Depression Screening Scale (PDSS) scores from 2 weeks to 6 months postpartum compared with those who received placebo (P=0.016).

Observational Studies

Six prospective studies were identified that assessed the effects of prenatal maternal n-3 FA intake or status on antenatal, perinatal, or postnatal depression (see Table 11). Two studies measured dietary n-3 FA intake,[92, 93] one study measured n-3 supplement intake,[94] one study measured plasma total n-3 FA,[95] and two studies measured the percent of total RBC phospholipid FAs.[96, 97]

Dietary n-3 FA intake

Strom (2009) analyzed data from 54,202 women enrolled in the Danish National Birth Cohort.[92] They examined the association between deciles of n-3 FA intake estimated from a food frequency questionnaire administered mid-pregnancy and either admittance to a psychiatric hospital due to postpartum depression (PPD-admission) or purchase of antidepressants in a pharmacy with a prescription (PPD-prescription). No association was seen between any decile of intake of n-3 FAs and risk of either PPD-admission or PPD-prescription after adjusting for confounders.

Miyake (2006) assessed the association of n-3 FA intake with risk of postpartum depression among 865 Japanese women enrolled in the Osaka Maternal and Child Health Study (OMCHS).[93] The authors observed no significant dose-response relationship between intakes of total n-3 FAs, EPA, DHA, or n-3/n-6 FA ratio and postpartum depression (as measured by the EPDS), even after adjusting for confounders.

Supplementary n-3 FA intake

Leung (2013) analyzed data from 475 Canadian women enrolled in the Alberta Pregnancy Outcomes and Nutrition (APrON) study who completed the EPDS questionnaire at least twice during pregnancy and at 12 weeks postpartum.[94] Mean supplementary intake of n-3 FA differed significantly between women with a postpartum EPDS score <10 (n=416) and those with a postpartum EPDS score≥ 10 (n=59) (180 vs. 90 mg, p=0.01); however, the association did not persist in multivariate analyses. No association was observed between supplementary n-3 FA intake and prenatal EPDS scores measured in the second and third trimesters.

n-3 FA Biomarkers

Sallis (2014) reported results from 3,397 women enrolled in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort in England.[96] The authors examined the association between percent of total RBC phospholipid FAs measured from antenatal blood samples and ante-, peri-, and postnatal depression as measured by the EPDS. EPDS score >12 was the cutoff used to define depression. A weak association between prenatal EPA levels and perinatal onset depression was observed after adjusting for social class and maternal age (OR 1.07, 95% CI 0.99, 1.15). Levels of n-3 FAs were not associated with antenatal or postnatal depression in multivariate models.

Parker (2015) analyzed 895 women at 36 weeks of pregnancy for whom PUFA data were available.[97] Postpartum depression status was measured by the Mini International Neuropsychiatric Interview (MINI) and EPDS scores. No associations were observed between any of the maternal PUFA measures and the MINI outcome after adjusting for other non-PUFA variables. When PUFA variables were added individually, only lower n-3 (OR=1.1, $P<0.05$), lower EPA (OR=2.7, $P<0.05$), and higher n-6 (OR=1.1, $P<0.05$) remained significant associated with postnatal depression measured by EPDS after adjusting for non-PUFA variables.

Chong et al (2015) analyzed the associations between prenatal plasma n-3 FAs and postpartum depression in 698 women from the Growing Up in Singapore Toward healthy Outcomes (GUSTO) study.[95] The results showed no significant associations in either univariate or adjusted multivariate analyses between total plasma n-3 FAs or plasma AA:DHA ratio and risk of postpartum depression measured by EPDS at 3 months.

Postnatal maternal n-3 FA interventions/exposures

Randomized Controlled Trials

One RCT conducted in the U. that assessed the effects of a postnatal intervention on risk for PPD was identified.[98] Llorente (2003) enrolled 138 pregnant women who planned to breast feed for at least 4 months to receive an algae-derived triglyceride capsule containing 0.200 g/day of DHA or placebo, beginning within a week of delivery for four months. Eighty nine (64%) lactating women, mean age 31.5 years, completed four months of the study (44 in the DHA group and 45 in the placebo group) and were assessed for depressive symptoms using the BDI. Sixty three (46%) women were followed up to 18 months (31 in the DHA group and 32 in the placebo group) and were assessed for depressive symptoms using the EPDS. No significant differences in depressive symptom scores were found between groups at any of the time points (3 weeks, 2 months, 4 months, or 18 months postpartum).

Table 10. RCTs for ante postnatal depression

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Doornbos et al., 2009[90] Study name: NR Study dates: Not reported Study design: Trial randomized parallel Location: Netherlands Funding source / conflict: Industry Study follow-up: 3 months/12 weeks postpartum	Study Population: Healthy pregnant women Pregnant enrolled 182 Pregnant withdrawals 63 Pregnant completers 119 Pregnant age: NR (NR) NR Race of Mother: NR (100) Baseline biomarker information: Placebo group: DHA- 4.44 (3.00–6.92); AA-12.91 (9.95–14.95) DHA group: DHA-5.51 (3.98–8.20); AA-12.13 (9.63–15.22) DHA+AA group: DHA-5.57 (2.48–8.32); AA-13.60 (11.17–15.52)	Inclusion Criteria: women with first or second, singleton pregnancies Exclusion Criteria: women with a vegetarian or vegan diet or gestational diabetes and preterm delivery (<37 weeks)	Start time: Pregnant 16.5 (14-20) week of pregnancy Duration: Pregnant till 3 months after delivery Arm 1: Control group Description: Placebo-soybean oil Arm 2: DHA group Brand name: NR Manufacturer: NR DHA: 220mg Arm 3: DHA + AA group Brand name: NR Manufacturer: NR DHA: 220 mg AA: 220mg	Outcome: Edinburgh Postnatal Depression Scale (EPDS) (Secondary) Follow-up time: 36 weeks pregnant Arm 1: Sample size 34; median 4.0; IQR Arm 2: Sample size 40; median 4.0; IQR Arm 3: Sample size 37; median 6.0; IQR Follow-up time: 6 weeks post-partum Arm 1: Sample size 32; median 5.0; IQR Arm 2: Sample size 38; median 4.0; IQR Arm 3: Sample size 30; median 5.0; IQR
Judge et al., 2014[91] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: US Funding source / conflict: Multiple foundations and Societies, None Original, same study, or follow-up studies: none	Study Population: Healthy pregnant women Pregnant enrolled 73 Pregnant completers 42 Pregnant age: 18-35 Race of Mother: NR (100)	Inclusion Criteria: No other births in the previous two years; 20 weeks pregnant; and 18-35 years of age. Exclusion Criteria: with a self-reported significant medical history (i.e., currently being treated for depression/psychiatric illness, addiction problems, hyperlipidemia, hypertension, renal disease, liver disease, or diabetes).	Start time: Pregnant 24 weeks gestation Duration: Pregnant 24 weeks gestation until delivery Arm 1: Placebo Description: corn oil capsule Dose: 1 capsule, 5 days/week Blinding: Identical package and only ID information Arm 2: DHA group Description: 300mg DHA fish oil capsule Dose: 1 capsule, 5 days/week DHA: 300mg	Outcome: Postpartum Depression Screening Scale (PDSS) total score (Primary) Follow-up time: 2 weeks Arm 1: Sample size 22; mean 53.86; SD (15.25) Arm 2: Sample size 20; mean 47.65; SD (12.96) Follow-up time: 3 months Arm 1: Sample size 22; mean 42.63; SD (9.52) Arm 2: Sample size 20; mean 45.28; SD (12.25) Follow-up time: 6 months Arm 1: Sample size 22; mean 48.42; SD (17.18) Arm 2: Sample size 20; mean 45.55; SD (13.5)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Follow-up time: 6 weeks Arm 1: Sample size 22; mean 47.4; SD (12.42) Arm 2: Sample size 20; mean 47.61; SD (14.31)
Llorente et al., 2003[98] Study name: Unnamed Trial A Study dates: <2002 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product Study follow-up: 18 months Original, same study, or follow-up studies: Isaacs, 2011[99]	Study Population: Breast-feeding women Lactating enrolled 138 Lactating completers 101 Lactating enrolled 138 Lactating completers 101 Lactating age: 31.5 years (4.5 years) 18 - 42 Race of Mother: White European (82%) Black (14%) Hispanic (2.3%) Other race/ethnicity (1.6%) Baseline biomarker information: Placebo group Total saturated 49.7 ± 2.3 Total monounsaturated 12.2 ± 1.9 Total __6 33.7 ± 2.2 Total __3 4.37 ± 0.91 Intervention group Total saturated 49.3 ± 2.7 Total monounsaturated 12.3 ± 1.3 Total __6 34.2 ± 2.0 Total __3 4.14 ± 0.89	Inclusion Criteria: pregnant women who were 18 to 42 years old and planned to breast feed for at least 4 months Exclusion Criteria: those with chronic medical conditions, or taking dietary supplements other than vitamins, or smokers, or who had been pregnant >5 times	Start time: Lactating birth Duration: Lactating 4 months Arm 1: placebo Description: placebo capsule Manufacturer: Martek Biosciences Corporation, Columbia, MD Dose: 1 capsule Blinding: capsules were identical in appearance Arm 2: omega 3 capsule Description: algae-derived triglyceride capsule Brand name: DHASCO Manufacturer: Martek Biosciences Corporation, Columbia, MD Dose: 1 capsule DHA: 200 mg	Outcome: Beck Depression Inventory (BDI) (Unspecified) Follow-up time: 2 months Arm 1: Sample size 45; mean 4.4; SD (4.2) Arm 2: Sample size 44; mean 5.5; SD (4.3) Follow-up time: 3 weeks Arm 1: Sample size 45; mean 6.3; SD (4.7) Arm 2: Sample size 44; mean 7.1; SD (5.7) Follow-up time: 4 months Arm 1: Sample size 45; mean 4.8; SD (5.9) Arm 2: Sample size 44; mean 5.8; SD (5.2) Outcome: Edinburgh Postnatal Depression Scale (EPDS) (Unspecified) Follow-up time: 18 months Arm 1: Sample size 32; mean 6.3; SD (4.1) Arm 2: Sample size 31; mean 6.3; SD (5.2) Outcome: responder: BDI<10 (Unspecified) Follow-up time: at either 2, 4 or 18 months Arm 1: 36/45 (79.0%) Arm 2: 33/44 (76.0%) Outcome: responder: BDI<20 (Unspecified) Follow-up time: at either 2, 4 or 18 months Arm 1: 43/45 (95.5%) Arm 2: 40/44 (91.1%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Makrides et al., 2010[35] Study name: DOMInO Study dates: 2005-2008 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Manufacturer supplied product Original, same study, or follow-up studies: Smithers, 2011[53]; Palmer, 2012[54]; Zhou, 2012[55]; Palmer, 2013[56]; Makrides, 2014 [57]	Study Population: Healthy pregnant women Pregnant enrolled 2399 Pregnant withdrawals 1 Infants enrolled 605 Infants withdrawals 32 Infants completers 726 Pregnant age: 28.9 (DHA5.7___ control5.6) Race of Mother: NR (NR)	Inclusion Criteria: with singleton pregnancies at less than 21 weeks' gestation were approached by study research assistants while attending routine antenatal appointments Exclusion Criteria: already taking a prenatal supplement with DHA, their fetus had a known major abnormality, they had a bleeding disorder in which tuna oil was contraindicated, were taking anticoagulant therapy, had a documented history of drug or alcohol abuse, were participating in another fatty acid trial, were unable to give written informed consent, or if English was not the main language spoken at home	Start time: Pregnant < 21 week's gestation Duration: NR Arm 1: vegetable oil capsules Description: a blend of 3 nongenetically modified oils (rapeseed, sunflower, and palm) in equal proportions Manufacturer: Efamol, Surrey, England. Dose: 3* 500mg capsule / day Blinding: All capsules were similar in size, shape, and color Arm 2: DHA Description: DHA-rich fish oil concentrate Manufacturer: ; Incromega 500 TG, Croda Chemicals, East Yorkshire, England Dose: 500mg capsule *3/day DHA: 800mg EPA: 100mg	Outcome: % with Edinburgh Postnatal Depression Scale (EPDS) > 12 (Primary) Follow-up time: 6 months Arm 1: 138/1202 (11.5%) Arm 2: 117/1197 (9.74%) Follow-up time: 6 weeks Arm 1: 131/1202 (10.88%) Arm 2: 115/1197 (9.61%)
Mozurkewich et al., 2013[42] Study name: NR Study dates: Oct 2008 - May 2011 Study design: Trial randomized parallel Location: US Funding source / conflict: Government,	Study Population: Healthy pregnant women Pregnant enrolled 126 Pregnant withdrawals 8 Pregnant completers 118 Pregnant age: EPA 29.9; DHA 30.6; placebo 30.4 (EPA 5.0; DHA 4.5; placebo 5.9) Race of Mother: White European (85%; 76%; 83%) Black (10%; 11%;	Inclusion Criteria: past history of depression, an EPDS score 9-19 (at risk for depression or mildly depressed), singleton gestation, a maternal age of 18 years or older, and a gestational age of 12-20 weeks Exclusion Criteria: had a history of a bleeding disorder, thrombophilia requiring anticoagulation, multiple gestation, bipolar	Start time: Pregnant 12-20 week gestation Duration: Pregnant assuming till birth Arm 1: Control/Placebo Description: 98% soy oil and 1% each of lemon and fish oil Manufacturer: Nordic Naturals Corporation in Watsonville, CA Viability: centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose: 2 large and 4 small placebo capsules Blinding: The placebos were formulated to be identical in appearance to both the EPA- and DHA-rich supplements	Outcome: Beck Depression Inventory (BDI) (Primary) Follow-up time: 26-28 weeks Arm 1: Sample size 41; mean 6.3; SD (3.9) Arm 2: Sample size 39; mean 8.7; SD (4.2) Arm 3: Sample size 38; mean 7.0; SD (4.6) Follow-up time: 34-36 weeks Arm 1: Sample size 41; mean 7.4; SD (5.5) Arm 2: Sample size 39; mean 8.2; SD (5.7) Arm 3: Sample size 38; mean 6.9; SD (6.3) Follow-up time: 6-8 weeks post-partum Arm 1: Sample size 41; mean 5.9; SD (6.1) Arm 2: Sample size 39; mean 6.6; SD (5.2) Arm 3: Sample size 38; mean 5.7; SD (4.8)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Manufacturer supplied product	5%) Asian (3%; 3%; 2%) Hispanic (0%; 11%; 7%) Inuit Eskimo (0%; 0%; 2%) Pacific Islander (NR) Baseline biomarker information: EPA group: EPA 0.29+-0.18; DHA 4.24+-2.30; total n3 FA: 22.10+-3.72 DHA group: EPA 0.31+-0.24; DHA 4.66+-2.29; total n3 FA 36.41+-9.71 placebo: EPA .34+-0.22; DHA 3.85+-1.77; omega3 fa 322.86+-5.02	disorder, current major depressive disorder, current substance abuse, lifetime substance dependence, or schizophrenia. Women were also ineligible if they were currently taking omega-3 fatty acid supplements or antidepressant medications or eating more than 2 fish meals per week.	Arm 2: EPA-rich fish oil Description: an approximate 4:1 ratio of EPA to DHA (1060 mg EPA plus 274 mg DHA) Brand name: ProEPAXtra, Nordic Naturals Viability: centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose: 2 large EPA capsule and 4 small placebo DHA: 274 mg EPA: 1060 mg Arm 3: DHA-rich fish oil Description: DHA and EPA in an approximate 4:1 ratio o (900 mg DHA plus 180 mg EPA) Brand name: ProDHA, Nordic Naturals Viability: centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose: 2 large placebo oil and 4 small DHA rich DHA: 900 mg EPA: 180 mg	

Table 11. Observational studies for ante postnatal depression

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Chong, et al., 2015[95] Outcome domain: Depression Study dates: 2009-2010 Study design: Observational prospective Location: NR Funding source / conflict: Industry, Government Follow-up: 3 months postpartum	Study Population: Healthy pregnant women Postpartum women Pregnant enrolled 997 Pregnant completers 698 Pregnant age: NR (NR) Race of Mother: Asian (100)	Inclusion Criteria: Within range of 18-50 years, recruited from 2 major public maternity units in NUH and KKH. Were Singaporean citizens or permanent resident of Chinese, Malay, Indian ethnicity with parents of homogeneous ethnic background, with the intention to deliver in the two hospitals and residing in Singapore for next 5 years and willing to donate birth tissues including cord, placenta, cord blood at delivery Exclusion Criteria: pre-existing health conditions such as type 1 diabetes, depression, or mental health related disorders self-reported during recruitment	Adjustments: Adjusted for ethnicity, parity, education level, marital status, maternal body mass index at 26-28 week's gestation, maternal age, employment status, obstetric and neonatal complications, smoking status and smoke exposure before and during pregnancy, alcohol consumption before and during pregnancy, history of abortion, miscarriage, stillbirth, exercise frequency, and reported fish oil supplementation
Leung, et al., 2013[94] Outcome domain: Depression Study name: Alberta Pregnancy Outcomes and Nutrition (APrON) study Study dates: %n Study design: Observational prospective Location: Canada Funding source / conflict: NR	Study Population: Healthy pregnant women Pregnant enrolled 600 Pregnant withdrawals 125 Pregnant completers 475 Pregnant age: 31.2 not depressed 31.6 depressed (4.16 not depressed 4.7 depressed) not reported Race of Mother: White European (87%) Other race/ethnicity (13%)	Inclusion Criteria: at least 16 years old with gestational age =27 weeks. Women must be in the first (T1) or second (T2) trimester Exclusion Criteria: Any woman who was 28 weeks or beyond, Non-English speakers, known drug and alcohol abusers, and those planning to move out of the region within 6 months	Adjustments: Born in Canada, prenatal and postnatal social support, prenatal EPDS, selenium
Parker, et al., 2015[97] Outcome domain: Depression Study dates: NR Study design: Observational prospective Location: Australia Funding source / conflict: Government	Study Population: Healthy pregnant women Postpartum women Pregnant enrolled 1232 Pregnant completers 831 Pregnant age: 31.0 (5.7) Race of Mother: NR (100)	Inclusion Criteria: Women between 34 and37 weeks of pregnancy and attending an obstetric service. Participants had to be more than 18 years of age, be proficient in English and able to provide informed consent Exclusion Criteria: nr	Adjustments: Age, education level, income level, marital status, number of children, neuroticism scores, the presence or absence of a lifetime mood disorder, coffee drinking, cigarette smoking and alcohol intake, as well as stress levels during pregnancy
Sallis, et al., 2014[96] Outcome domain: Depression	Study Population: Healthy pregnant women Pregnant enrolled 14,541 Pregnant withdrawals	Inclusion Criteria: All women with an expected due date between April 1991 and December 1992 were eligible for the study. Only women with data	Adjustments: Social class (I/II, III or IV/V) and maternal age

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Study name: Avon Longitudinal Study of Parents and Children (ALSPAC) Study dates: 1991-1992 Study design: Observational prospective Location: NR Funding source / conflict: Industry, Government	11,144 Pregnant completers 3,397 Pregnant age: 28.9 (4.5) not reported Race of Mother: White European (100%)	available on genotype, FA levels and depressive symptoms during pregnancy or at 8 weeks postnatally and women with a self-reported ethnicity of White European were included in this analysis. Exclusion Criteria: Mothers who lost a child during the neonatal period and those with a still birth; mothers with multiple births.	
Strom, et al., 2009[92] Outcome domain: Depression Study name: Danish National Birth Cohort Study dates: 1996-2002 Study design: Observational prospective Location: Denmark Funding source / conflict: Government, Multiple foundations and Societies, Funding Affiliations trade group, March of Dimes	Study Population: Healthy pregnant women Pregnant enrolled 86,453 Pregnant withdrawals 32,251 Pregnant completers 54,202 Pregnant age: not reported (not reported) not reported Race of Mother: NR (100%)	Inclusion Criteria: All pregnant women living in Denmark between 1996 and 2002, who were fluent in Danish Exclusion Criteria: NR	Adjustments: Total energy intake, prepregnant BMI, maternal age, parity, alcohol intake, smoking, occupation, education, homeownership, marital status, social support, and history of previous depression
Yoshihiro Miyake, et al., 2006[93] Outcome domain: Depression Study name: Osaka maternal and child health study Study dates: 2001-2003 Study design: Observational prospective Location: Japan Funding source / conflict: Government, Multiple foundations and Societies, None	Study Population: Healthy pregnant women Pregnant enrolled 1002 Pregnant withdrawals 137 Pregnant completers 865 Pregnant age: age reported in categories Race of Mother: Asian (100%)	Inclusion Criteria: women who became pregnant in Neyagawa City, Osaka Prefecture, Japan Exclusion Criteria: NR	Adjustments: Age, gestation, parity, cigarette smoking, family structure, family income, education, changes in diet in the previous month, season when data at baseline were collected, body mass index, time of delivery before the second survey, medical problems in pregnancy, baby's sex and baby's birth weight

Key Question 2: Fetal/Childhood Exposures

What is the influence of maternal intakes of n-3 fatty acids or the n-3 fatty acid content of maternal breast milk (with or without knowledge of maternal intake of n-3 FA) or n-3 FA-supplemented infant formula or intakes of n-3 FA from sources other than maternal breast milk or supplemented infant formula on the following outcomes in term or preterm human infants?

- Postnatal Growth patterns
- Neurological development
- Visual function
- Cognitive development
- **Autism**
- **Learning disorders**
- **ADHD**
- **Atopic dermatitis**
- **Allergies**
- **Respiratory illness**

What are the associations of the n-3 FA content or the n-6/n-3 FA ratio of maternal or fetal or child biomarkers with each of the outcomes identified above?

Postnatal Growth Patterns

Key Findings and Strength of Evidence

- There is moderate evidence that prenatal maternal supplementation of fish oil or DHA+EPA supplements has no effect on weight, length, or head circumference at 18 months. Pooled analysis of 5 RCTs shows null effects for weight (0.22, 95% CI [-0.62, 0.19]), length (0.01 [-0.52, 0.54]), and head circumference (-0.01 [-0.28, 0.27]).
- There is low evidence that prenatal maternal supplementation of fish oil or DHA+EPA supplements continuing postpartum has no effect on growth outcomes.
- There is low evidence that supplementation of DHA+AA formula in preterm infants has no effect on overall weight and length. Pooled analysis of three studies showed null effects for weight at 4 months (-0.01 [-0.48, 0.47]) and length at 4 months (-0.03 [-0.91, 0.85]).
- There is low evidence that supplementation of DHA+AA formula in term infants has no effect on growth outcomes.
- There is low evidence from three observational studies that biomarkers associated with n-3s in infant red blood cells are consistently associated with increased weight gain, length gain, and BMI at 7 years.
- There is insufficient evidence to determine whether prenatal and postnatal maternal supplementation with DHA+AA has an effect on growth outcomes.

- There is insufficient evidence to determine whether postnatal maternal supplementation with DHA+EPA has an effect on growth outcomes.
- There is insufficient evidence to determine whether prenatal maternal supplementation in combination with postnatal infant supplementation with DHA+EPA has an effect on growth outcomes.
- There is insufficient evidence to determine whether supplementation of preterm infants with DHA+AA+EPA has an effect on growth outcomes.

Description of Included Studies

The original review included 42 RCTs and two observational studies for the outcomes of postnatal growth patterns, including one RCT that assessed the effects of prenatal maternal intake of n-3 FAs during pregnancy in term and preterm infants; one RCT and one cohort study on n-3 FA content of breast milk with or without known maternal intake in term infants only (no studies assessed the effects of n-3 FA intake by breastfeeding mothers on growth patterns of preterm infants); 20 RCTs on postnatal n-3 FA supplementation in preterm infants; 18 RCTs on postnatal n-3 FA supplementation in term infants; five RCTs that also assessed associations of n-3 FA biomarkers with growth patterns of preterm infants; five RCTs and a prospective cohort study that assessed associations of n-3 FA biomarkers with postnatal growth patterns in term infants; and one RCT that assessed the associations of n-3 FA biomarkers with postnatal growth patterns in very low birth weight (VLBW) term and preterm infants.

The present review identified 24 additional RCTs and three observational studies that included pediatric growth pattern outcomes. Three of the RCTs also included associations of growth patterns with biomarkers of n-3 FA. Of these, seven RCTs and two observational studies evaluated prenatal maternal n-3 FA interventions or exposures, four RCTs examined a combination of prenatal and postnatal maternal n-3 FA interventions or exposures, and one RCT and one observational study examined postnatal maternal n-3 FA interventions or exposures. Nine RCTs examined postnatal infant n-3 FA interventions or exposures, and two RCTs examined a mixed set of postnatal maternal and postnatal infant n-3 FA interventions or exposures. Six RCTs that assessed the effects of n-3 FA supplementation in infants on growth patterns were conducted among healthy infants or infants born to healthy women, while four RCTs were conducted among preterm or low birth weight infants.

Prenatal Maternal Interventions/Exposures

In the original review, one good quality RCT found no difference in weight, length, and head circumference from birth to 12 months between infants (590 enrolled, 341 completers) born to mothers who used n-3 FA and n-6 FA supplements or predominantly n-6 FA supplements during pregnancy.

Randomized Controlled Trials

DHA+EPA

The present review identified seven studies of prenatal maternal DHA, DHA+EPA, fish oil, or algal oil supplementation[34, 41, 44, 60, 75, 77, 100] and four studies of prenatal and postnatal maternal DHA, DHA+EPA, or fish oil supplementation (see Table 12).[37, 52, 66, 76]

Dunstan (2008) assessed the effects of prenatal supplementation with 4 g fish oil capsules daily compared to olive oil in 72 pregnant Australian women with allergies starting at 20 weeks of gestation until delivery, but found no differences in infant weight, length, or head circumference at 30 months.[44]

Bergmann and coworkers (2007) compared the effects of a vitamin and mineral supplement, the supplement plus a prebiotic, and the supplement plus prebiotic and DHA (0.200 g/d) on the offspring of 144 healthy pregnant women in Germany, supplemented from the 21st to 37th weeks of pregnancy. The authors report that mothers whose supplements included DHA had infants that were not significantly different from the control infants at 1 or 3 months for BMI, weight, length, or head circumference, but BMI (-0.76, 955 CI -1.46, -0.07) and weight (kg) (-0.601, 95% CI -1.46, -0.07) for infants taking DHA were actually less than in control infants at 21 months, although length and head circumference were not significantly different.[41]

Stein and coworkers (2011) randomized 1,094 pregnant Mexican women in weeks 18-22 of gestation to daily olive oil capsules or 0.200 g/d DHA through term.[34] Data from the 739 infants followed up at 18 months indicated no overall effects on weight, length, BMI, or head circumference, although infants born to primigravid women (women pregnant for the first time) supplemented with DHA were significantly longer by 0.7 cm (95% CI 0.1, 1.3; P = 0.02).

Another study in Mexico by Gonzalez-Casanova et al. (2015) randomized 1,040 pregnant women to daily supplementation of 400 mg DHA from an algal source or soy/corn placebo from 18-22 weeks gestation until delivery. No effect on attained size (weight, height, BMI, or any of the "for-age" z-scores for these metrics) was observed at five years.[60]

Similarly, Malcolm and coworkers (2003) randomized 100 pregnant women from 15 weeks gestation until birth to receive either sunflower oil or fish oil (DHA 0.200 g/d) and found no differences in weight, length, or head circumference between the groups at 50 or 66 weeks.[100]

Tofail et al. (2006) compared supplementation of 249 pregnant women in Bangladesh with DHA (1.2 g) and EPA (1.8 g) daily from 25 weeks until delivery with that of soy oil alone, and found no differences in head circumference at 10 months.[77]

A recent study by Mulder et al. (2014) compared 270 subjects supplemented with 400 mg/day DHA or placebo capsules from less than 16 weeks gestation until delivery. No significant differences in weight-for-length, length-for-age, or weight-for-age Z-scores were observed at 2, 6, 9, 12, or 18 months by ANOVA ($P \geq 0.05$).[75]

Van Goor and colleagues (2011) randomized pregnant Dutch women in the 14th-20th weeks of pregnancy to soybean oil capsules with (n=41) or without (n=34) DHA (0.220 g/d) until 3 months after delivery; again, no significant differences with regard to weight, length, or head circumference were found at 18 months.[66]

Bergmann et al. (2012) enrolled 144 pregnant women in a study comparing a basic supplement (vitamins and minerals only) to a basic supplement with fructooligosaccharide prebiotic, to the basic prebiotic supplement with fish oil (200 mg DHA and 60 mg EPA) from 21 weeks gestation until 3 months after delivery. While the weight, length, BMI, head circumference, and skin-fold thickness at 6 years were similar among the DHA+EPA-supplemented and control groups at 6 years, the BMI z-scores increased at a later age in the DHA+EPA group. There was a negative correlation between height at 6 years and the increase in red blood cell DHA concentration of mothers from 22 to 37 weeks of pregnancy (p=0.007).[52]

We identified a long-term (7-year) follow-up of a study conducted in Norway that was discussed in the original report. In this study, pregnant women were randomized at 18 weeks gestation to receive 10 mL cod liver oil daily (1.183 g/10 mL DHA, 0.803 g/10 mL EPA, and a total of 2.494 g/10 mL *n*-3 PUFAs) or 10 mL corn oil (4.747 g/10 mL LA and 0.092 g/10 mL ALA) through 3 months postpartum. This study found no significant differences in weight, height, or BMI at 7 years.[76]

A study by Hauner et al. (2012) compared the effect of fish oil supplements (DHA 1.020 g/d and EPA 0.180 g/d) and nutritional counseling to that of nutritional counseling alone in German women from 15 weeks gestation to four months postpartum.[37] No differences were seen between treatments in weight, length, BMI, or head circumference at 6 weeks, 4 months, or 12 months.

Pooling the results of four RCTs,[34, 41, 66, 100] on the effects of DHA given to pregnant women compared to placebo on weight, length, and head circumference at 18 months showed no statistically significant effects (WMD [95% CI] in weight (kg): -0.22, [-0.62, 0.19], I^2=52%; WMD [95% CI]in length (cm): 0.01 [-0.52, 0.54]], I^2=0%; WMD [95% CI]in head circumference (cm): -0.01, [-0.28, 0.27], I^2=0%. These studies are further summarized in Table 11 and the forest plots are shown in Figures 11, 12, and 13.

Figure 11. Weight (kg) at 18 months – DHA versus placebo, given to pregnant women

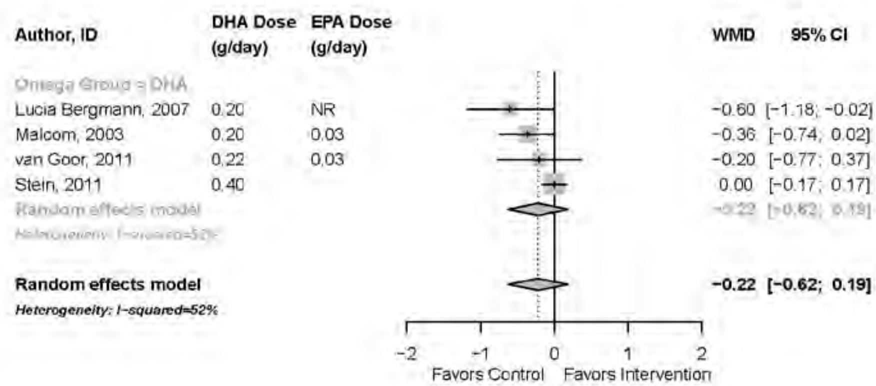


Figure 12. Length (cm) at 18 months – DHA versus placebo, given to pregnant women

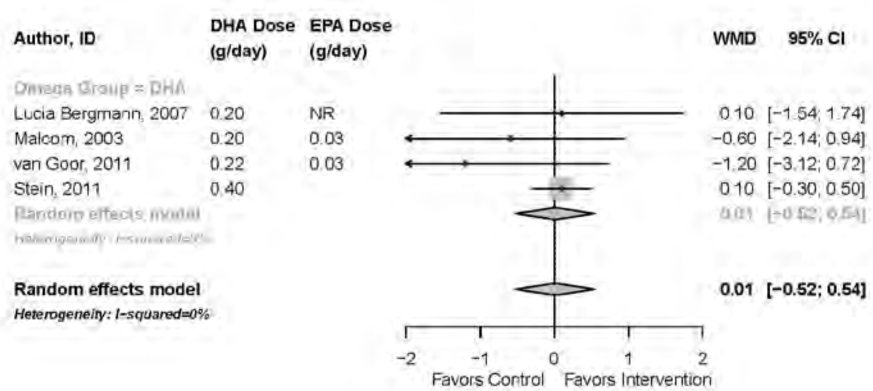
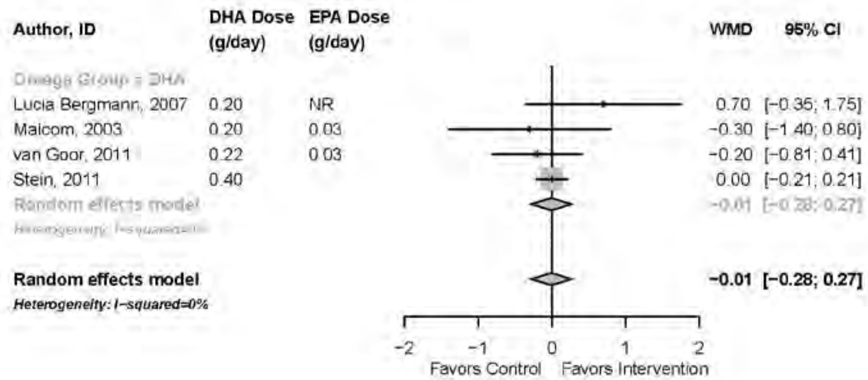


Figure 13. Head circumference (cm) at 18 months – DHA vs. placebo, given to pregnant women



DHA+AA

Only one study was identified that compared the effects on postnatal growth patterns of administering supplemental DHA+AA to pregnant women with that of placebo. Van Goor (2011) randomized pregnant Dutch women in the 14^{th}-20^{th} weeks of pregnancy to soybean oil capsules with (n=39) or without DHA+AA (0.220 g/d) (n=34) until 3 months after delivery. Again, no significant differences with regard to weight, length, or head circumference were found at 18 months.[66]

Observational Studies

The outcomes of the INFAT study[101] were used to assess the association of n-3 FAs in breast milk (in 208 women who had been following their usual diet or supplementing their usual diet with 1.200 g/d LCPUFAs) Negative associations were observed between length at one year and both DHA and n-3 LCPUFA in breast milk ($p<0.05$); no other significant associations were observed between breast milk FA concentrations and weight, length, BMI, or head circumference outcomes.

Another analysis of data from the INFAT study[83] found no significant growth outcome associations of LCPUFA content of maternal red blood cells at 32 weeks gestation with weight, length, BMI, or head circumference at 6 weeks, 4 months, or one year (see Table 13).

Postnatal Maternal Interventions/Exposures

The original review identified one good quality RCT, one poor quality RCT, and an observational study on the effect of maternal supplementation of n-3 FA after delivery on postnatal growth patterns. Neither RCT showed effects of maternal intake of n-3 FA or n-6 FA on growth patterns at any time point. The observational study showed a positive correlation between the breast milk AA/DHA content and the infant's rate of increase in head circumference at 1 and 3 months.

Randomized Controlled Trials

DHA+EPA

Only one RCT on the effect of postnatal maternal interventions on growth patterns was identified for the current report. Lauritzen and colleagues (2005) randomized Danish breastfeeding women less than 2 weeks postpartum to olive oil or fish oil in the form of capsules, musli bars, and/or cookies, providing either 0.62 g/d EPA and 0.79 g/d DHA or 0.36 g/d EPA and 0.99 g/d DHA daily, depending on the dosage form. Of the 100 children completing the trial, 72 were followed up to 2.5 years. While growth in weight, length, and head circumference did not differ between the randomized groups up to 9 months, children in the fish oil group had larger BMI (p = 0.022), and head circumference (p = 0.028) than those in the olive oil group at 2.5 years ([102]).

Observational studies

The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study enrolled 244 mothers in the Netherlands. Concentrations by weight of total LCPUFAs, DHA, EPA, or ALA in breast milk samples provided by the mothers showed no significant associations with mean gain in weight, length, or BMI in the first year of life.[103]

Combination of Postnatal Maternal and Preterm Infant Interventions/Exposures

The original review did not describe any interventions that combined both maternal and infant exposures.

Randomized Controlled Trials

DHA+EPA

The DINO study was an Australian RCT[104, 105] that investigated the effect of both n-3 FA tuna oil supplements for lactating mothers of preterm (<33 weeks gestation) infants and formula supplemented with and without DHA from 2-5 days after delivery through the estimated due date (n=657). DHA supplementation had no observable effects on weight or head circumference at 4,12, and 17 months, but DHA-supplemented infants were 0.7 cm (95% CI 0.1, 1.4 cm; P=0·02) longer in length at 18 months corrected age. An interaction effect was observed between DHA supplementation and birth weight strata for weight (P=0.01) and length (P=0.04). Infants who weighed ≥1250 g at birth and received supplemental DHA had greater length at 4 months corrected age and greater weight and length at 12 and 18 months corrected age.

Observational Studies

No observational studies were identified with both maternal and preterm infant exposures.

Preterm Infant Interventions/Exposures

The original review identified 20 RCTs, all of poor quality, that studied the effects of n-3 FA supplementation of preterm infants on postnatal growth patterns. Eighteen of the 20 studies found no effect on growth parameters at any time point. Two trials found that the n-3 FA-supplemented group actually had significantly lower weight at 6-18 months than the placebo-supplemented group. A meta-analysis in the original review of studies comparing formula with DHA+AA and control formula on mean weight and length at 4 months showed no significant effect (MWD for weight: -0.01, 95% CI -0.48, 0.47; MWD for length: -0.03, 95% CI -0.91, 0.86).

Randomized Controlled Trials

DHA+AA

Three studies examined differences in growth outcomes among preterm or VLBW infants supplemented with DHA and AA compared with controls.

Groh-Wargo compared 60 preterm infants in the U.S. given n-3 FA supplements (0.15%-0.24% DHA and 0.41% AA) to those given a placebo until one year corrected age. No significant differences were observed at any time point in weight, length, or head circumference. However, at 12 months corrected age, DHA+AA supplemented infants had significantly greater lean body mass ($p < 0.05$) and significantly less fat mass ($p < 0.05$) than the control infants.[106]

A study of 141 VLBW preterm infants in Norway supplemented with human milk with added oils containing DHA (6.9%) and AA (6.7%) from birth until discharge from the hospital (9 weeks on average) found no differences in growth outcomes between the groups at 6 months.[107]

A study by Clandinin and colleagues (2005) of 361 preterm infants in the U.S. also compared the effects of administering two different kinds of DHA sources (algal sources and fish oil, both 0.32-0.33%) with AA (0.64-0.67%) from fungal sources with that of a placebo until 92 weeks postmenstrual age. Since the results were shown only on a graph, they were not abstracted into the evidence tables. However, the algal-DHA group was significantly greater than the control group in terms of weight (66 to 118 weeks) and length (48, 79, and 92 weeks). The algal-DHA group also exceeded the fish-DHA group in weight at 118 weeks PMA and in length at 57, 79, and 92 weeks PMA. Mean head circumference did not differ between the DHA groups and control groups at any follow-up time.[108]

Results for the effects of DHA+AA compared to placebo on weight and length of preterm infants at 4 months were pooled[106] with the outcomes of two studies from the original report, but the pooled effect sizes were not statistically significant (WMD [95% CI] in weight (kg): -0.01[-0.48, 0.47] I^2=33.5%; WMD [95% CI]in length (cm): -0.03[-0.91, 0.85] I^2=0%. The summary if this study and the results are shown in Table 12 and Figures 14 and 15.

Figure 14. Weight (kg) at 4 months – DHA + AA versus placebo, given to preterm infants

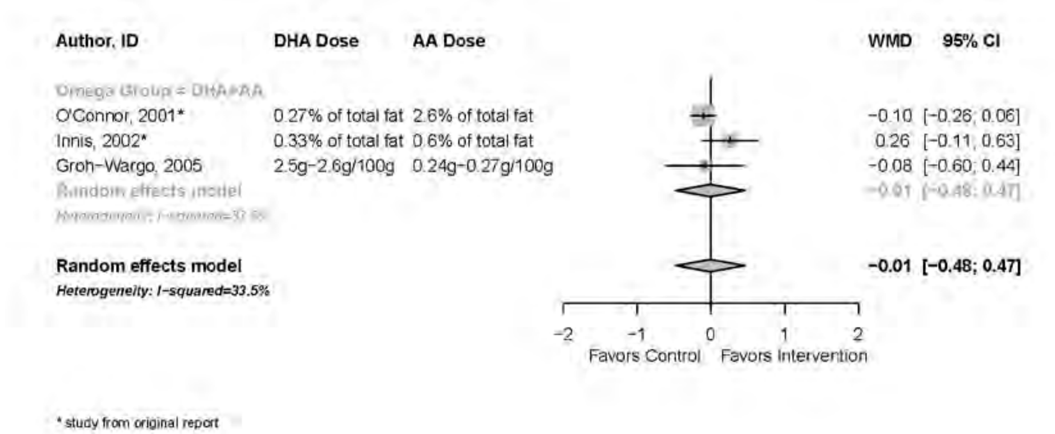
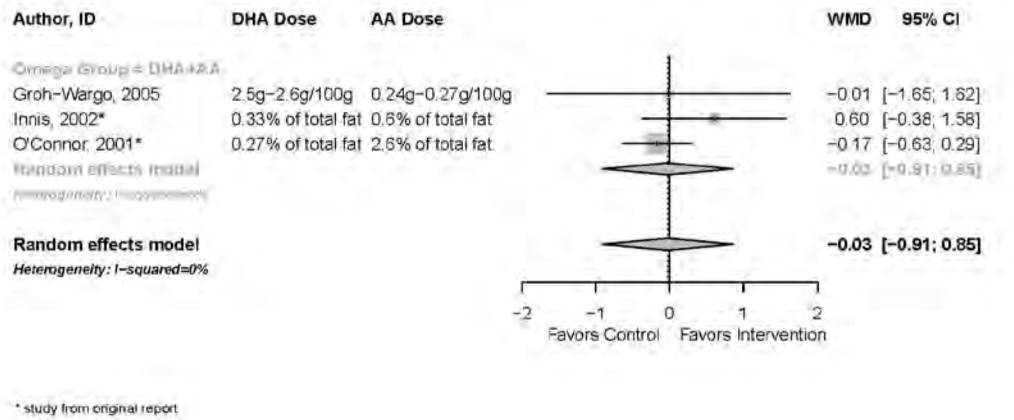


Figure 15. Length (cm) at 4 months – DHA + AA versus placebo, given to preterm infants



DHA+AA+EPA

Groh-Wargo compared the effects of n-3 FA supplements (0.16%-0.27% DHA, 0.43% AA, and 0.08% EPA) and placebo given to 60 U.S. preterm infants until one year corrected age. No significant differences were observed at any time point in weight, length, or head circumference (although at 12 months corrected age, DHA+AA+EPA-supplemented infants had significantly greater lean body mass ($p < 0.05$) and significantly less fat mass ($p < 0.05$) than the control infants).[106]

A study of 139 preterm infants in the Netherlands supplemented with either preterm formula (0.14% DHA, 0.14% AA, and 0.039% EPA), term formula (0.07% DHA and 0.07% AA), or human milk found no significant differences in weight, length, or head circumference at 3 and 6 months corrected age.[109]

Observational studies

No observational studies were identified for preterm infant exposures.

Term infant interventions/exposures

The original review identified 18 RCTs, all of good quality, that assessed the effect of n-3 FA supplementation in term infants on growth patterns. While the effects on growth patterns were not significantly different between study arms overall, certain time points and subgroups showed inconsistent differences. The meta-analysis showed a non-statistically significant overall effect of formulas containing DHA+AA at 4 months (MWD for weight: -0.06, 95% CI -0.45, 0.34; MWD for length: -0.33, 95% CI -1.07; 0.40) and 12 months (MWD for weight: -0.33, 95% CI -0.87, 0.21; mean weight difference for length: 0.37, 95% CI -1.26, 0.51; MWD for head circumference 0.14, 95% CI -0.83, 1.12). Similarly, formulas containing DHA showed a non-statistically significant overall effect at 4 months (MWD for weight: -0.12, 95% CI -0.44, 0.20, MWD for length: -0.43, 95% CI -1.20, 0.34; MWD for head circumference: 0.04, 95% CI -0.37, 0.46) and 12 months (MWD for weight: -0.33, 95% CI -0.87, 0.21; MWD for length: : -0.71, 95% CI -2.18, 0.76; MWD for head circumference -0.04, 95% CI -0.45, 0.38). Four trials adjusted results for confounders, but failed to find any difference in the results.

Randomized Controlled Trials

DHA+AA

The current review identified six RCTs that studied the effect of DHA+AA supplementation in term infants.

Sala-Vila et al. (2004) compared growth outcomes in 35 term infants in Spain supplemented with human milk (0.4 and 0.3 g/100 g total FA as AA and DHA) to growth outcomes of infants supplemented with n-3 FA from eggs and to growth outcomes of infants supplemented with n-3 FA from fungi and algae (both 0.4 and 0.1 g/100 g total FA as AA and DHA). After three months supplementation, no differences in weight, length, or head circumference were observed.[110]

Birch and colleagues (2005) randomized 103 term infants in the United States to DHA and AA (0.36% and 0.72% of total FA) from five days to 52 weeks. They observed no significant differences in weight, length, and head circumference at 6, 17, 39, or 52 weeks.[111] Since results were shown only graphically, they were not pooled.

Another study compared 30 term infants supplemented with term infant formula or a high DHA (0.20%) and AA (0.34%) formula for an unknown duration, commencing less than 14 days after birth. No significant differences were seen among either group at age 6 weeks or 2 years.[112]

The BeMIM (Belgrade-Munch Infant Milk) Trial [113] recruited and randomized 213 infants to term infant formula or to a high DHA (7.2g/100mL) and AA (7.2g/100mL) formula from younger than 1 month to 4 months of life. While the rates of change of head circumference and weight gain were not statistically different between formula groups (high DHA+AA formula: 30.2 ± 6.3 vs. control formula: 28.3 ± 6.5 g/day, mean ± SD, P = 0.06), rates of length gain were higher in the high DHA+AA group than in the term infant formula group (0.11 ± 0.02 vs. 0.10 ± 0.02 cm/day, P = 0.02).[114]

Currie and coauthors (2015) compared 54 healthy term infants in a trial of infant formula that combined three arms of DHA+AA (0.32% DHA and 0.64% AA, 0.64% DHA and 0.64% AA, and 0.64% DHA and 0.32% AA) and to a placebo group of 15 infants up to 6 years. DHA+AA supplementation in infancy predicted higher length from birth to 18 months (p=0.033) and higher weight (p=0.02) and stature-for-age (p=0.0007) percentiles from 2 to 6 years. No differences in BMI (p=0.38) or BMI-for-age (p=0.20) percentile from infancy to age six were observed.[115]

Observational studies

No observational studies were identified for term infant exposures.

Maternal and Infant Biomarkers

The original report included eleven studies on the relationship between n-3 FA biomarkers in children and growth patterns. Five were RCTs in preterm infants, five were RCTs in term infants, and one was a prospective cohort study of term infants. A negative correlation was seen between weight and the plasma or red blood cell content of DHA, and a positive correlation between weight and the content of AA in plasma or red blood cells was seen in some but not all studies. As biomarkers, n-6 FA (AA) may be related to infant weight gain, whereas DHA seems to be inversely related, but no significant clinical outcomes were detected.

The current report identified three additional studies with biomarker results related to growth patterns. A follow-up of studies on maternal n-3 FA supplementation during pregnancy and breastfeeding reviewed in the original report found no significant correlations between umbilical plasma phospholipid concentrations of LA, AA, ALA, DHA, or the ratio of n-3/n-6 fatty acids and the children's BMI at 7 years.[76] In addition, no significant correlations between umbilical plasma phospholipid concentrations of LA, AA, ALA, DHA, or the ratio of n-3/n-6 fatty acids at 4 weeks or 3 months and BMI at 7 years were found.

The DINO study[104]) in preterm (<33 weeks gestation) infants in Australia (n=657) found no consistent relations between erythrocyte phospholipid polyunsaturated fatty acids and weight, length, and head circumference at 4 months corrected age. Changes in RBC-DHA were positively associated with gain in weight ($p<0.001$) and length ($p<0.001$) and negatively associated with gain in head circumference ($p<0.05$) between term and 6 months corrected age.

A study of 139 preterm infants in the Netherlands supplemented with preterm formula, term formula, or human milk found that changes in RBC-AA were positively associated with gain in head circumference ($p<0.001$) and negatively associated with gain in weight ($p<0.001$) and length ($p<0.05$), while changes in RBC-DHA/AA ratios were positively associated with weight gain ($p<0.001$) and length gain ($p<0.001$) but negatively associated with increases in head circumference ($p<0.001$) between term and six months corrected age. Changes in RBC-EPA showed no associations with gain in weight, length, or head circumference between term and six months corrected age.[109]

Table 12. RCTs for postnatal growth patterns

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Bergmann et al., 2012[52] Study name: NR Study dates: 2000-2009 Study design: Trial randomized parallel Location: Germany Funding source / conflict: NR, None, Manufacturer supplied product Study follow-up: 6 years Original, same study, or follow-up studies: Bergmann, 2012[41]	Study Population: Healthy infants Pregnant enrolled 144 Pregnant completers 115 Infants enrolled 123 Infants completers 115 Pregnant age: 30.9 years (4.89) Infant age: 21 weeks gestation Race of Mother: White European (100) Baseline biomarker information: In previous study, see Bergmann, 2012 [41]	Inclusion Criteria: Healthy pregnant Caucasian women who were at least 18 years and willing to breastfeed for at least 3 months were enrolled at 21 weeks of gestation Exclusion Criteria: Mothers: increased risk of premature delivery or multiple pregnancy, allergy to cow milk protein, lactose intolerance, diabetes, smoking, consumption of alcohol (>20 g/week), or participation in another study Infants: Premature at birth (<37 weeks' gestation), had any major malformations, or were hospitalized for more than one week	Start time: Pregnant 21 weeks gestation Duration: Pregnant 21 weeks until 3 months after delivery Arm 1: Vitamins and minerals ("basic") Description: Control 1 Manufacturer: Nestle Arm 2: Basic supplements plus a prebiotic fructooligosaccharide (FOS) Description: Control 2 Manufacturer: Nestle Arm 3: Basic supplements, FOS, and fish oil Description: Intervention Manufacturer: Nestle DHA: 200 mg EPA: 60 mg	Outcome: BMI (kg/m2) (Secondary) Follow-up time: 6 yrs Arm 1: Sample size 74; mean 15.5; SD (1.3) Arm 2: Sample size 41; mean 15.7; SD (1.5) Outcome: head circumference (cm) (Secondary) Follow-up time: 6 yrs Arm 1: Sample size 74; mean 52.7; SD (1.3) Arm 2: Sample size 41; mean 52.5; SD (1.6) Outcome: height (cm) (Secondary) Follow-up time: 6 yrs Arm 1: Sample size 74; mean 119.6; SD (4.6) Arm 2: Sample size 41; mean 119.2; SD (5.3) Outcome: weight (kg) (Secondary) Follow-up time: 6 yrs Arm 1: Sample size 74; mean 22.3; SD (2.9) Arm 2: Sample size 41; mean 22.4; SD (3.1)
Birch et al., 2005[111] Study name: NR Study dates: Not reported Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product	Study Population: Healthy infants Infants enrolled 103 Infants completers 86 Pregnant age: 31 years (4 years) Infant age: 3.6 _x0004_days (1.3 days) 1-5 days Race of Mother: NR	Inclusion Criteria: All were born at 37– 40 wk after conception. Only singleton births with birth weight appropriate for gestational age Exclusion Criteria: Family history of milk protein allergy, genetic or familial eye disease, vegetarian or vegan maternal dietary patterns, maternal metabolic disease or infection, jaundice, perinatal asphyxia,	Start time: Infants 1-5 days Duration: Infants 52 wks Arm 1: Control Description: Commercial infant formula Brand name: Enfamil with Iron Manufacturer: Mead Johnson Nutritionals, Evansville, IN Active ingredients: Linoleic acid-8.48g/L (14.6%); 14.7 g protein/L, 37.5 g fat/L, 69.0 g carbohydrate/L Blinding: Each diet was masked by 2 color and 2 number codes, for a total of 4 possible diet assignments. The randomization schedule had random-length blocks (block length varied from 6 to 12) and was provided in individual sealed envelopes	data only reported on graph Outcome: (Secondary)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		meconium aspiration, or any perinatal event that resulted in placement of the infant in the neonatal intensive care unit.	to the study site. ALA: 1.5% of total fatty acids Arm 2: LCPUFA-supplemented formula Description: Commercial formula supplemented with LCPUFA Brand name: Enfamil with Iron plus DHASCO and ARASCO Manufacturer: Formula: Mead Johnson; DHA+ARA: Martek Biosciences Active ingredients: 15% linoleic acid,14.7 g /L protein, 37.5 g /L fat, 69.0 g /L carbohydrate ALA: 1.5% of total fatty acids DHA: 0.36% of total fatty acids AA: 0.72% of total fatty acids	
Clandinin et al., 2005[108] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: Canada Funding source / conflict: Industry	Study Population: Preterm infants Infants enrolled 361 preterm+105 term breastfed Infants completers 179 preterm and 76/105 term breastfed Infant age: 30.6 weeks postmenstrual age 24-36 weeks postmenstrual age Race of Mother: NR (100)	Inclusion Criteria: Phase I: gestational age <35 weeks PMA and received <10 total days of enteral feedings of >30 mL/kg per day. Infants initially fed human milk were not enrolled unless formula was started within 10 days after completing the first day of human milk feeding Phase II: completion of phase I and >=80% enteral intake from study formula during hospitalization and 100% of caloric intake from study formula at completion of phase 1. Birth weight<1500g Exclusion Criteria: congenital abnormalities of the gastrointestinal tract, hepatitis, hepatic or biliary pathology, necrotizing enterocolitis confirmed before	Start time: Infants 10 days of age Duration: Infants 118 weeks Arm 1: Control Description: Non-supplemented premature, discharge, and term formula Dose: Ad lib Blinding: Not reported Infant conditions Pre-term birth 119 (100%) Arm 2: Algal-DHA Description: supplemented premature infant formula supplemented with DHA from algal oil Manufacturer: Martek Biosciences Dose: ad lib DHA: 17mg/100kcal (0.33% by weight) EPA: 0.1% by weight AA: 34mg/100kcal (0.67% by weight) Arm 3: Fish-DHA Description: Premature infant formula supplemented with DHA from tuna fish oil Manufacturer: Martek Biosciences Dose: ad lib DHA: 17mg DHA/100 kcal AA: 34mg/100 kcal	data only reported on graph Outcome: (Unspecified)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		enrollment, or history of underlying disease or congenital malformation likely to interfere with evaluation	Arm 4: Reference Description: Breast fed term infants	
Collins et al., 2011[105] Study name: DINO Study dates: 2001-2007 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Manufacturer supplied product Study follow-up: 18 months Original, same study, or follow-up studies: Smithers, 2008[104]; Makrides, 2009[116]; Smithers, 2010[117]; Manley, 2011[118]; Atwell, 2013[119]; Collins, 2015[120]	Study Population: Preterm infants Postpartum women Breast-feeding women Pregnant enrolled 545 Infants enrolled 657 Infants completers 598 Pregnant age: high DHA group 29.9; standard DHA group 30.2 (high DHA group 5.8; standard DHA group 5.4) Infant age: 4 day high DHA 3-6; standard 2-5 Race of Mother: NR (100)	Inclusion Criteria: infant born <33 weeks gestation Exclusion Criteria: Infants were excluded if they had major congenital or chromosomal abnormalities; were a multiple birth where not all live births were eligible; were in other trials of fatty acid supplementation or had a lactating mother where tuna oil was contraindicated (bleeding disorders, anticoagulants).	Start time: Infants birth Duration: NR Arm 1: standard DHA Description: placebo soya oil capsules for lactating women and/or standard pre-term formula Manufacturer: Capsule: Clover Corporation; Formula: Mead Johnson Nutritionals and Nutricia Australasia Dose: 6*500mg placebo soya oil capsules Blinding: All capsules were similar in size, shape and color. Formula was packaged by color code. Parents, clinicians and all research personnel were blinded to the participant's study group Arm 2: High DHA Description: tuna oil capsules or DHA pre-term formula Manufacturer: Capsule: Clover Corporation; Formula: Mead Johnson Nutritionals and Nutricia Australasia Dose: six 500 mg DHA-rich tuna oil capsules per day	Outcome: head circumference (cm) (Secondary) Follow-up time: 12 months Arm 1: Sample size 231; mean 46.2; SD (1.8) Arm 2: Sample size 225; mean 46.1; SD (1.8) Follow-up time: 18 months Arm 1: Sample size 305; mean 47.8; SD (1.7) Arm 2: Sample size 282; mean 47.8; SD (1.8) Follow-up time: 4 months Arm 1: Sample size 312; mean 41.8; SD (1.7) Arm 2: Sample size 289; mean 41.6; SD (1.7) Outcome: length (cm) (Secondary) Follow-up time: 12 months Arm 1: Sample size 239; mean 74.1; SD (3.7) Arm 2: Sample size 226; mean 74.3; SD (3.6) Follow-up time: 18 months Arm 1: Sample size 306; mean 81.2; SD (3.9) Arm 2: Sample size 286; mean 81.9; SD (4) Follow-up time: 4 months Arm 1: Sample size 311; mean 61.2; SD (3.4) Arm 2: Sample size 294; mean 61.3; SD (3.2) Outcome: weight (g) (Secondary) Follow-up time: 12 months Arm 1: Sample size 240; mean 9195.0; SD (1410) Arm 2: Sample size 231; mean 9317.0; SD (1455)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Follow-up time: 18 months Arm 1: Sample size 306; mean 10775.; SD (1520) Arm 2: Sample size 292; mean 11029.; SD (1764) Follow-up time: 4 months Arm 1: Sample size 316; mean 6203.0; SD (1059) Arm 2: Sample size 299; mean 6218.0; SD (1013)
Currie et al., 2015[115] Study name: Diamond Study dates: 2003-2011 Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Government, Manufacturer supplied product Study follow-up: 6 years Original, same study, or follow-up studies: Birch, 2010[121]; Drover, 2011[122]; Drover. 2012[123]; Colombo, 2013[124]	Study Population: Healthy infants Infants enrolled 159 Infants completers 92 Mother age: 22.9 y (4.1 y) Race of Mother: White European (NR) Black (59-87%) Asian (NR) Hispanic (0-9%) Inuit Eskimo (NR) Other race/ethnicity (NR) Non-black (13-41%)	Inclusion Criteria: Healthy, singleton, term (37–42 weeks gestation), formula-fed infants were eligible for the study if they weighed between 2490 and 4550 g at birth. All were born between September 2003 and October 2005. Only one child per family could participate. Exclusion Criteria: Infants were excluded if they were older than 9 days, had received human breast milk within 24 h of randomization or if there were newborn health conditions known to interfere with normal growth and development or cognitive function (e.g., intrauterine growth restriction, congenital anomalies or established genetic disorders associated with intellectual disability). Infants were also excluded if they previously demonstrated	Start time: Infants birth Duration: Infants 12 months Arm 1: Placebo Manufacturer: Mead Johnson Nutrition Blinding: eight colored labeling scheme and provided to participants by courier Arm 2: DHA < ARA Description: 0.32% DHA 0.64% ARA Manufacturer: Mead Johnson Nutrition DHA: 0.32% AA: 0.64% Arm 3: DHA = ARA Description: 0.64% DHA 0.64% ARA Manufacturer: Mead Johnson Nutrition DHA: 0.64% AA: 0.64% Arm 4: DHA > ARA Description: 0.96% DHA 0.64% ARA Manufacturer: Mead Johnson Nutrition DHA: 0.96% AA: 0.64%	Outcome: BMI (Secondary) Follow-up time: 2-6 years Arm 1: Sample size 15; mean 16.6; SE (0.4) Arm 2: Sample size 54; mean 16.9; SE (0.4) Outcome: BMI-for-age percentile (Secondary) Follow-up time: 2-6 years Arm 1: Sample size 15; mean 61.2; SE (4.8) Arm 2: Sample size 54; mean 67.8; SE (3.2) Outcome: Length-for-age percentile (Secondary) Follow-up time: 2-6 years Arm 1: Sample size 15; mean 46.5; SE (4.6) Arm 2: Sample size 54; mean 59.1; SE (3.5) Follow-up time: birth-18 months Arm 1: Sample size 15; mean 53.1; SE (3.7) Arm 2: Sample size 54; mean 61.8; SE (2.4) Outcome: Weight-for-age percentile (Secondary) Follow-up time: 2-6 years Arm 1: Sample size 15; mean 49.8; SE (12) Arm 2: Sample size 54; mean 68.0; SE (10.8) Follow-up time: birth-18 months Arm 1: Sample size 15; mean 50.0; SE

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		any evidence of cows' milk formula intolerance or if born to mothers with physician-documented chronic illness (e.g., HIV, renal or hepatic disease, type 1 or 2 diabetes, alcoholism or other substance abuse).		(3.8) Arm 2: Sample size 54; mean 54.5; SE (2.6)
Dunstan et al., 2008[44] Study name: Dunstan Study dates: 2000-2003 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Multiple foundations and Societies Original, same study, or follow-up studies: Dunstan, 2003[50]; Meldrum, 2015[51]	Study Population: Healthy infants Pregnant women with allergies Pregnant enrolled 98 Pregnant completers 83 Infants enrolled 83 Infants withdrawals 11 (7 FO, 4 control) Infants completers 72 Pregnant age: Fish oil: 30.9 Control: 32.6 (Fish oil: 3.7 Control: 3.6) Infant age: Term (mean gestational period 275 days) Race of Mother: NR (NR) Baseline biomarker information: Cord blood erythrocyte (as % total fatty acids) 20:4n-6 14.9 (1.4) 17.6 (1.0) ,0.001 20:5n-3 1.3 (0.5) 0.4 (0.3) ,0.001 22:3n-6 2.8 (0.5) 3.9 (0.5) ,0.001 22:4n-6 0.8 (0.2) 1.5 (0.3) ,0.001 22:5n-3 6.3 (0.8) 6.0 (0.5) 0.037 22:6n-3 10.3 (1.1) 7.4	Inclusion Criteria: Healthy term infants of pregnant women enrolled in RCT of gestational supplementation Exclusion Criteria: Women were ineligible for the study if they smoked, had medical problems, a complicated pregnancy, seafood allergy, or if their normal dietary intake exceeded two meals of fish per week. Children were excluded from the study if they were born before 36 weeks' gestation or with major disease (to avoid the confounding effects on immune response) or if cord blood was not collected	Start time: Pregnant 20 weeks gestation Duration: Pregnant to term Arm 1: Control Description: olive oil placebo Blinding: capsules image matched Maternal conditions Current smoker 0% Maternal allergies 100% Arm 2: Fish oil Description: same Manufacturer: Ocean Nutrition, Halifax Nova Scotia Active ingredients: 3-4mg/g vitamin E Viability: none reported Dose: 4 1-gm capsules fish oil per day Maternal conditions DHA: 2.2 EPA: 1.1 Other dose 1: fish oil supplying 2,2g/d DHA and 1.1g/day EPA Current smoker 0% Maternal allergies 100%	Outcome: head circumference (cm) (Secondary) Follow-up time: 30 months Arm 1: Sample size 36; mean 49.8; SD (1.7) Arm 2: Sample size 28; mean 49.4; SD (1.6) Outcome: length (cm) (Secondary) Follow-up time: 30 months Arm 1: Sample size 36; mean 93.3; SD (4.6) Arm 2: Sample size 28; mean 93.8; SD (3.8) Outcome: weight (kg) (Secondary) Follow-up time: 30 months Arm 1: Sample size 36; mean 14.1; SD (2) Arm 2: Sample size 28; mean 14.5; SD (2)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	(0.9) ,0.001 Total n-6 PUFAs* 25.0 (1.8) 29.6 (1.1) ,0.001 Total n-3 PUFAs{ 17.9 (1.9) 13.7 (1.3) ,0.001 Total n-3 to n-6{ 0.8 (0.1) 0.5 (0.1) ,0.001			
Field et al., 2008[112] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: Canada Funding source / conflict: Industry	Study Population: Healthy infants Infants enrolled 30 Infants completers 30 Infant age: 2 weeks 7 to 14 days Race of Mother: NR (100)	Inclusion Criteria: Inclusion criteria for all infants stipulated that by age 14 d infants were receiving 100 % of their intake by mouth from human milk or commercial infant formula and that infants were healthy with birth weight, length and head circumference between the 10th and 90th percentile for gestational age, according to the National Center for Health Statistics growth charts14. Exclusion Criteria: Infants with major congenital malformations, documented systemic or congenital infection, significant neonatal morbidity, diagnosed maternal autoimmune disorders, acute illness precluding oral feedings, or conditions requiring infant feedings other than standard formula or human milk were excluded from the study. None of the infants had received corticosteroids,	Start time: Infants no later than 14 days Duration: NR Arm 1: Formula (unsuppl) Description: Placebo/control formula Brand name: S-26 Manufacturer: Wyeth Nutrition ALA: 2.3% by weight Arm 2: Formula + LCP Description: LCP supplemented formula Brand name: S-26 Gold Manufacturer: Wyeth Nutrition Active ingredients: arachidonic acid - see below ALA: 1.9% DHA: 0.20% AA: 0.34% Arm 3: Breastfed comparison Description: Breastfed group, not randomized	Outcome: head circumference (cm) (Secondary) Follow-up time: 6 wk Arm 1: Sample size 14; mean 38.6; SD (1.1) Arm 2: Sample size 16; mean 38.4; SD (1.4) Arm 3: Sample size 16; mean 38.9; SD (1.2) Outcome: length (cm) (Secondary) Follow-up time: 6 wk Arm 1: Sample size 14; mean 56.0; SD (2) Arm 2: Sample size 16; mean 56.0; SD (2) Arm 3: Sample size 16; mean 58.0; SD (3) Outcome: weight (g) (Secondary) Follow-up time: 6 wk Arm 1: Sample size 14; mean 4901.0; SD (590) Arm 2: Sample size 16; mean 5076.0; SD (646) Arm 3: Sample size 16; mean 5045.0; SD (516)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		erythrocyte or plasma transfusions, or intravenous lipid emulsions before entering the study		
Fleddermann et al., 2014[113] Study name: BeMIM (Belgrade-Munch Infant Milk Trial) Study dates: Jan 2010 to May 2011 Study design: Trial randomized parallel Location: Serbia Funding source / conflict: Industry	Study Population: Healthy infants Infants enrolled 207 Infants completers 164 Mother age: Control: 30.6 Intervention: 30.7 Breastfed: 30.1 (Control: 5.5 Intervention: 5.5 Breastfed: 4.7) Infant age: Gestation (weeks) Control: 39.2 Intervention: 39.2 Breastfed: 39.2 (Gestation (weeks) Control: 1.1 Intervention: 1.0 Breastfed: 1.1) until 28 days Race of Mother: NR (100%)	Inclusion Criteria: Eligible infants had to be born apparently healthy from singleton pregnancies after 37-41 weeks of gestation, with a birth weight between the 3rd and 97th weight-for-age percentile according to the EURO-Growth charts. Exclusion Criteria: Infants with malformations, congenital heart defects, congenital vascular diseases, severe diseases of gastrointestinal tract, kidney, liver, central nervous system, or metabolic disease.	Start time: Infants within 28 days Duration: Infants until 120 days Arm 1: Control Formula (CF) Description: Placebo/control formula Manufacturer: HiPP GmbH & Co. Vertrieb KG (Pfaffenhofen, Germany) Blinding: 600g cartons and labeled by random numbers. The products were packed in identical white boxes and labeled with the same product name. ALA: 0.1g/100mL Arm 2: Intervention Formula (IF) Manufacturer: HiPP GmbH & Co. Vertrieb KG (Pfaffenhofen, Germany) ALA: 0.1g/100mL DHA: 7.2g/100mL AA: 7.2g/100mL Arm 3: Breastfed Description: Breastfeeding reference group	Outcome: head circumference gain (g/day) (Secondary) Follow-up time: about 92 days Arm 1: Sample size 82; mean 0.05; SD (0.01) Arm 2: Sample size 82; mean 0.05; SD (0.01) Outcome: length gain (g/day) (Secondary) Follow-up time: about 92 days Arm 1: Sample size 82; mean 0.1; SD (0.02) Arm 2: Sample size 82; mean 0.11; SD (0.02) Outcome: weight gain (g/day) (Primary) Follow-up time: about 92 days Arm 1: Sample size 82; mean 28.3; SD (6.5) Arm 2: Sample size 82; mean 30.2; SD (6.3)
Gonzalez-Casanova et al., 2015[60] Study name: POSGRAD Study dates: 2005-2012 Study design: Trial randomized parallel Location: Mexico Funding source / conflict: Government, None	Study Population: Healthy infants Preterm infants Pregnant enrolled 1040 Pregnant completers 968 Infants enrolled 973 Infants completers 802 Pregnant age: 26.3 y (4.7 y) Infant age: 20.5 weeks gestation (2.0)	Inclusion Criteria: Pregnant women 18–35 y of age, in week 18–22 of gestation, and planned to deliver at the hospital, breastfeed for >3 mo, and reside in the area for >2 y after delivery Exclusion Criteria: NR	Start time: Pregnant 18-22 weeks gestation Duration: Pregnant 18-22 weeks gestation until delivery Arm 1: Placebo Description: Soy and corn placebo Dose: 2 200 mg capsules/day Blinding: Soy-corn placebo of similar taste and appearance Arm 2: DHA (algal) Dose: 2 200 mg capsules/day DHA: 400mg	Outcome: BMI-for-age z score (Primary) Follow-up time: 5 years Arm 1: Sample size 399; mean 0.1; SD (1.1) Arm 2: Sample size 403; mean 0.1; SD (1.1) Outcome: height (cm) (Primary) Follow-up time: 5 years Arm 1: Sample size 399; mean 108.4; SD (4.5) Arm 2: Sample size 403; mean 108.3; SD (4.4) Outcome: height-for-age z-score (Primary) Follow-up time: 5 years Arm 1: Sample size 399; mean -0.4; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study follow-up: 60 months Original, same study, or follow-up studies: Ramakrishnan, 2010[32]; Stein, 2012[33]; Imhoff-Kunsch, 2011[58]; Escamilla-Nunez, 2014[59]; Ramakrishnan, 2015[61]	Race of Mother: NR (100)			(0.9) Arm 2: Sample size 403; mean -0.4; SD (0.9) Outcome: weight (kg) (Primary) Follow-up time: 5 years Arm 1: Sample size 399; mean 18.4; SD (3) Arm 2: Sample size 403; mean 18.3; SD (3) Outcome: weight-for-age z-score (Primary) Follow-up time: 5 years Arm 1: Sample size 399; mean -0.1; SD (1.1) Arm 2: Sample size 403; mean -0.2; SD (1.1)
van Goor et al., 2011[66] Study name: Groningen LCPUFA study Study dates: 2004-2009 Study design: Trial randomized parallel Location: Netherlands Funding source / conflict: Industry Study follow-up: 18 months Original, same study, or follow-up studies: Bouwstra, 2003[62]; Bouwstra, 2005[63]; de Jong, 2010[64]; de Jong, 2012[65]; van Goor, 2010[36]	Study Population: Healthy infants Pregnant enrolled 119 Infants enrolled 119 Infants completers 114 Pregnant age: Placebo: 32.7 DHA: 32.5 DHA+AA: 32.9 (Placebo: 5.1 DHA: 4.4 DHA+AA: 4.8) Infant age: 18 months Race of Mother: NR (100)	Inclusion Criteria: women with a first or second low-risk singleton pregnancy, between the 14th and 20th weeks of pregnancy Exclusion Criteria: women with vegetarian or vegan diets; women with diabetes mellitus; birth complications	Start time: Pregnant 14th-20th week pregnancy Lactating 3 months after delivery Mothers 3 months after delivery Infants NR Duration: Pregnant NR Lactating 33-39 weeks Mothers 33-39 weeks Infants NR Arm 1: placebo Description: Soy bean oil Brand name: none Arm 2: DHA Description: DHA plus soy bean oil Brand name: Marinol D40 Manufacturer: Lipid Nutrition B.V., Wormerveer, The Netherlands; AA: Dose: 1 capsule DHA and 1 capsule soy bean oil once a day ALA: 32 mg/d DHA: 220 mg/d EPA: 34 mg/d Arm 3: DHA+AA Description: DHA plus AA Brand name: AA: no brand name Manufacturer: Wuhan Alking Bioengeneering Co. Ltd., Wuhan, China Dose: 2 capsules once a day ALA: 7 mg/d DHA: 220 mg/d	Outcome: head circumference (cm) (Unspecified) Follow-up time: 18 months Arm 1: Sample size 34; mean 47.8; SD (1.5) Arm 2: Sample size 41; mean 47.6; SD (1.1) Arm 3: Sample size 39; mean 47.5; SD (1.4) Outcome: length (cm) (Unspecified) Follow-up time: 18 months Arm 1: Sample size 34; mean 84.0; SD (3.8) Arm 2: Sample size 41; mean 82.8; SD (4.7) Arm 3: Sample size 39; mean 83.6; SD (2.9) Outcome: weight (kg) (Unspecified) Follow-up time: 18 months Arm 1: Sample size 34; mean 11.5; SD (1.1) Arm 2: Sample size 41; mean 11.3; SD (1.4) Arm 3: Sample size 39; mean 11.5; SD (1.3)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			EPA: 36 mg/d AA: 220 mg per capsule	
Groh-Wargo et al., 2005[106] Study name: NR Study dates: Sept 1997 - Sept 1998 Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Government	Study Population: Preterm infants Infants enrolled 60 Infants withdrawals 3 Infants completers 57 Infant age: GA= 30 weeks (0.5) NR Race of Mother: NR	Inclusion Criteria: Preterm infants with birth weights from 750 to 1800 g and GA at birth <33 wk were recruited between September 1997 and September 1998 from the neonatal intensive care unit. No restrictions on the type of feeding before study entry. Exclusion Criteria: Congenital abnormalities that could affect growth or development, major surgery, periventricular hemorrhage greater than grade II (Papile classification), asphyxia resulting in severe and permanent neurologic damage, treatment with extracorporeal membrane oxygenation, maternal incapacity (including substance abuse), or uncontrolled systemic infection at the time of enrollment.	Start time: Infants first enteral formula feeding Duration: Infants 24 kcal/fl oz formula until 40 wk corrected age; 22 kcal/fl oz formula from 40 wk CA to 1 year CA Arm 1: Control Description: Control formula without DHA or ARA Brand name: Similac Special Care to 40 wk GA; and NeoSure until 1 year ALA: 2.4 g/100 g (to 40 wk GA); 2.4 g/100 g (to 1 year) DHA: 0 EPA: 0 AA: 0 Arm 2: DHA+ARA (FF) Description: DHA or ARA from fish/fungal oil Brand name: Similac Special Care to 40 wk GA; and NeoSure until 1 year ALA: 2.6 g/100 g (to 40 wk GA); 2.4 g/100 g (to 1 year) DHA: 0.27 g/100 g (to 40 wk GA); 0.16 g/100 g (to 1 yr) EPA: 0.08 g/100 g (to 40 wk GA); 0 (to 1 yr) AA: 0.43 g/100 g (to 40 wk GA); 0 (to 1 yr) Arm 3: DHA+ARA (EF) Description: DHA or ARA from egg-derived triglyceride and fish oil Brand name: Similac Special Care to 40 wk GA; and NeoSure until 1 year ALA: 2.5 g/100 g (to 40 wk GA); 2.4 g/100 g (to 1 year) DHA: 0.24 g/100 g (to 40 wk GA); 0.15 g/100 g (to 1 yr) EPA: 0 AA: 0.41 g/100 g	Outcome: head circumference (cm) (Secondary) Follow-up time: 12 months (corrected age) Arm 1: Sample size 14; mean 46.2; SE (0.4) Arm 2: Sample size 14; mean 46.0; SE (0.4) Arm 3: Sample size 13; mean 46.2; SE (0.4) Follow-up time: 35 weeks (corrected age) Arm 1: Sample size 18; mean 30.8; SE (0.2) Arm 2: Sample size 17; mean 30.6; SE (0.5) Arm 3: Sample size 18; mean 30.3; SE (0.4) Follow-up time: 4 months (corrected age) Arm 1: Sample size 14; mean 41.9; SE (0.4) Arm 2: Sample size 16; mean 41.1; SE (0.6) Arm 3: Sample size 14; mean 42.0; SE (0.3) Follow-up time: 40 weeks (corrected age) Arm 1: Sample size 18; mean 25.4; SE (0.3) Arm 2: Sample size 18; mean 34.5; SE (0.5) Arm 3: Sample size 17; mean 35.0; SE (0.3) Outcome: length (cm) (Secondary) Follow-up time: 12 months (corrected age) Arm 1: Sample size 14; mean 73.9; SE (0.9) Arm 2: Sample size 14; mean 75.2; SE (0.9) Arm 3: Sample size 13; mean 76.3; SE (0.8) Follow-up time: 35 weeks (corrected age) Arm 1: Sample size 18; mean 42.5; SE (0.5)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 2: Sample size 17; mean 42.7; SE (0.7) Arm 3: Sample size 18; mean 42.7; SE (0.5) Follow-up time: 4 months (corrected age) Arm 1: Sample size 14; mean 61.8; SE (0.7) Arm 2: Sample size 16; mean 60.9; SE (0.6) Arm 3: Sample size 14; mean 62.8; SE (0.7) Follow-up time: 40 weeks (corrected age) Arm 1: Sample size 18; mean 48.0; SE (0.7) Arm 2: Sample size 18; mean 48.2; SE (0.7) Arm 3: Sample size 17; mean 48.1; SE (0.5) Outcome: weight (g) (Secondary) Follow-up time: 12 months (corrected age) Arm 1: Sample size 14; mean 9343.0; SE (307) Arm 2: Sample size 14; mean 8977.0; SE (293) Arm 3: Sample size 13; mean 9505.0; SE (243) Follow-up time: 35 weeks (corrected age) Arm 1: Sample size 18; mean 1916.0; SE (73) Arm 2: Sample size 17; mean 1871.0; SE (118) Arm 3: Sample size 18; mean 1874.0; SE (85) Follow-up time: 4 months (corrected age) Arm 1: Sample size 14; mean 6524.0; SE (220) Arm 2: Sample size 16; mean 6454.0; SE (212) Arm 3: Sample size 14; mean 6432.0; SE (217) Follow-up time: 40 weeks (corrected age) Arm 1: Sample size 18; mean 3280.0; SE (135) Arm 2: Sample size 18; mean 3147.0; SE

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(149) Arm 3: Sample size 17; mean 3136.0; SE (105)
Hauner et al., 2012[37] Study name: INFAT Study dates: July 14 2006 - may 22 2009 Study design: Trial randomized parallel Location: Germany Funding source / conflict: Industry, Government, Multiple foundations and Societies	Study Population: Healthy pregnant women Pregnant enrolled 208 Pregnant withdrawals 38 Pregnant completers 170 Infants enrolled 188 Infants withdrawals 18 Infants completers 170 Pregnant age: 31.9 (4.9) 18-43 Race of Mother: NR (NR) Baseline biomarker information: Maternal fatty acid profile in RBCs at 15th wk: EPA, DHA, AA, and n-6:n-3 LCUFA ratio (reported in Table 2 by intervention and control groups). No significant differences between groups. Baseline Omega-3 intake: 7-d dietary records completed by participants at the 15th (baseline) and 32nd wk of gestation but only dietary intake at 32nd we of gestation was reported (in Table 2). At week 32 of gestation, the dietary n-6:n-3 PUFA ratio was .5:1 in the intervention group compared with :1	Inclusion Criteria: healthy pregnant women before the 15th wk of gestation, between 18 and 43 y of age, prepregnancy BMI (in kg/m2) between 18 and 30, willingness to implement the dietary recommendations, sufficient German language skills. Exclusion Criteria: high-risk pregnancy (multiple pregnancy, rhesus incompatibility, hepatitis B infection, or parity .4); hypertension; chronic diseases (e.g., diabetes) or gastrointestinal disorders accompanied by maldigestion, malabsorption, or elevated energy and nutritional requirements (e.g., gluten enteropathy); known metabolic defects (e.g., phenylketonuria); psychiatric diseases; hyperemesis gravidarum; supplementation with n–3 LCPUFAs before randomization; and alcohol abuse and smoking.	Start time: Pregnant 15th wk of gestation Duration: Pregnant to 4 mo postpartum Arm 1: Control Description: brief semistructured counseling on a healthy balanced diet according to the guidelines of the German Nutrition Society and were explicitly asked to refrain from taking fish oil or DHA supplements N-6 N-3: 2.80 +- 1.17 (SD) at 32nd wk of gestation AA: 10.15 +- 3.89 SD) at 32nd wk of gestation Arm 2: Intervention Description: Fish-oil supplement + nutritional counseling (to normalize the consumption of AA Brand name: Marinol D-40 Manufacturer: Lipid Nutrition DHA: 1020 mg EPA: 180 mg N-6 N-3: 1.54 +- 0.63 (SD) at 32nd wk of gestation AA: 8.82 +- 2.84 (SD) at 32nd wk of gestation Other dose 1: Vit E 9 mg	Outcome: BMI (kg/m2) (Secondary) Follow-up time: 12 months Arm 1: Sample size 83; mean 16.7; SD (1.4) Arm 2: Sample size 87; mean 16.9; SD (1.5) Follow-up time: 4 months Arm 1: Sample size 87; mean 16.2; SD (1.3) Arm 2: Sample size 87; mean 16.5; SD (1.4) Follow-up time: 6 weeks Arm 1: Sample size 91; mean 15.3; SD (1.2) Arm 2: Sample size 89; mean 15.2; SD (1.4) Outcome: head circumference (cm) (Secondary) Follow-up time: 12 months Arm 1: Sample size 83; mean 46.1; SD (1.5) Arm 2: Sample size 87; mean 46.5; SD (1.6) Follow-up time: 4 months Arm 1: Sample size 87; mean 41.0; SD (1.3) Arm 2: Sample size 87; mean 41.2; SD (1.3) Follow-up time: 6 weeks Arm 1: Sample size 90; mean 38.8; SD (1.2) Arm 2: Sample size 89; mean 38.4; SD (1.1) Outcome: length (cm) (Secondary) Follow-up time: 12 months Arm 1: Sample size 83; mean 74.9; SD (2.8) Arm 2: Sample size 87; mean 75.5; SD (2.4) Follow-up time: 4 months

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	in the control group, as originally intended.			Arm 1: Sample size 87; mean 62.4; SD (2.2) Arm 2: Sample size 88; mean 62.6; SD (2) Follow-up time: 6 weeks Arm 1: Sample size 91; mean 55.6; SD (2.6) Arm 2: Sample size 89; mean 56.0; SD (2) Outcome: weight (g) (Secondary) Follow-up time: 12 months Arm 1: Sample size 83; mean 9379.0; SD (1035) Arm 2: Sample size 87; mean 9650.0; SD (1025) Follow-up time: 4 months Arm 1: Sample size 87; mean 6303.0; SD (724) Arm 2: Sample size 87; mean 6476.0; SD (679) Follow-up time: 6 weeks Arm 1: Sample size 91; mean 4736.0; SD (625) Arm 2: Sample size 89; mean 4793.0; SD (606)
Helland et al., 2008[76] Study name: NR Study dates: 1994-2003 Study design: Trial randomized parallel Location: Norway Funding source / conflict: Industry, Government, Multiple foundations and Societies Study follow-up: 7 years Original, same study, or follow-up studies:	Study Population: Healthy infants Healthy pregnant women Breast-feeding women Infants enrolled 262 Infants completers 143 Pregnant age: cod oil 28.6 n=175 corn oil 27.6 n=166 (cod oil 3.4; corn oil 3.2) Race of Mother: NR (100) Baseline biomarker information: from id 10331 cod(n148) corn (n137) n-3 cod: 73.7	Inclusion Criteria: Healthy nulliparous or primiparous women, aged 19-35 with single pregnancies Exclusion Criteria: Unhealthy neonates	Start time: Pregnant week 18 of pregnancy Duration: NR Arm 1: Cod oil Manufacturer: NR Active ingredients: Vit 1: 117 ug/mL, Vit D3: 1 ug/mL, vit E: 1.4 mg/mL Viability: frozen at _x0003_ 70 ° C under nitrogen. Before storage, the samples were sonicated and ethylenediaminetetraacetic acid and butylated hydroxytoluene were added to a final concentration of 1.85 mg/mL and 75 _x0003_ g/mL, respectively DHA: 1183mg/10 mL EPA: 803 mg/10mL Total N-3: 2494 mg/10mL Arm 2: corn oil Active ingredients: Vit 1: 117 ug/mL, Vit D3: 1 ug/mL, vit E: 1.4 mg/mL	Outcome: BMI (kg/m2) (Secondary) Follow-up time: 7 years Arm 1: Sample size 61; mean 16.3; SD (1.7) Arm 2: Sample size 82; mean 16.4; SD (1.7) Outcome: length (cm) (Secondary) Follow-up time: 7 years Arm 1: Sample size 61; mean 128.6; SD (5) Arm 2: Sample size 82; mean 127.5; SD (5.5) Outcome: weight (kg) (Secondary) Follow-up time: 7 years Arm 1: Sample size 61; mean 27.0; SD (4.1) Arm 2: Sample size 82; mean 26.8; SD (4.1)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Helland, 2001[86] and Helland, 2003[87] and which are both included in the original report	(30.0) corn 52.0 (14.9)*** 20:5n-3 cod: 10.8 (7.6) corn: 2.5 (1.8)*** 22:5n-3 cod: 5.0 (2.6) corn: 2.9 (1.3)*** 22:6n-3 cod: 55.8 (20.6) corn: 45.3 (12.8)*** Baseline Omega-3 intake: from 10331 cod n147 corn n159 18:3 n-3: cod: 1.3 (0.5) corn: 1.2 (0.5) 20:5 n-3 cod: 0.2 (0.2) corn:0.2 (0.2) 22:5 n-3 cod: 0.05 (0.03) corn: 0.05 (0.03) 22:6 n-3 cod: 0.3 (0.3) corn: 0.3 (0.3)		Viability: frozen at _x0003_ 70 ° C under nitrogen. Before storage, the samples were sonicated and ethylenediaminetetraacetic acid and butylated hydroxytoluene were added to a final concentration of 1.85 mg/mL and 75 _x0003_ g/mL, respectively ALA: 92 mg/10mL	
Henriksen et al., 2008[107] Study name: Unnamed Trial D Study dates: 2003-2006 Study design: Trial randomized parallel Location: Norway Funding source / conflict: Multiple foundations and Societies, Manufacturer supplied product Study follow-up: 6 months Original, same study, or follow-up studies: Westerberg, 2011[125]; Almaas, 2015[126]	Study Population: Preterm infants Infants enrolled 141 Infants completers 129 Mother age: Median: Intervention: 31 years Control: 32 years 28-35 years Infant age: Median Gestational age: Control: 28.9 weeks Intervention: 28.4 weeks Gestational age: 26.6-30.9 weeks Race of Mother: White European (Intervention: 79%; Control 84%)	Inclusion Criteria: All VLBW infants (<1500g) born between December 2003 and November 2005 at Rikshospitalet-Radiumhospitalet Medical Center, Akershus University Hospital, Buskerud Hospital, and Vestfold Hospital in Norway Exclusion Criteria: Major congenital abnormalities or cerebral hemorrhage (grade 3 or 4, as determined through ultrasonography)	Start time: Infants (intervention began when the infant received most of his nutrients enterally: >100ml human milk/kg body weight/day Duration: Infants Until discharge or bottle of study oil was empty (average 63 days of age) Arm 1: Control Description: Study oil: soy oil and medium chain triglycerides Active ingredients: 127mg linolenic acid/100 ml milk(27.1% total fatty acids) Dose: 0.5 ml study oil/100 ml human milk Blinding: Study oils packed in numbered bottles in hospital pharmacy ALA: 16mg/100 ml milk; 3.4% total fatty acids Arm 2: Intervention Description: DHA and AA-containing oil Manufacturer: Martek Biosciences Active ingredients: 88mg/100 ml linoleic acid per 100 ml milk (18.8%) Dose: 0.5 ml study oil per 100 ml milk, ad lib Maternal conditions Infant conditions DHA: 32mg/100ml milk (6.9%)	Outcome: head circumference (mm/day) (Secondary) Follow-up time: day 65 Arm 1: Sample size 50; mean 1.0; SD (0.4) Arm 2: Sample size 50; mean 1.2; SD (0.7)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			AA: 31 mg/100 ml milk (6.7% total fatty acids Current smoker 22% during pregnancy Low birth weight 100% (median 1090 g)	
Hoffman et al., 2008[114] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Manufacturer supplied product	Study Population: Healthy infants Infants enrolled 244 Infants withdrawals 3 Infants completers 241 Infant age: 14 days Race of Mother: NR	Inclusion Criteria: 12–16 days of age, had a minimum birth weight of 2,500 g, and solely received formula at least 24 h prior to randomization Exclusion Criteria: history of underlying disease or malformation that could interfere with growth and development; large-for-gestational-age infants whose mothers were diabetic; breastfeeding within 24 h prior to randomization; evidence of formula intolerance or poor intake at time of randomization; weight at randomization less than 98% of birth weight; enlarged liver or spleen; or plans to move outside of the study area within the study time frame (120 days)	Start time: Infants 14 day Duration: NR Arm 1: Control Description: soy formula without supplementation Brand name: Enfamil ProSobee1, Mead Johnson & Company, Evansville, IN Blinding: Aside from the addition of DHA and ARA, the formulas were identical in all other respects. Arm 2: DHA + ARA Description: soy formula supplemented with a minimum 17 mg DHA/100kcal from algal oil and 34 mg ARA/100kcal from fungal oil Brand name: Enfamil ProSobee1 LIPIL1, Mead Johnson & Company, Evansville, IN) DHA: 0.3% AA: 0.6%	Outcome: head circumference (cm/day) (Secondary) Follow-up time: 14-120d Arm 1: Sample size 86; mean gain 0.05; SE (0.001) Arm 2: Sample size 93; mean gain 0.05; SE (0.001) Outcome: length (cm/day) (Secondary) Follow-up time: 14-120d Arm 1: Sample size 86; mean change 0.1; SE (0.002) Arm 2: Sample size 93; mean change 0.1; SE (0.002) Outcome: weight (g/day) (Secondary) Follow-up time: 14-120d Arm 1: Sample size 86; mean change 27.8; SE (0.8) Arm 2: Sample size 93; mean change 27.3; SE (0.7)
Lagemaat et al., 2011[109] Study name: NR Study dates: 2003 - 2006 Study design: Trial randomized parallel Location: Netherlands Funding source / conflict:	Study Population: Preterm infants Low birth weight infants Infants enrolled 152 Infants completers 139 Infant age: Gestational age (week) PDF: 30.5 TF: 30.5 HM: 30.0 (PDF: 1.4 TF: 1.4 HM: 1.6)	Inclusion Criteria: infants born at gestational ages of 32 weeks or less and/or with birth weights of 1500 g or less Exclusion Criteria: NR	Start time: Infants at term Duration: Infants 6 months Arm 1: Term Formula (TF) Description: Placebo/control formula Brand name: Friso 1 normaal Manufacturer: FrieslandCampina, Leeuwarden, The Netherlands Blinding: NR ALA: 63mg / 100ml DHA: 7mg / 100ml	Outcome: head circumference (cm) (Unspecified) Follow-up time: term age Arm 1: Sample size 41; mean 35.8; SD (1.5) Arm 2: Sample size 52; mean 35.9; SD (1.2) Arm 3: Sample size 46; mean 35.6; SD (1.5) Outcome: length (cm) (Unspecified) Follow-up time: term age Arm 1: Sample size 41; mean 48.7; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Industry	Race of Mother: NR (100) Baseline biomarker information: Baseline (at term) Mean(SD) AA PDF: 13.74 (0.89) TF: 13.86 (0.93) HM: 14.06 (1.17) DHA PDF: 4.71 (0.70) TF: 4.59 (0.76) HM: 4.08 (0.55) EPA PDF: 0.34 (0.05) TF: 0.32 (0.06) HM: 0.33 (0.13) DHA/AA ratio PDF: 0.34 (0.05) TF: 0.33 (0.06) HM: 0.29 (0.04)		AA: 7mg/ 100ml Arm 2: PDF Description: Post-discharge formula (LCPUFA enriched) Brand name: Friso 1 premature Manufacturer: Friesland Foods ALA: 59mg/ 100ml DHA: 14mg/ 100ml EPA: 3.9mg/ 100ml AA: 14mg/ 100ml Arm 3: HM Description: Human milk	(2.1) Arm 2: Sample size 52; mean 48.7; SD (2.3) Arm 3: Sample size 46; mean 48.2; SD (2.5) Outcome: weight (g) (Unspecified) Follow-up time: term age Arm 1: Sample size 41; mean 3193.0; SD (489) Arm 2: Sample size 52; mean 3137.0; SD (511) Arm 3: Sample size 46; mean 3138.0; SD (513)
Lauritzen et al., 2005[102] Study name: Danish National Birth Cohort-Lactating Women Study dates: Recruitment: April 1999-February 2000 Follow-up 2.5 years Study design: Trial randomized parallel Location: Denmark Funding source / conflict: Industry, Government Study follow-up: 2.5 years Original, same study, or follow-up studies: Lauritzen, 2004[127]; Lauritzen, 2005[128]; Cheatham, 2011[129];	Study Population: Breast-feeding women Infants enrolled 100 Infants completers 72 Mother age: High fish: 31.9 Fish oil: 29.6 Olive oil: 30.2 (High fish: 4.1 Fish oil: 4.3 Olive oil: 4.1) Race of Mother: NR (100%)	Inclusion Criteria: Pregnant women who were recruited for the Danish National Birth Cohort (DNBC) (16), all from the greater Copenhagen area, who were in their eighth month of gestation and had a fish intake below the median (0.40 g/d n-3LCPUFA) (554 women with a fish intake in the upper quartile (0.82 g/d n-3LCPUFA) were invited to participate in the study as a high fish intake reference group); uncomplicated pregnancy; body mass index (BMI) <30 kg/m2; no metabolic disorders; intention to breastfeed for at least 4 mo.; willingness to begin supplement within 2 weeks of birth. Newborns	Start time: Lactating within 2 weeks of delivery Duration: Lactating 4 months Arm 1: Olive oil Description: Control group receiving olive oil supplement Dose: 2 müsli bars daily; or 4 1000-mg capsules Blinding: Investigators and families were blinded to the randomization throughout the first year of life of the infants. Fish oil as well as olive oil supplements were given as microencapsulated oils concealed in two müsli bars (produced by Halo Foods Ltd., Tywyn Gwynedd, Wales, UK) daily for the first 4 mo of lactation. Arm 2: Fish oil Description: Intervention group receiving fish oil supplement Manufacturer: BASF Health and Nutrition A/S, Ballerup, Denmark Dose: 2 müsli bars providing 0.62g EPA and 0.79g DHA; or fish oil capsules providing 0.36g EPA and 0.99g DHA DHA: 0.79g/d EPA: 0.62g/d Total N-3: 1.5g/d	Outcome: BMI (kg/m2) (Secondary) Follow-up time: 2 months Arm 1: Sample size 51; mean 15.93; SD (1.37) Arm 2: Sample size 52; mean 15.74; SD (1.24) Arm 3: Sample size 50; mean 15.63; SD (1.36) Follow-up time: 2.5 years Arm 1: Sample size 28; mean 15.86; SD (1.21) Arm 2: Sample size 42; mean 16.51; SD (1.08) Arm 3: Sample size 29; mean 16.11; SD (1.08) Follow-up time: 4 months Arm 1: Sample size 46; mean 17.04; SD (1.7) Arm 2: Sample size 52; mean 16.93; SD (1.23) Arm 3: Sample size 49; mean 16.57; SD (1.66) Follow-up time: 9 months Arm 1: Sample size 47; mean 17.64; SD (1.52) Arm 2: Sample size 53; mean 17.91; SD (1.24)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		had to be healthy (no admission to a neonatal department), term (37–43 wk of gestation), singleton infants with normal weight for gestation (17) and an Apgar score 7 at 5 min after delivery. Exclusion Criteria: NR	Arm 3: High fish Description: Group with high fish intake as reference group	Arm 3: Sample size 48; mean 17.27; SD (1.39) Outcome: head circumference (cm) (Secondary) Follow-up time: 1 week Arm 1: Sample size 56; mean 35.72; SD (1.53) Arm 2: Sample size 54; mean 36.11; SD (1.25) Arm 3: Sample size 51; mean 36.18; SD (1.59) Follow-up time: 2 months Arm 1: Sample size 50; mean 39.28; SD (1.16) Arm 2: Sample size 50; mean 39.7; SD (1.22) Arm 3: Sample size 47; mean 39.68; SD (1.27) Follow-up time: 2.5 years Arm 1: Sample size 30; mean 49.74; SD (1.34) Arm 2: Sample size 41; mean 50.42; SD (1.2) Arm 3: Sample size 29; mean 50.62; SD (1.23) Follow-up time: 4 months Arm 1: Sample size 46; mean 41.84; SD (1.12) Arm 2: Sample size 45; mean 42.17; SD (1.16) Arm 3: Sample size 45; mean 42.4; SD (1.38) Follow-up time: 9 months Arm 1: Sample size 45; mean 45.29; SD (1.4) Arm 2: Sample size 52; mean 45.85; SD (1.53) Arm 3: Sample size 42; mean 45.81; SD (1.36) Outcome: length (cm) (Secondary) Follow-up time: 2 months Arm 1: Sample size 51; median 58.7; 10th, 90th percentile Arm 2: Sample size 52; median 58.8; 10th,

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				90th percentile Arm 3: Sample size 50; median 59.1; 10th, 90th percentile Follow-up time: 2.5 years Arm 1: Sample size 28; mean 92.65; SD (3.04) Arm 2: Sample size 42; mean 92.58; SD (3.14) Arm 3: Sample size 29; mean 93.74; SD (2.93) Follow-up time: 4 months Arm 1: Sample size 46; mean 64.02; SD (2.16) Arm 2: Sample size 52; mean 64.21; SD (2.08) Arm 3: Sample size 50; mean 64.7; SD (1.71) Follow-up time: 9 months Arm 1: Sample size 47; mean 72.15; SD (2.04) Arm 2: Sample size 53; mean 72.66; SD (2.35) Arm 3: Sample size 48; mean 72.75; SD (2.01) Outcome: weight (kg) (Secondary) Follow-up time: 2 months Arm 1: Sample size 51; mean 5.4; 10th, 90th percentile Arm 2: Sample size 53; median 5.5; 10th, 90th percentile Arm 3: Sample size 50; median 5.3; 10th, 90th percentile Follow-up time: 2.5 years Arm 1: Sample size 30; mean 13.71; SD (1.26) Arm 2: Sample size 42; mean 14.16; SD (1.26) Arm 3: Sample size 29; mean 14.18; SD (1.43) Follow-up time: 4 months Arm 1: Sample size 47; mean 7.0; SD (0.85) Arm 2: Sample size 53; mean 7.0; SD (0.73)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 3: Sample size 49; mean 6.93; SD (0.67) Follow-up time: 9 months Arm 1: Sample size 47; mean 9.19; SD (0.94) Arm 2: Sample size 53; mean 9.47; SD (0.94) Arm 3: Sample size 48; mean 9.15; SD (0.9)
Lucia Bergmann et al., 2007[41] Study name: NR Study dates: 2000-2002 Study design: Trial randomized parallel Location: Germany Funding source / conflict: NR Original, same study, or follow-up studies: Lucia, 2007[52]	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 144 Pregnant withdrawals 51 Pregnant completers 69 Pregnant age: 31 (DHA 4.69; control 4.89) Infant age: DHA 39.1; control 39.5 weeks (DHA 1.64; control 1.38) Race of Mother: White European (100) Baseline biomarker information: DHA % of all identified fatty acid in RBC: Vitamin: 5.76 +-2.45 (47); DHA: Prebiotic:5.94+-2.37(48) DHA: DHA: 5.69+-2.40(47) ARA Vitamin: 14.01+-4.04(47) ARA Prebiotic 14.82+-3.60(48) ARA DHA: 14.18+-4.32(47) EPA Vitamin: 0.72+-0.32(47) EPA Prebiotic: 0.78+-0.38(48) EPA DHA: 0.79+-0.41(47)	Inclusion Criteria: at least 18 years of age and willing to breastfeed for at least three months were enrolled at 21 weeks' gestation during the period October 2000 to August 2002 Exclusion Criteria: increased risk of premature delivery or multiple pregnancy, allergy to cow milk protein, lactose intolerance, diabetes, smoking, consumption of alcohol ()20 g/week), or participation in another study. Infants excluded if they were premature at birth (<37 week gestation, or had any major malformations or hospitalized for more than one week.	Start time: Pregnant 21th week Duration: Pregnant 37th week Arm 1: Vitamins and minerals Manufacturer: Nestle´ (Vevey, Switzerland) Arm 2: Prebiotic Description: basic supplement plus the prebiotic, fructooligosaccharide (FOS) (4.5 g) Manufacturer: Nestle´ (Vevey, Switzerland) Active ingredients: fructooligosaccharide (FOS) (4.5 g) Arm 3: DHA Description: basic supplement with FOS and DHA (200 mg) Manufacturer: Nestle´ (Vevey, Switzerland) Dose: 200 mg DHA prepared from fish oil (assuming that some EPA but dose was not reported) DHA: 200 mg EPA: NR	Outcome: BMI (kg/m2) (Unspecified) Follow-up time: 1 month Arm 1: Sample size 74; mean 14.2; SE (0.37) Arm 3: Sample size 43; mean 14.06; SE (0.4) Follow-up time: 21 months Arm 1: Sample size 74; mean 15.46; SE (0.32) Arm 3: Sample size 43; mean 14.7; SE (0.36) Follow-up time: 3 months Arm 1: Sample size 74; mean 15.58; SE (0.38) Arm 3: Sample size 43; mean 16.14; SE (0.44) Outcome: head circumference (cm) (Unspecified) Follow-up time: 1 month Arm 1: Sample size 74; mean 37.4; SE (0.41) Arm 3: Sample size 43; mean 37.1; SE (0.44) Follow-up time: 21 months Arm 1: Sample size 74; mean 47.7; SE (0.36) Arm 3: Sample size 43; mean 48.4; SE (0.4) Follow-up time: 3 months Arm 1: Sample size 74; mean 40.6; SE (0.43) Arm 3: Sample size 43; mean 40.6; SE (0.5) Outcome: length (cm) (Unspecified)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Follow-up time: 1 month Arm 1: Sample size 74; mean 55.6; SE (0.64) Arm 3: Sample size 43; mean 56.3; SE (0.69) Follow-up time: 21 months Arm 1: Sample size 74; mean 85.4; SE (0.56) Arm 3: Sample size 43; mean 85.5; SE (0.62) Follow-up time: 3 months Arm 1: Sample size 74; mean 61.9; SE (0.65) Arm 3: Sample size 43; mean 61.7; SE (0.76) Outcome: weight (kg) (Unspecified) Follow-up time: 1 month Arm 1: Sample size 74; mean 4.45; SE (0.226) Arm 3: Sample size 43; mean 4.52; SE (0.244) Follow-up time: 21 months Arm 1: Sample size 74; mean 11.35; SE (0.197) Arm 3: Sample size 43; mean 10.75; SE (0.22) Follow-up time: 3 months Arm 1: Sample size 74; mean 6.03; SE (0.23) Arm 3: Sample size 43; mean 6.19; SE (0.269)
Malcolm et al., 2003[100] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: NR Funding source / conflict:	Study Population: NR Pregnant enrolled 100 Pregnant withdrawals 37 Pregnant completers 63 Infants enrolled 60 Infants withdrawals 5 Infants completers 55 Infant age: 279.6 (8.5)	Inclusion Criteria: d women who were expected to deliver their infants at term and planned to feed them on breast and/or formula milk Exclusion Criteria: diabetes, twin pregnancies, pre-eclamptic toxaemia, a	Start time: Pregnant week 15 Infants birth Duration: Pregnant birth Arm 1: Placebo Description: contained 323 mg sunflower oil with high levels of oleic acid and was free of any significant amounts of LCPUFAs or their precursors Manufacturer: R P Scherer Limited (Swindon, Wiltshire, UK) Dose: 323 mg per capsule * 2 Blinding: e identical in appearance and could not be	Outcome: head circumference (cm) (Secondary) Follow-up time: 50 weeks PCA (postconceptional age) Arm 1: Sample size 27; mean 40.1; SD (2.3) Arm 2: Sample size 28; mean 39.9; SD (1.5) Follow-up time: 66 weeks (post conceptional age) Arm 1: Sample size 27; mean 44.1; SD (1.7)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
NR	Race of Mother: NR (NR) Baseline biomarker information: Only reported: "The fish oil and placebo groups did not differ in maternal RBC and plasma fatty acid composition at enrollment"	past history of abruption or postpartum haemorrhage, allergy to fish products, a thrombophilic tendency, or who were receiving drugs that affect thrombocyte function (non-steroidal anti-inflammatories)	identified on the basis of scent or taste Total N-3: 0 Arm 2: DHA Description: f a blended fish oil, Marinol D40, and contained 100 mg DHA in 323 mg oil per capsule Manufacturer: R P Scherer Limited (Swindon, Wiltshire, UK) Dose: 323 mg capsule * 2 DHA: 200 mg EPA: .64 mg (estimated based on the FA composition)	Arm 2: Sample size 28; mean 43.8; SD (2.4) Outcome: length (cm) (Secondary) Follow-up time: 50 weeks PCA (postconceptional age) Arm 1: Sample size 27; mean 60.5; SD (2.9) Arm 2: Sample size 28; mean 60.0; SD (2.6) Follow-up time: 66 weeks (post conceptional age) Arm 1: Sample size 27; mean 69.1; SD (3.2) Arm 2: Sample size 28; mean 68.5; SD (2.6) Outcome: weight (g) (Secondary) Follow-up time: 50 weeks PCA (postconceptional age) Arm 1: Sample size 27; mean 5995.7; SD (827.9) Arm 2: Sample size 28; mean 5894.4; SD (662.3) Follow-up time: 66 weeks (post conceptional age) Arm 1: Sample size 27; mean 8626.7; SD (208.2) Arm 2: Sample size 28; mean 8263.7; SD (999.4)
Mulder et al., 2014[75] Study name: NR Study dates: 2004 to 2008 Study design: Trial randomized parallel Location: Canada Funding source / conflict: Government	Study Population: Healthy pregnant women Pregnant enrolled 271 Pregnant completers 200 Pregnant age: 33 years (4 years) NR Race of Mother: White European (73%) Other race/ethnicity (27%) Baseline biomarker information: maternal	Inclusion Criteria: at least 16 wk gestation, not taking any lipid or fatty acid supplement, and were expected to deliver one infant at full-term gestation, with no maternal or fetal complications Exclusion Criteria: NR	Start time: Pregnant 16 weeks gestation Duration: Pregnant Until birth Arm 1: placebo Description: corn and soybean oil supplement Manufacturer: Martek Biosciences Blinding: supplements were identical in appearance, contained an orange flavor mask Arm 2: DHA supplement Description: algal oil DHA supplement Manufacturer: Martek Biosciences DHA: 400 mg	Outcome: length-for-age z score (Unspecified) Follow-up time: 12 months Arm 1: Sample size 94; mean 0.44; SD (1.11) Arm 2: Sample size 84; mean 0.11; SD (1.06) Follow-up time: 18 months Arm 1: Sample size 82; mean 0.41; SD (1.14) Arm 2: Sample size 76; mean 0.16; SD (1.11) Follow-up time: 2 months Arm 1: Sample size 102; mean 0.29; SD (1.08)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study follow-up: 18 months	RBC Phusphatidylethanolamine DHA: placebo group 6.25 (1.60) g/ 100g DHA group 6.36 (1.62) g/ 100g Baseline Omega-3 intake: median (2.5 to 97.5th percentile range) intake: placebo group 80.0 (0.00-334) mg/day, DHA group 90.0 (6.00-472) mg/d			Arm 2: Sample size 92; mean 0.17; SD (1.04) Follow-up time: 6 months Arm 1: Sample size 101; mean 0.25; SD (1.06) Arm 2: Sample size 95; mean 0.17; SD (1.04) Follow-up time: 9 months Arm 1: Sample size 95; mean 0.22; SD (1.08) Arm 2: Sample size 88; mean -0.06; SD (1.05) Outcome: weight-for-age z score (Unspecified) Follow-up time: 12 months Arm 1: Sample size 94; mean 0.15; SD (1.02) Arm 2: Sample size 81; mean 0.12; SD (1.05) Follow-up time: 18 months Arm 1: Sample size 70; mean 0.27; SD (0.99) Arm 2: Sample size 74; mean 0.21; SD (1.04) Follow-up time: 2 months Arm 1: Sample size 101; mean 0.06; SD (1.08) Arm 2: Sample size 90; mean -0.19; SD (1.08) Follow-up time: 6 months Arm 1: Sample size 101; mean 0.1; SD (1.01) Arm 2: Sample size 95; mean -0.06; SD (1.11) Follow-up time: 9 months Arm 1: Sample size 94; mean 0.03; SD (0.99) Arm 2: Sample size 87; mean 0.04; SD (1.11) Outcome: weight-for-length z score (Unspecified) Follow-up time: 12 months Arm 1: Sample size 93; mean -0.04; SD (0.99)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 2: Sample size 81; mean 0.14; SD (1.09) Follow-up time: 18 months Arm 1: Sample size 70; mean 0.14; SD (1.05) Arm 2: Sample size 74; mean 0.14; SD (1.05) Follow-up time: 2 months Arm 1: Sample size 101; mean -0.16; SD (1.08) Arm 2: Sample size 90; mean -0.42; SD (1.2) Follow-up time: 6 months Arm 1: Sample size 101; mean 0.04; SD (1.04) Arm 2: Sample size 95; mean -0.11; SD (1.02) Follow-up time: 9 months Arm 1: Sample size 94; mean -0.04; SD (0.99) Arm 2: Sample size 87; mean 0.17; SD (1.05)
Sala-Vila et al., 2004[110] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: Spain Funding source / conflict: Multiple foundations and Societies, Manufacturer supplied product	Study Population: Healthy infants Infants enrolled 35 Infants completers 35 Pregnant age: 28.3 Infant age: NR Race of Mother: NR (100)	Inclusion Criteria: full-term infants (37–42 wk gestation), of appropriate weight-for-gestation-age Exclusion Criteria: NR	Start time: Infants birth Duration: Infants 3 mo Arm 1: Human Milk (HM) Description: breast milk with composition of protein carbohydrate fat ash Arm 2: E-PL formula Description: E-PL formula provided 10% of its fat from egg PLs Brand name: Ovotin 120, Lucas Meyer DHA: 1.25% AA: 1.9% Arm 3: S-TG formula Description: single-cell (SC)-TG formula provided _x0004_0.3 and 0.5% of its fat from TGs synthesized by single cells of algal and fungal microorganisms Manufacturer: Martek Biosciences	Outcome: head circumference (cm) (Unspecified) Follow-up time: 3 months Arm 1: Sample size 11; mean 41.86; SE (1.78) Arm 2: Sample size 12; mean 42.01; SE (1.46) Arm 3: Sample size 12; mean 43.98; SE (1.38) Outcome: length (cm) (Unspecified) Follow-up time: 3 months Arm 1: Sample size 11; mean 60.5; SE (6.31) Arm 2: Sample size 12; mean 61.08; SE (5.31) Arm 3: Sample size 12; mean 60.98; SE (3.98) Outcome: weight (g) (Unspecified) Follow-up time: 3 months Arm 1: Sample size 11; mean 6460.1; SE (630.6)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			DHA: 0.1g/100g; 0.3% of 40-45% DHASCO AA: 0.4g/100g, 0.5% of 38-44% ARASCO	Arm 2: Sample size 12; mean 6640.8; SE (741) Arm 3: Sample size 12; mean 6491.9; SE (906.1)
Smithers et al., 2008[104] Study name: DINO Study dates: 2001-2004 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Manufacturer supplied product Study follow-up: 2 months, 4 months Original, same study, or follow-up studies: Makrides, 2009[116]; Smithers, 2010[117]; Manley, 2011[118]; Collins, 2011[105]; Atwell, 2013[119]; Collins, 2015[120]	Study Population: Preterm infants Lactating enrolled unclear Infants enrolled 143 Infants completers 125 Lactating enrolled unclear Mother age: Control: 31 Treatment: 29 (Control: 6 Treatment: 6) Infant age: 5 days (control) (mean gestational age at birth 29.4 weeks) 6 days (Treatment) (3) Race of Mother: NR (NR) Baseline Omega-3 intake: Intervention begun at birth: see below	Inclusion Criteria: infants born_x0001_33 wk gestation at the Women's and Children's Hospital of the Child, Youth, and Women's Health Service, Adelaide, Australia, between April 2001 and September 2003 Exclusion Criteria: Infants with major congenital or chromosomal abnormalities, lactating mothers for whom tuna oil was contraindicated (women with blood-thinning disorders or currently taking anticoagulants)	Start time: Lactating approximately 5 days after birth Infants approximately 5 days after birth Duration: Lactating to estimated due date Infants to estimated due date Arm 1: Control group Description: Placebo capsules and/or formula Active ingredients: Linoleic acid 53.4% of fatty acids Dose: 6 500-mg capsules per day to mothers Blinding: The soy and tuna oil capsules were identical in size, color, and shape ALA: 5.9% of total fatty acids Arm 2: Treatment Description: DHA supplemented breastfeeding mothers and/or formula Active ingredients: Linoleic acid 2.7% of fatty acids Dose: 6 capsules or formula ad lib ALA: 0.4% total FA DHA: 29.5% total FA EPA: 6.5% total FA AA: 1.8% total FA	duplicate data of id 8885 Outcome: (Secondary)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Stein et al., 2011[34] Study name: POSGRAD Study dates: 02. 2005-02.2007 Study design: Trial randomized parallel Location: Mexico Funding source / conflict: Government, Multiple foundations and Societies Original, same study, or follow-up studies: Stein, 2012[33]; Imhoff-Kunsch, 2011[58]; Escamilla-Nunez, 2014[59]; Gonzalez-Casanova, 2015[60]; Ramakrishnan, 2015[61]; Ramakrishnan, 2011[32]	Study Population: Healthy infants Pregnant enrolled 1094 Pregnant completers 973 Pregnant age: placebo 26.3; DHA 26.4 (placebo 4.6; DHA 4.9) Infant age: 39.1 (placebo 1.6; DHA 1.8) Race of Mother: NR	Inclusion Criteria: women were 18–35 y, were in gestation wk 18–22, and planned to deliver at the IMSS General Hospital in Cuernavaca, exclusively or predominantly breast-feed for at least 3 mo, and to live in the area for at least 2 y after delivery Exclusion Criteria: NR	Start time: Pregnant 18-22 Gestational week Infants birth Duration: Pregnant birth Arm 1: Placebo Description: Olive oil Manufacturer: Martek Biosciences Dose: 2 capsules olive oil Blinding: Similar in appearance and taste to DHA capsules Arm 2: DHA Description: algal DHA capsules Manufacturer: Martek Biosciences Dose: 2 capsules * 200mg DHA: 400 mg	Outcome: head circumference (cm) (Primary) Follow-up time: 18 months Arm 1: Sample size 370; mean 47.0; SD (1.4) Arm 2: Sample size 369; mean 47.0; SD (1.5) Outcome: length (cm) (Primary) Follow-up time: 18 months Arm 1: Sample size 370; mean 79.5; SD (2.8) Arm 2: Sample size 369; mean 79.6; SD (2.8) Outcome: weight (kg) (Primary) Follow-up time: 18 months Arm 1: Sample size 370; mean 10.4; SD (1.2) Arm 2: Sample size 369; mean 10.4; SD (1.1)
Tofail et al., 2006[77] Study name: NR Study dates: Enrollment January to March 2000 Study design: Trial randomized parallel Location: Bangladesh Funding source / conflict: Government Study follow-up: 10 months	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 400 Pregnant completers 151 Pregnant age: 22.7 years (4.35 years) NR Race of Mother: Asian (100%)	Inclusion Criteria: seems as if all pregnant women at 25 weeks gestation were enrolled, no inclusion criteria specified Exclusion Criteria: NR	Start time: Pregnant 25 weeks gestation Duration: Pregnant until birth Arm 1: placebo Description: soy oil capsule Dose: 4 one gram capsules per day Blinding: capsules were identical in appearance Other dose 1: LNA 0.27 g Other dose 2: linoleic acid 2.25 g Arm 2: DHA supplement Description: fish oil capsules Dose: 4 one gram capsules per day DHA: 1.2 g EPA: 1.8 g	Outcome: head circumference (cm) (Unspecified) Follow-up time: 10 months Arm 1: Sample size 124; mean 43.2; SD (1.4) Arm 2: Sample size 125; mean 43.0; SD (1.4)

Table 13. Observational studies for postnatal growth patterns

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Mohanty, et al., 2015[85] Outcome domain: Growth Study dates: 1996-2008 Study design: Observational prospective Location: US Funding source / conflict: Government	Study Population: Healthy infants Healthy pregnant women Pregnant completers 534 Race of Mother: White European (88)	Inclusion Criteria: initiated prenatal care at or before 20 weeks gestation, were aged = 18 years, able to speak and read English, planned to carry the pregnancy to term, and to deliver at either of the two hospitals Exclusion Criteria: multi-fetal pregnancies, implausible total energy intake of <500 or >3500 kcal/day, pregnancies complicated by fetal demise (after 20 weeks of gestation), missing labor and delivery information, missing information on fetal growth indices, missing seafood intake information	Adjustments: Adjusted for maternal age (years), non-Hispanic white race, post high-school education, unmarried marital status, pre-pregnancy body mass index (indicator variables: 18.5-24.9, 25-29.9, =30 kg/m2), total energy (kcal/day), current recreational physical activity, current smoking, current alcohol intake, nulliparity, intake of red/processed meats (servings/day), male infant sex.
Much, et al., 2013[101] Outcome domain: Growth Study name: INFAT Study dates: Recruitment: 2006-2009 Followup: 1 year Study design: Observational prospective Location: Germany Funding source / conflict: Industry, Government, Some authors employed by industry (companies that make the supplements) Follow-up: 1 year Original, same study, or follow-up studies: Hauner, 2012[37]	Study Population: Healthy infants Breast-feeding women Pregnant enrolled 208 Lactating enrolled 152 at 6 weeks/120 at 4 months Infants enrolled 56 at 4 months/31 at 12 months Lactating enrolled 152 at 6 weeks/120 at 4 months Pregnant age: Intervention: 31.9 Control: 31.6 (Intervention: 4.9 Control: 4.5) Race of Mother: NR (NR)	Inclusion Criteria: Gestational age =15th wk of gestation, between 18 and 43 y of age, prepregnancy BMI (in kg/m2) between 18 and 30, willingness to implement the dietary recommendations, sufficient German language skills, and written informed consent Exclusion Criteria: High-risk pregnancy (multiple pregnancy, rhesus incompatibility, hepatitis B infection, or parity >4); hypertension; chronic diseases (e.g., diabetes) or gastrointestinal disorders accompanied by maldigestion, malabsorption, or elevated energy and nutritional requirements (e.g., gluten enteropathy); known metabolic defects (e.g., phenylketonuria); psychiatric diseases; hyperemesis gravidarum; supplementation with n–3 LCPUFAs before randomization; and alcohol abuse and smoking	Adjustments: Gestational age, parity, infant sex, group, ponderal index at birth, breastfeeding status of infants at 6 wk, 4 mo, and 1 yr.

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Much, et al., 2013[83] Outcome domain: Growth Study name: INFAT Study dates: >2009-<2013 Study design: Observational prospective Location: Germany Funding source / conflict: Industry, Government, Some authors employed by industry (companies that make the supplements), Multiple foundations and Societies, None	Study Population: Healthy infants Breast-feeding women Pregnant enrolled 208 Infants completers 187 Race of Mother: NR (NR)	Inclusion Criteria: Healthy pregnant women at 14th week of gestation Exclusion Criteria: None reported	Adjustments: Pregnancy duration, group, parity, and sex
Scholtens, et al., 2009[103] Outcome domain: Growth Study name: The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study Study dates: Recruitment: 1996-1997 Followup: 1 year Study design: Observational prospective Location: Netherlands Funding source / conflict: Industry, Government, Multiple foundations and Societies, None Follow-up: 1 year Original, same study, or follow-up studies: Study described in Brunekreef, 2002	Study Population: NR Pregnant enrolled 4146 Infants enrolled 276 Infants completers 244 Infant age: Birth Race of Mother: NR (NR)	Inclusion Criteria: Children of mothers recruited from the general population during pregnancy Exclusion Criteria: None reported	Adjustments: Age of child at breast-milk collection and total breast-feeding duration

Neurological Development

Key Findings and Strength of Evidence

Antepartum supplementation:

- The original report identified one study that supplemented pregnant women with fish oil and found no effects on infant EEG.
- The current report identified four RCTs that reported on the effects of prenatal DHA supplementation on indices of neurological development infants or children. One large RCT reported no effects on brain auditory evoked potentials despite low baseline intakes; one small RCT on sleep patterns reported significant effect on arousal at days 1 and 2 but no other findings among any of the many other measures; one RCT reported no effects on Bayley Infant Development Motor Subscale scores at 18 months; and another reported no change in the Bayley Psychomotor Development Index at 18 months.
- Among four RCTs that reported on the effects of prenatal supplementation with fish oil, two large RCTs found no differences in motor development at 10 or 18 months, and two reported no differences in neurological optimality scores at 4 or 5.5 years or the Developmental Test of Visual-Motor Integration at 12 years.
- The current report identified two prospective cohort studies and four biomarker studies that assessed the association between prenatal exposures or biomarkers and neurodevelopmental outcomes. One prospective cohort study found an association between the lowest quintile of n-3FA and risk for epilepsy; one prospective cohort study found no association of n-3, n-6, or n-6/n-3 FA with a measure of fine motor development. One biomarker study found no association of any maternal n-3 or n-6 FA biomarkers and the Bailey psychomotor development index (PDI). A second study found an inverse association of videographically assessed (mildly abnormal) movement at 3 months with arterial but not venous cord blood biomarkers; at 18 months, the same cohort showed an association of umbilical vein DHA with NOS but not PDI; umbilical arterial LC-PUFA were no longer associated with any neurodevelopmental indices. A third study found no significant association of cord blood DHA with NOS at 4 years but did identify an association at 5.5 years. The fourth study found no association between umbilical DHA or AA and Maastricht motor scores at 7 years of age.

Pre and postpartum maternal supplementation

- One RCT that compared DHA vs DA+AA vs placebo had inconsistent effects on mildly abnormal movement and PDI at 0.5, 3, and 18 months. Maternal biomarkers showed inconsistent associations with infant movement.

Postpartum maternal supplementation and infant outcomes:

- Healthy term infants breastfed by mothers who received supplemental DHA showed significantly improved adjusted PDI scores at 30 months but not at12 months. At 5 years a different battery of age-appropriate motor tests showed no difference between groups.

Postpartum supplementation of preterm infants

- The original report identified six RCTs that could not be pooled and reported mixed findings with respect to neurological developmental outcomes. The current report identified three RCTs that could not be pooled due to different interventions, outcome measures, and follow-up times; supplementation showed mixed effects.

Postpartum infant supplementation healthy term

- The original report identified seven RCTs with mixed interventions, durations, and outcome measures; pooling three RCTs of DHA+AA showed no effect on PDI at 12 months compared with placebo. The current report identified five additional RCTS. In a small Turkish study, DHA-supplemented formula improved brainstem maturation at 4 months. In a large Italian study, DHA affected only one out of four measures of gross motor development at 12 months. One larger Dutch study showed significant impact of DHA+AA on mildly abnormal movement at 2 months compared with placebo; at 18 months, intervention, placebo, and breastfed children had similar PDI scores; at 9 years, the fine motor control of both supplemented and placebo children was similar but poorer than that of breastfed. A large US study that randomized infants to one of four different levels of DHA-supplemented formula found no differences in PDI scores from placebo among any of the supplemented groups. An Australian study that supplemented infant formula with DHA-enriched fish oil also found no differences in the BSID Composite motor score, the Categorical Child Behavior Checklist, or several indices of sleep.

Description of Included Studies

We identified 17 RCTs and five large observational studies that assessed the effects of n-3 FA interventions on, or the associations of n-3 FA exposures with, neurodevelopment in the developing infant and child, as distinct from cognitive development. Outcomes varied and included the Bailey's Psychomotor Development Index (PDI), brainstem auditory evoked potentials, neurological optimality scores, general movement assessment, and the Touwen Neurological Assessment, among others.

This section reports the findings of studies that assessed the effects of prenatal, postnatal maternal (breast milk), or postnatal infant PUFA supplementation or exposure on these outcomes. Studies identified for this report are summarized in Table 13 and briefly summarized below.

Antepartum Maternal Supplementation with or Exposure to n-3 Fatty Acids and Infant Neurodevelopmental Outcomes

Randomized Controlled Trials

The original report identified one RCT that assessed the effects of an n-3 intervention (cod liver oil) with pregnant women on neurodevelopmental outcomes; the outcome was brain maturity as assessed by infant electroencephalogram (EEG) recordings at 1 day and again at 6 months of age; this study found no effect of maternal supplementation at either time point. No studies were identified for the current report that assessed effects of maternal supplementation on infant EEG patterns.

For the current report, we identified nine RCTs that assessed the effects of antepartum maternal supplementation with n-3 FA on neurodevelopmental outcomes (see Table 14). We also identified five articles that reported the results of three prospective cohort studies that assessed the association between antepartum maternal n-3 FA exposures and infant neurodevelopment (two of these articles were post hoc assessments of the association between maternal n-3 FA status and subsequent neurodevelopmental outcomes in RCTs).

DHA Versus Placebo

Brainstem Auditory Evoked Potentials. For the current report, we identified one 2012 RCT that randomized 1,094 pregnant women in Mexico to 0.4g/d algal DHA or corn and soy bean oil from approximately 17 weeks of gestation through term and assessed the effect of supplementation on brainstem auditory evoked potentials (a measure of brainstem maturation).[33] The women had low baseline intakes of DHA. No differences were seen in any comparisons (latency and interpeak latency at 1, 3, and 5 milliseconds) between infants of placebo and DHA-supplemented women at either time point.

Sleep/Wakefulness. A 2013 RCT randomized 48 U.S. women to consume five cereal bars per week from 24 weeks of gestation until delivery; 27 of the women received bars that contained 0.3g DHA each (for an average of 0.21g/d DHA and a trace amount [0.023 g/d] EPA) and the remaining women received bars without DHA.[40] Early infant sleep patterns, a predictor of subsequent neurological development, were measured at 1 and 2 postnatal days using a pressure sensitive mattress. On both days 1 and 2, infants of DHA-supplemented mothers showed fewer arousals in both quiet (adjusted p=0.006 for day 1, adjusted p=0.011 for day 2) and active (adjusted p=0.012 for day 1) sleep than did infants of control mothers. No differences were observed between groups in arousal from active sleep on day 2, quiet sleep, sleep transitions, active sleep, wakefulness, sleep bout lengths, mean sleep period, and longest sleep period.

Neonatal Behavioral Assessment Scale (Motor and Autonomic Clusters). Carlson and colleagues (Gustafson et al., 2013) randomized 46 pregnant women (average 14 weeks gestation) to receive 600 mg per day of DHA or placebo.[74] At one week of age, 27 infants (15 from mothers given DHA and 12 from mothers given placebo capsules) completed the Neonatal Behavioral Assessment scale (NBAS). Infants from women randomized to the DHA intervention during showed significantly higher (better) scores on the Motor (t_{25}=1.87, P=0.038) and Autonomic clusters(t_{25}=1.99, P=0.029).

Bayley PDI. Ramakrishnan and colleagues (in the POSGRAD study) examined the effects of prenatal maternal algal DHA supplementation (400 mg daily) on neurodevelopmental outcomes of 730 Mexican infants at 18 months.[61] The effects of supplementation on birth outcomes were reported previously.[32] Toddlers of supplemented mothers did not differ from toddlers of placebo-treated mothers in adjusted (-0.46; -1.80, 0.88) or unadjusted PDI scores (-0.26; -1.63, 1.10).

Bayley Scales of Infant Development Motor Subscales. Innes and colleagues (Mulder et al., 2014) developed a risk-reduction model to examine whether the DHA-status in some pregnant women, and therefore their fetuses, is sufficiently low as to increase the risk for neurological and cognitive developmental delay. The study, conducted in Canada, randomized pregnant women at 16 weeks gestation or less to 400mg DHA daily in the form of algal oil or to a corn and soy oil placebo.[75] This amount of DHA was chosen as it is the equivalent of about two weekly servings of fish. At 18 months, toddlers of placebo mothers did not differ from those of DHA-fed mothers in the likelihood of scoring in the highest quartile for fine (P=0.33) and gross (P=0.40) motor skills (outcomes for the cognitive subscales and visual acuity are described elsewhere in this report).

Fish Oil Versus Placebo

Bayley's PDI or Motor Standardized Score. For the current report, we identified three studies that assessed the effects of supplementing pregnant women with fish oil on infant psychomotor development, compared with those of placebo.[35, 77]

In one 2006 study, four hundred healthy pregnant women in Dhaka Bangladesh were randomized to receive fish oil (1.2g/d DHA and 1.8g/d EPA) or placebo (soy oil) from the 25th week of gestation through term. No differences were seen in PDI scores between the two groups of infants (n=249) at 10 months of age (effect size -2.1±1.1[-4.3, 0.1]).

A 2010 study, the DOMInO Study,[35] randomized 2,399 women seen at five hospitals in Australia to a daily DHA-rich fish oil supplement (0.8g/d DHA; 0.1g/d EPA) or placebo beginning at 21 weeks of gestation or earlier through term. The primary outcome of the study was risk for depression; however infant neuro- and cognitive development were assessed as secondary outcomes in 726 infants at 18 months of age. No differences were seen in unadjusted or adjusted effect sizes among boys or girls between treatment group offspring (-0.69[-2.31, 0.93]p=0.40) for girls; (0.85[-1.00, 2.70] p=0.37)).

Beery-Buktenica Developmental Test of Visual-Motor Integration. Meldrum and coworkers[51] reported on a group of 50 children at 12 years' follow-up whose mothers were randomized prenatally to receive fish oil or placebo capsules.[44] Secondary outcomes included the Beery-Buktenica Developmental Test of Visual-Motor Integration (TVMI). No differences were observed between the groups on TVMI scores, and no association was observed between these scores and blood levels of DHA at 12 years of age.

Neurological Optimality Score. Koletzko's group (Escolano-Margarit et al, 2011) randomized 315 healthy pregnant women at 20 weeks gestation to receive a milk-based supplement containing fish oil that delivered 500mg DHA and 50mg EPA daily or a placebo oil, with or without 400 micrograms 5-methylline tetrahydrofolate (5-MTHF) through term.[130] Infants whose mothers had received fish oil and were not breastfed received infant formula that contained fish oil. Children were examined at the age of 4 years with the Hempel assessment and also received a neurological optimality score (NOS). At 5.5 years, they were reassessed using the Touwen assessment. No differences were seen in any of the assessments between children who received fish oil pre- and postnatally and those who were exposed to placebo only. Associations between cord blood n-3 FA levels and outcomes are described below.

Observational Studies

We identified two prospective cohort studies that assessed the association between maternal intakes of n-3 FA during pregnancy and infant neurodevelopmental outcomes (see Table 15).[89, 131] We also identified four studies (reported in five publications) that assessed the association between umbilical venous LC-PUFA and these outcomes (one of these studies was a follow-up to a study described in the original report, and another was a follow-up to a study described below).

Prospective Cohort Studies

A 2010 study used data from the Danish National Birth Cohort, which estimated n-3 FA intake from self-administered FFQ around 25 weeks gestation.[131] The authors followed 65,754 live-born infants up to 11 years of age to determine their risk for a diagnosis of epilepsy (according to ICD-10 criteria) associated with quintiles of total n-3 FA intake. Based on the middle quintile as the reference (0.31±0.07g/d, adjusted for energy intake), infants born to women with the lowest quintile of pregnancy n-3 FA intake (0.12±0.04g/d) were at a slightly but not significantly increased risk for epilepsy (adjusted incidence rate ratio, 1.28[0.98, 1.67]) and infants born to women with the highest quintile (0.0.82 ±0.35g/d) of intake were at a significantly increased risk for epilepsy (IRR 1.33[1.02, 1.74]). Restricting the analyses to children for whom information on breastfeeding was actually available, the risk increase remained insignificant for the lowest quintile of n-3FA intake (IRR 1.35[0.99, 1.83]), and the risk for infants of mothers with the highest quintile of intake was no longer significant (IRR 1.24[0.90, 1.69]).

A 2013 study assessed the association between n-3 FA/ n-6 FA intake during pregnancy among 1,335 French women enrolled in the EDEN cohort study and performance of their children at 2 years of age on tests of cognitive and motor development, included the Peg Movement Task (PMT)-5.[89] Neither breastfed nor never-breastfed children showed any association between performance on the PMT-5 and maternal intake of n-6 FA, n-3 FA or the n-6/n-3 ratio.

Biomarker Studies

A 2013 study whose primary outcome of interest was the association between prenatal mercury exposure, LC-PUFA, and infant neurodevelopment assessed the association between maternal serum n-3 and n-6 FA and Bailey Scale of Infant Development composite motor scores at 18 months of age among a population-based cohort of 606 mother-child pairs in Italy.[132] No significant association was found between motor scores and maternal EPA, DHA, ALA, DPA, or AA status or n-6:n-3 ratio.

Bouwstra and colleagues utilized a cohort of children enrolled in a RCT to assess the effect of DHA and AA-supplemented infant formula (compared with standard formula and breast milk) on neurological development to assess the associations between umbilical venous and arterial n-3FA status and neurological development at 3 months[133] (the RCT is described below). Neurological development was assessed by videographically recording and analyzing general movement quality: Movements were classified as normal optimal, normal suboptimal (both normal optimal and normal suboptimal are considered clinically normal), mildly abnormal or definitely abnormal. At 3 months, the quality of general movements among 269 infants was not associated with the DHA or AA concentration of venous cord blood. However movement quality was associated with the FA content of arterial cord blood. An increase in mildly abnormal movements was associated with adjusted lower arterial cord blood levels of total monounsaturated FA; several n-6 FA, including AA; n-9 FA; and total n-3 and n-6 FA.

Bouwstra and colleagues reassessed neurologic development of the same cohort at 18 months (n=317), this time using the Hempel neurological exam to obtain a neurologic optimality score (NOS) and the Bailey PDI. Children whose umbilical vein DHA concentrations were in the lowest quartile had significantly lower adjusted NOS but no difference in PDI scores compared with children whose umbilical vein DHA concentrations were higher (β=0.17; p=0.003). Umbilical venous AA concentrations were not associated with NOS or PDI scores in multivariate analysis, and umbilical arterial LC-PUFA concentrations were not associated with neurodevelopmental indices.

In a follow-up to a 2003 cohort study described in the original report (but not originally including neurological outcomes), Bakker and colleagues also assessed the association between umbilical venous LC-PUFA and neurological development, as indicated by motor development, in another Dutch cohort.[134] The cohort comprised 750 white children born between 1990 and 1994 and seen at the University Hospital Maastricht, for whom umbilical blood LC-PUFA had been assessed. At 7 years of age, 306 children were given the Maastricht Motor Test (MMT) by a blinded tester. The composite (total) score comprises a quantity score (whether the participant can perform the movement) and a quality score (how well the participant performs the movement). MMT total score and quality score were significantly positively associated with umbilical plasma DHA in multivariate models (β=0.13, p=0.01; β=0.14, p=0.10, respectively). Umbilical DHA was not significantly associated with MMT quantity score. Umbilical AA was not significantly associated with MMT scores ((β=-0.10, p=0.069; β=-0.11, p=0.052, for total and quality scores, respectively).

Koletzko's group assessed the association between maternal cord blood DHA and AA status and NOS in their trial of fish oil and 5-MTHF supplementation.[130] At 4 and 5.5 years of age, the risk for MND was not associated with maternal plasma or erythrocyte DHA, AA or AA:DHA or with cord blood DHA, AA or AA:DHA. At 4 years of age, children's NOS were not associated with plasma or erythrocyte DHA or AA levels or the AA:DHA ratio. However, at 5.5 years, NOS was significantly associated with cord blood DHA, such that the odds of achieving the maximal NOS score increased with every unit increase in cord blood plasma phospholipid DHA (95% CI 1.094, 2.262) and in erythrocyte phosphatidyl ethanolamine (95% CI 1.091, 2.417) and phosphatidyl choline DHA (95% CI 1.003, 2.643). Term maternal erythrocyte DHA was positively associated and the AA:DHA ratio was negatively associated with NOS.

Ante- and Postpartum Maternal Supplementation with n-3 FA and Infant Neurodevelopment

For the current report, we identified one study that examined the effects of both prenatal and postnatal maternal supplementation with LCPUFA on infant neurological development.

DHA or DHA plus AA Versus Placebo

For the current report, we identified one study, reported in two publications, that examined the effects of both prenatal and postnatal maternal supplementation with DHA or DHA plus AA on infant neurological development compared with those of placebo.

One study, reported in two publications, enrolled 183 healthy pregnant women between 14 and 20 weeks of pregnancy (80% between 15.6 and 17.4 weeks) in the Netherlands and randomized them to receive a daily supplement of vitamins and minerals alone, vitamins and minerals along with DHA (0.22 g/d), or vitamins and minerals along with DHA (0.22g/d from fish oil) and AA (0.22g/d) from enrollment to 3 weeks after delivery.[36] Infant neurological development was assessed at 0.5 months, 3 months,[36] and 18 months[66] of age using two instruments. At 0.5 months and 18 months, a standard neurological assessment was conducted, resulting in a NOS. At all time points, general movement quality was assessed videographically as described above. And at 18 months, infants were assessed using the PDI. No significant differences in NOS were seen among the three groups of infants at 0.5 months of age (n=183). At 0.5 months of age, infants of mothers supplemented only with DHA showed significantly more mildly abnormal movements than the infants of control mothers (adjusted β 3.867, p=0.021); no significant difference was seen between infants of DHA-supplemented mothers and those of mothers who received DHA plus AA (adjusted β, p=0.19), and controls did not differ from the DHA plus AA group (p=0.29). At 3 months (n=96), the adjusted differences attained significance for DHA vs. controls (p=0.014), and for DHA vs. DHA plus AA (p=0.017). At 18 months (n=114), no difference in PDI scores was observed among the three groups of infants.[66]

Maternal Biomarkers

The study by van Goor that assessed the effects of maternal pre- and postnatal supplementation with DHA or DHA plus AA on neurological development also assessed the association between maternal[36] biomarkers of n-3 FA status and infant neurological development. They reported no correlations between prenatal (3 weeks gestation) maternal erythrocyte n-3, n-6 FA, or the DHA:AA ratio and the NOS. Mildly abnormal infant general movements at 2 weeks were correlated with lower maternal erythrocyte AA compared with normal general movements (median 12.25 vs. 13.03, p=0.02). No associations were found at 3 months.[36]

Postpartum Maternal Supplementation with n-3 FA and Infant Neurodevelopment

For the current report, we identified one new RCT, reported in two publications, that examined the effects of supplementing lactating mothers with n-3 FA on infant neurological development.

DHA Versus Placebo

We identified two new articles reporting on one RCT that examined the effects of postpartum maternal DHA supplementation on infant neurological development.[135, 136]

Jensen and colleagues randomly assigned 227 pregnant U.S. women who planned to breastfeed for at least 4 months to either algal DHA (approximately 0.2g/d) or placebo, to begin at 5 days postpartum and continue for 4 months.[135] Mothers of preterm or low birth weight infants were excluded. Compliance with the supplement was 95 percent to 100 percent. The Bailey PDI and the Gesell Developmental Inventory were used to assess motor development at 12 and 30 months of age in the 230 infants (including 3 twin pairs). At 12 months, no differences were seen between groups in either of the tests. At 30 months, infants of DHA-supplemented mothers had significantly higher adjusted PDI scores than infants of placebo-supplemented mothers (p=0.0008), although no difference was seen using the Gesell Inventory.[136]

A subsequent article reported on psychomotor development as measured by the K-ABC Hand movement scale; McCarthy Leg Coordination component; Purdue Peg board Test; and the Developmental Test of Visual Motor Integration Motor component at 5 years of age in the same population (n=60 children of DHA-supplemented mothers and 57 children of placebo mothers).[135] No differences were seen between the two groups of infants in performance on any of the tests.

Maternal and Infant Biomarkers

Jensen and colleagues assessed the association between infant plasma phospholipid DHA and psychomotor development and found no association (data not reported).[136]

Infant Formula Supplementation with n-3 FA and Neurodevelopment in Preterm Infants

The original report identified six RCTs that examined the effects of supplementing formula with n-3 FA with or without breast feeding on neurological development among preterm infants; the studies dated from 1999 to 2004. Duration of supplementation varied. Follow-ups ranged from 1 month to 24 months: in some studies, the intervention ended several months before follow-up assessment. Three RCTs assessed the use of formula supplemented with DHA plus AA, two RCTs assessed the use of formula supplemented with DHA plus EPA plus AA, and one used DHA plus gamma-linoleic acid. Across the studies, outcomes were mixed: two studies reported a positive effect of DHA plus AA on PDI scores, whereas four reported no or negative effects. No studies were pooled because of differences in intervention duration and follow-up.

DHA, DHA plus AA, or DHA plus EPA Versus Placebo

Three RCTs were identified for the current report that assessed the effects of providing infant formula supplemented with DHA with or without EPA and AA on PDI scores of preterm infants. The outcomes could not be pooled because of differences in the interventions and follow-up times.

A 2005 RCT randomized 27 preterm infants in Taiwan (born at 30 to 37 weeks gestation and over 2kg body weight) to oral formula supplemented with DHA (0.05%) and AA (0.1%) or a control formula for 6 months.[137] PDI scores in the supplemented group were not significantly different from the unsupplemented group at 6 months (102.2±10.5 vs. 95.4±13.2) but significantly higher in this group at 12 months (98.0±5.8 vs. 86.7±11.1, p=0.008) compared to the unsupplemented group.

Another 2005 RCT randomized 361 preterm U.S. infants (≤35 weeks gestation) to one of three groups: oral formula supplemented with algal DHA (0.017g/100kcal) plus algal AA (0.034g/100kcal); oral formula supplemented with fish DHA and algal AA in the same concentrations; or standard formula for approximately 18 months (until 118 weeks postmenstrual age [PMA]).[108] At 118 weeks PMA, both supplemented groups had significantly higher PDI scores than the unsupplemented group but significantly lower than a group of term breastfed infants of similar ages.

The DINO trial, a 2009 RCT, randomized 657 preterm infants (≤33 weeks gestation) to receive "high DHA" (1% of total fatty acids) or "standard DHA" (0.3% of total fatty acids) enteral formula from day 2 to 4 until term-corrected age (expected date of delivery) and assessed the effects of the two supplements at 18 months corrected age on a number of outcomes, including neurological development. In an intention to treat analysis, the authors reported no differences between groups in PDI scores.[116]

Infant Formula Supplementation with n-3 FA and Neurodevelopment in Term Infants

The original report identified seven RCTs that examined the effects of supplementing infant formula with various combinations of n-3 and n-6 FA on neurodevelopmental outcomes of term infants. Across these RCTs, effects of supplementation on neurodevelopment, usually assessed using the Bailey PDI, were mixed.

For the current report we identified five new studies reported in seven publications that assessed the effects of n-3 FA with or without other LCPUFA on neurodevelopmental outcomes. None of these studies could be pooled with studies in the original report.

DHA Versus Placebo

We identified two RCTs that assessed the effects of DHA supplementation alone on neurodevelopmental outcomes.

A 2004 RCT randomized 54 healthy term infants in Turkey within the first week of life to 4 months of Farleys First Milk (a DHA-supplemented infant formula [0.5% DHA]), or Nutrilon, a control formula.[138] A group of 23 infants breastfed from birth served as a reference. At 4 months, brainstem maturation was assessed in the remaining 44 infants by measuring the decrease in brainstem auditory evoked potentials: All six measures (three absolute wave and three interpeak latencies) showed significantly greater maturation in the infants given the DHA-supplemented formula (p=0.038-0.001) and the breast fed infants (P=P=0.04-0.001), compared with the infants fed non-supplemented formula.

A 2011 RCT randomized 1,160 healthy term newborns in Italy to a daily supplement of oil containing DHA and vitamin D (0.4g/d DHA and 400IU, respectively) or vitamin D alone for 12 months to assess the effect on four measures of gross motor development.[139] At 12 months, among the remaining 1,091 infants, only one of the outcome measures, time to sitting without support, was achieved significantly faster in the DHA-supplemented infants. The remaining three outcome measures did not differ between intervention groups.

Fish Oil Versus Placebo

The Infant Fish Oil Supplementation Study (IFOS) randomized 420 healthy term infants at high family risk for allergy to receive DHA-enriched fish oil (250-280mg DHA daily and 110 mg EPA) or olive oil placebo from birth to 6 months of age.[140] At 18 months of age, toddlers were given a battery of cognitive and neurodevelopmental tests, including the Bayley Scales of Infant and Toddler Development (BSID, 287 toddlers) and Categorical Child Behavior Checklist (269 toddlers). Composite motor scores on the BSID were not significantly different between the fish oil treated and placebo-treated infants (P=0.097). Sleep problems also did not differ between the groups (P=0.453). Cognitive and respiratory outcomes are described elsewhere in this report.

DHA Plus AA Versus Placebo

The original report pooled the results of three RCTs (n=184) that assessed the effects of supplementing term infants with DHA plus AA on PDI scores at 12 months: the pooled weighted mean difference was -2.80 (95% CI -7.43, 1.82; I^2 36%), thus showing no significant effect of the supplemented formula.

For the current report, we identified two RCTs that assessed the effects of supplementing infant formula with DHA plus AA, but could not be pooled with the earlier studies.

The DIAMOND Study randomized healthy term U.S. infants born at one of 7 hospitals at two study sites to one of four intervention groups within 9 days of birth (study sites differed significantly by race, ethnicity, parental education, and gestational length). Children who had received breast milk were excluded. Three of the intervention groups received a standard formula fortified with 0.32% DHA (0.017g/100kcal), 0.64% DHA (0.034g/100 kcal), or 0.96% DHA; all intervention formulae also included 0.64% fatty acids as AA (0.034 g/100kcal). The control group received the standard formula with no DHA or AA. The intervention was continued for 12 months and no other foods were introduced prior to 4 months of age. A subset of participants at one of the two sites received neurodevelopmental assessments at 18 months and a series of cognitive developmental assessments through 6 years of age (described elsewhere in this report).[121-124] PDI scores at 18 months did not differ significantly among the four groups of infants (statistics not reported); scores for the placebo group actually slightly exceeded those of the three active treatment groups combined.

A 2003 multisite study conducted around Groningen in the Netherlands randomized 312 healthy term infants to one of two infant formulas: Nutricia Nutrilon formula supplemented with 0.30% DHA from egg yolk and tuna oil and 0.45% AA from egg yolk and fungal oil or the same formula without DHA and AA. The fatty acid patterns of the fortified formula were similar to those of breast milk. A third group of 160 breastfed infants was also included. The intervention was continued for 2 months. Videographed general movements were analyzed at 3 months and quality was classified as described above.[62] The occurrence of mildly abnormal movements was significantly less frequent in the supplemented formula group than in the control group (adjusted OR 0.49[0.26, 0.92]p=0.032) and not significantly different from the breastfed group (p=0.87).

At 18 months' follow-up, toddlers were re-assessed with the PDI, the Hempel Test (to assess minor neurological dysfunction [MND]), and assessment of NOS (attrition was 5.5% and not selective).[63] In both univariate and multivariate analysis, the rate of MND, the NOS, and the PDI scores did not differ among the three groups (supplemented formula, control formula, and breast fed).

At 9 years of age, the children were re-assessed (attrition was 28% and boys with lower MDI scores were more heavily represented among the dropouts).[64] The primary outcome was the NOS, based on the Touwen Neurological assessment of neurological dysfunction, and the MND. No differences were seen between the supplemented formula-fed group and the control group in the NOS or the ratios of neurologically normal, simple MND, and complex MND children. However, breastfed children were less likely to show fine manipulative dysfunction than either group of formula-fed children.

Table 14. RCTs for neurological development

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Agostoni et al., 2009[139] Study name: NR Study dates: Enrollment occurred May and June 2005; 1-year followup Study design: Trial randomized parallel Location: Italy Funding source / conflict: Manufacturer supplied product	Study Population: Healthy infants Infants enrolled 1160 Infants withdrawals 69 Infants completers 1091 Mother age: 32 years (4.5 years) NR Infant age: intervention began 1 day after discharge (NA) NA Race of Mother: White European (100%)	Inclusion Criteria: weight at birth 2500 g or more, gestational age between 37 and 42 completed weeks, single birth, absence of neonatal or birth abnormalities, Apgar score 7 or higher at 5 min, and white parents. Exclusion Criteria: presence of neonatal diseases requiring hospitalization for 7 days or more; involvement of neonate in another clinical study; unknown father; and parents unable to understand the protocol requirements, to fill out the infant's diary, or to understand and speak the Italian language adequately.	Start time: Infants 1 day after discharge from birth hospital Duration: Infants 1 year Arm 1: placebo Description: oral liquid Manufacturer: Humana Italia SpA Active ingredients: 400 IU vitamin D3 Viability: Parents were advised to store the bottles in a dry and fresh environment. Dose: 1 mL once per day Blinding: Intervention and placebo preparations were identical in aroma, taste, and texture Total N-3: 0 Arm 2: Human Italia SpA Active ingredients: 400 IU vitamin D3 Viability: Parents were advised to store the bottles in a dry and fresh environment. Dose: 1 mL once per day DHA: 20 mg DHA/ml	Outcome: age achieving gross motor: hands-and-knees crawling (weeks) (Primary) Follow-up time: varies Arm 1: Sample size 476; mean 39.4; SD (6.2) Arm 2: Sample size 482; mean 38.9; SD (6.4) Outcome: age achieving gross motor: sitting without support (weeks) (Primary) Follow-up time: varies Arm 1: Sample size 542; mean 28.3; SD (4.2) Arm 2: Sample size 551; mean 26.8; SD (4.2) Outcome: age achieving gross motor: standing alone (weeks) (Primary) Follow-up time: varies Arm 1: Sample size 542; mean 50.1; SD (8.1) Arm 2: Sample size 549; mean 49.2; SD (7.6) Outcome: age achieving gross motor: walking alone (weeks) (Primary) Follow-up time: varies Arm 1: Sample size 542; mean 55.8; SD (6.7) Arm 2: Sample size 549; mean 54.9; SD (6.8)
Bouwstra et al., 2003[62] Study name: Groningen LCPUFA study Study dates: 1997-1999 Study design: Trial randomized parallel Location: Netherlands	Study Population: Healthy infants Infants enrolled 472 Infants completers 397 Mother age: 31 (5) NR Infant age: Gestational age 39.6 wk (1.3) NR Race of Mother: White	Inclusion Criteria: healthy term infants Exclusion Criteria: infants who had a congenital disorder that interfered with adequate functioning in daily life, infants from multiple births, infants whose mothers did not have mastery of the Dutch language or	Start time: Infants Birth Duration: Infants 2 months Arm 1: Control formula Description: Standard formula with no supplemental LCPUFA Brand name: Nutrilon premium Manufacturer: Zoetermeer, Netherlands Active ingredients: linoleic acid (11mol%); ALA 1.27 mol% Dose: ad lib	Outcome: mildly abnormal general movements (Primary) Follow-up time: 3 months Arm 1: 41/131 (31.0%) Arm 2: 23/119 (19.0%) Outcome: normal-optimal general movements (Primary) Follow-up time: 3 months Arm 1: 28/131 (21.0%) Arm 2: 21/119 (18.0%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Funding source / conflict: Industry Study follow-up: 3 months Original, same study, or follow-up studies: Bouwstra, 2005[63]; de Jong, 2010[64]; de Jong, 2012[65]; van Goor, 2010[36]; van Goor, 2011[66]	European (100)	suffered from significant illness or disability, adopted and foster infants, and formula-fed infants who had received human milk for >5 d.	Blinding: not reported Maternal conditions Current smoker 32% during pregnancy Maternal abuse of alcohol/psychotropic drugs Alcohol USE during pregnancy 10% Arm 2: LCPUFA formula Description: LCPUFA formula fortified with n-3s and n-6s Brand name: NR Maternal conditions DHA: 0.30% (by wt) AA: h 0.45% (by wt) Current smoker 32% smoked during pregnancy Maternal abuse of alcohol/psychotropic drugs 13% used alcohol during pregnancy Arm 3: breastfed group Description: breastfed, no formula, not randomized here - used as reference group Maternal conditions Current smoker 28% smoked during pregnancy Maternal abuse of alcohol/psychotropic drugs 38% consumed alcohol during pregnancy	
Bouwstra et al., 2005[63] Study name: Groningen LCPUFA study Study dates: 1997-2002 Study design: Trial randomized parallel Location: Netherlands Funding source / conflict: Industry Study follow-up: 18 months Original, same study, or	Study Population: Healthy infants Infants enrolled 472 Infants completers 446 Mother age: 31 years (5 years) NR Infant age: birth Race of Mother: White European (100%)	Inclusion Criteria: healthy term infants Exclusion Criteria: infants who had a congenital disorder that interfered with adequate functioning in daily life, infants from multiple births, infants whose mothers did not have mastery of the Dutch language or suffered from significant illness or disability, adopted and foster infants, and formula-fed infants who had received human milk for >5 d.	Start time: Infants Birth Duration: Infants 2 months Arm 1: Control group Description: Standard formula Brand name: Nutrilon premium Manufacturer: Zoetermeer, Netherlands Active ingredients: linoleic acid (11mol%); ALA 1.27 mol% Dose: ad lib Maternal conditions Current smoker 31% during pregnancy Maternal abuse of alcohol/psychotropic drugs Alcohol USE during pregnancy 8% Arm 2: LCPUFA formula Description: LCPUFA formula Dose: ad lib	Outcome: Bayley PDI (Secondary) Follow-up time: 18 months Arm 1: Sample size 169; mean 100.9; SD (13.6) Arm 2: Sample size 146; mean 99.4; SD (13.4) Outcome: neurological optimality score (Secondary) Follow-up time: 18 months Arm 1: Sample size 169; median 52.0; 5, 95 percentile Arm 2: Sample size 146; median 52.0; 5, 95 percentile Outcome: number of children with minor neurological dysfunction (Secondary) Follow-up time: 18 months Arm 1: 8/169 (5.0%) Arm 2: 10/146 (7.0%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
follow-up studies: Bouwstra, 2003[62]; de Jong, 2010[64]; de Jong, 2012[65]; van Goor, 2010[36]; van Goor, 2011[66]			Maternal conditions DHA: 0.30% DHA AA: 0.45% AA Current smoker 31% during pregnancy Maternal abuse of alcohol/psychotropic drugs 9% used alcohol during pregnancy Arm 3: breast feeding group Description: breast fed, no formula Maternal conditions Current smoker 19% smoked during pregnancy Maternal abuse of alcohol/psychotropic drugs 24% used alcohol during pregnancy	
Clandinin et al., 2005[108] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: Canada Funding source / conflict: Industry	Study Population: Preterm infants Infants enrolled 361 preterm+105 term breastfed Infants completers 179 preterm and 76/105 term breastfed Infant age: 30.6 weeks postmenstrual age 24-36 weeks postmenstrual age Race of Mother: NR (100)	Inclusion Criteria: Phase I: gestational age <35 weeks PMA and received <10 total days of enteral feedings of >30 mL/kg per day. Infants initially fed human milk were not enrolled unless formula was started within 10 days after completing the first day of human milk feeding Phase II: completion of phase I and >=80% enteral intake from study formula during hospitalization and 100% of caloric intake from study formula at completion of phase 1. Birth weight<1500g Exclusion Criteria: congenital abnormalities of the gastrointestinal tract, hepatitis, hepatic or biliary pathology, necrotizing enterocolitis confirmed before enrollment, or history of underlying disease or	Start time: Infants 10 days of age Duration: Infants 118 weeks Arm 1: Control Description: Non-supplemented premature, discharge, and term formula Dose: Ad lib Blinding: Not reported Infant conditions Pre-term birth 119 (100%) Arm 2: Algal-DHA Description: supplemented premature infant formula supplemented with DHA from algal oil Manufacturer: Martek Biosciences Dose: ad lib DHA: 17mg/100kcal (0.33% by weight) EPA: 0.1% by weight AA: 34mg/100kcal (0.67% by weight) Arm 3: Fish-DHA Description: Premature infant formula supplemented with DHA from tuna fish oil Manufacturer: Martek Biosciences Dose: ad lib DHA: 17mg DHA/100 kcal AA: 34mg/100 kcal Arm 4: Reference	Outcome: Bayley Scale of Infant Development II (Physical developmental index) (Unspecified) Follow-up time: 118 weeks Arm 1: Sample size 54; mean 83.0; SE (2) Arm 2: Sample size 46; mean 88.0; SE (2) Arm 3: Sample size 59; mean 88.0; SE (2) Arm 4: Sample size 59; mean 98.0; SE (2)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		congenital malformation likely to interfere with evaluation	Description: Breast fed term infants	
Collins et al., 2015[120] Study name: DINO Study dates: 2001-2013 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Industry, Government Study follow-up: 7 years Original, same study, or follow-up studies: Smithers, 2008[104]; Makrides, 2009[116]; Smithers, 2010[117]; Manley, 2011[118]; Collins, 2011[105]; Atwell, 2013[119]; Collins, 2015[120]	Study Population: Preterm infants Infants enrolled 657 Infants completers 604 Infant age: median 30 weeks gestational age 28-31 weeks Race of Mother: NR (100)	Inclusion Criteria: infants born at <33 weeks' gestation from five Australian tertiary hospitals between 2001 and 2005 Exclusion Criteria: a major congenital or chromosomal abnormality, multiple birth in which not all live-born infants were eligible, enrollment in other trials of fatty acid supplementation, or if fish oil was contraindicated in the lactating mother	Start time: Infants within 5 days of 1st enteral feeding Duration: Infants to expected due date Arm 1: standard DHA Description: DHA supplementation of infant formula or breastfeeding mothers to achieve DHA concentrations of term formula fed infants DHA: ___20 mg/kg/ day of DHA Arm 2: High DHA Description: DHA supplementation of infant formula or breastfeeding mothers to achieve DHA concentration of breastmilk DHA: ___50 mg/kg/ day of DHA	Outcome: Rey Auditory Verbal Learning Test: Delayed recall raw score (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 7.2; SD (3) Arm 2: Sample size 291; mean 7.3; SD (3.5) Outcome: Rey Auditory Verbal Learning Test: Delayed recognition correct words (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 13.1; SD (3) Arm 2: Sample size 291; mean 13.3; SD (2.6) Outcome: Rey Auditory Verbal Learning Test: Total (trials 1-5) correct words (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 34.8; SD (10.8) Arm 2: Sample size 291; mean 34.4; SD (12.1) Outcome: Rey Auditory Verbal Learning Test: Total intrusions (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 2.5; SD (4) Arm 2: Sample size 291; mean 2.1; SD (3.5) Outcome: Rey Auditory Verbal Learning Test: Total repetitions (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 3.7; SD (4.1) Arm 2: Sample size 291; mean 4.0; SD (4.5) Outcome: Rey Auditory Verbal Learning Test: Trial 1 correct words (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 4.3; SD (2) Arm 2: Sample size 291; mean 4.4; SD (2)
Colombo et al., 2013[124]	Study Population:	Inclusion Criteria:	Start time: Infants Birth	Outcome: Bayley PDI (Secondary)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study name: Diamond Study dates: 09/03/03-09/25/05 Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Government, Manufacturer supplied product Study follow-up: 18 months-6 years Original, same study, or follow-up studies: Birch, 2010[121]; Drover, 2011[122]; Drover. 2012[123]; Currie, 2015[115]	Healthy infants Infants enrolled 159 Infants completers 81 Pregnant age: 24.1 (5.1) Race of Mother: White European (34.9) Black (63.9) Other race/ethnicity (1.2)	Healthy, full term formula-fed singleton infants, 37-42 weeks gestation, 2490-4200 g birth weight, born in Kansas City between 9/3/03 and 9/25/05 Exclusion Criteria: Receipt of human milk within 24 h of randomization; maternal and newborn health conditions known to interfere with normal growth and development (e.g., intrauterine growth restriction) or with normal cognitive function (e.g., congenital anomalies or established genetic diagnoses associated with intellectual disability), poor formula intake, or intolerance to cow milk infant formula; mothers with physician-documented chronic illness (e.g., HIV, renal or hepatic disease, type 1 or type 2 diabetes, alcoholism, or substance abuse)	Duration: Infants 12 months Arm 1: 0.00% Description: Control, no DHA or AA Blinding: NR Arm 2: 0.32% Description: 0.32% DHA DHA: 17mg/100 kcal AA: 34 mg/100 kcal Arm 3: 0.64% DHA: 34mg/100 kcal AA: 34 mg/100 kcal Arm 4: 0.96% DHA: 51mg/100 kcal AA: 34 mg/100 kcal	Follow-up time: 18 months Arm 1: Sample size 18; mean 99.0; SEM (5) Arm 2: Sample size 21; mean 97.0; SEM (5) Arm 3: Sample size 18; mean 97.0; SEM (5) Arm 4: Sample size 24; mean 98.0; SEM (5)
Escolano-Margarit et al., 2011[130] Study name: NUHEAL Study dates: 2001-2008 Study design: Trial randomized parallel	Study Population: Healthy pregnant women Pregnant enrolled 315 Pregnant completers 157 Infants enrolled 315 Infants completers 148 Pregnant age: 31 (NR)	Inclusion Criteria: singleton pregnancy, gestation 20 week at enrollment, and intention to deliver in one of the obstetrical centers Exclusion Criteria: serious chronic illness (e.g., diabetes, hepatitis,	Start time: Pregnant week 22 of pregnancy Infants NA Duration: Pregnant until birth Arm 1: placebo Description: milk-based supplement Brand name: Blemil Plus Manufacturer: Ordesa Laboratorios, Barcelona, Spain)	Outcome: number considered normal on Hempel exam (Secondary) Follow-up time: 5.5 years Arm 1: 81/87 (93.0%) Arm 2: 74/80 (93.0%) Outcome: number considered normal on Towen exam (Secondary) Follow-up time: 5.5 years Arm 1: 48/69 (70.0%) Arm 2: 55/79 (70.0%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Location: Germany, Spain, Hungary Funding source / conflict: Manufacturer supplied product Study follow-up: 5.5 years Original, same study, or follow-up studies: Campoy, 2011[141].	18 to 41 Race of Mother: NR (100) Baseline biomarker information: For newborns mean plasma DHA Placebo group _x0007_6.9 Fish oil group 7.8 5-MHTF (folic acid) group 6.2 _x0007_Fish oil + 5-MHTF group _x0007_7.0 mean plasma AA Placebo group 17.6 Fish oil group 16.8 5-MHTF (folic acid) group 17.3 _x0007_Fish oil + 5-MHTF group 16.4	or chronic enteric disease), use of FO supplements since the beginning of pregnancy or folate or vitamin B-12 supplements after gestation week 16	Active ingredients: vitamins and minerals in amounts meeting the recommended intakes during the second half of pregnancy for European women Dose: one daily dose of 15 g Blinding: supplements were not distinguishable with respect to the appearance of the sachets or to their contents Arm 2: fish oil Description: fish oil in milk-based supplement Manufacturer: Pronova Biocare, Lysaker, Norway Active ingredients: vitamins and minerals in amounts meeting the recommended intakes during the second half of pregnancy for European women Dose: one daily dose of 15 g DHA: 500 mg EPA: 100 mg Arm 3: folic acid Description: 400 _x0001_g 5-MTHF Manufacturer: BASF, Ludwigshafen, Germany Active ingredients: vitamins and minerals in amounts meeting the recommended intakes during the second half of pregnancy for European women Dose: one dose of 15 g Arm 4: folic acid + fish oil Description: fish oil + 400 _x0001_g 5-MTHF Manufacturer: BASF, Ludwigshafen, Germany Active ingredients: vitamins and minerals in amounts meeting the recommended intakes during the second half of pregnancy for European women Dose: one dose of 15 g DHA: 500 mg EPA: 100 mg	
Fang et al., 2005[137] Study name: NR Study dates: NR Study design: Trial randomized parallel	Study Population: Preterm infants Infants enrolled 28 Infants withdrawals 1 Infants completers 27 Infant age: 1 week (mean	Inclusion Criteria: (1) A gestational age at birth between 30 and 37 weeks; (2) Normal fundus oculi; (3) Recruitment prior to commencement of feeding	Start time: Infants 1 week after birth Duration: Infants 24 weeks Arm 1: placebo Description: infant formula based on the composition of human milk Brand name: Neoangelac	Outcome: Bayley psychomotor development index (Primary) Follow-up time: 12 months Arm 1: Sample size 11; mean 86.7; SD (11.1) Arm 2: Sample size 16; mean 98.0; SD (5.8) Follow-up time: 6 months

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Location: Taiwan Funding source / conflict: Manufacturer supplied product	gestation age 33 weeks) (0.5 week) NA Race of Mother: NR (100)	Exclusion Criteria: (1) Breast feeding; (2) A maternal history of infection, diabetes mellitus, gestational diabetes mellitus, cocaine or alcohol abuse, systemic diseases or if intrauterine growth retardation had been diagnosed during pregnancy; (3) Major congenital abnormality; (4) Severe intraventricular hemorrhage > grade 2; (5) Cystic periventricular leukomalacia; (6) Retinopathy of prematurity stage 2; (7) Bronchopulmonary dysplasia on radiographs or oxygen usage 28 days; (8) Body weight less than the third percentile; (9) Surgical intervention for necrotizing enterocolitis (10) Mechanical ventilation after achieving enteral intake > 110 kcal/kg per day; (11) A 5-min Apgar score < 7; (12) Administration of blood transfusion, blood products, or parenteral lipids with DHA or AA.	Manufacturer: Multipower Enterprise Corporation Dose: Babies were given more than 110 kcal/kg per day during the first 4 months and more than 70 kcal/kg per day from 4 to 6 months N-6 N-3: 10:1 linoleic:linolenic Arm 2: Neoangelac Plus Description: Neoangelac supplemented with Omega 3 Brand name: Neoangelac Plus Manufacturer: Multipower Enterprise Corporation Dose: Babies were given more than 110 kcal/kg per day during the first 4 months and more than 70 kcal/kg per day from 4 to 6 months DHA: 0.05% AA: 0.10%	Arm 1: Sample size 11; mean 95.4; SD (13.2) Arm 2: Sample size 16; mean 102.2; SD (10.5)
van Goor et al., 2011[66] Study name: Groningen LCPUFA study	Study Population: Healthy infants Pregnant enrolled 119	Inclusion Criteria: women with a first or second low-risk singleton pregnancy, between the 14th and 20th weeks of pregnancy	Start time: Pregnant 14th-20th week pregnancy Lactating 3 months after delivery Mothers 3 months after delivery Infants NR Duration: Pregnant NR Lactating 33-39 weeks	Outcome: Bayley psychomotor development index (Unspecified) Follow-up time: 18 months Arm 1: Sample size 34; mean 91.7; SD (8.3)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study dates: 2004-2009 Study design: Trial randomized parallel Location: Netherlands Funding source / conflict: Industry Study follow-up: 18 months Original, same study, or follow-up studies: Bouwstra, 2003[62]; Bouwstra, 2005[63]; de Jong, 2010[64]; de Jong, 2012[65]; van Goor, 2010[36]	Infants enrolled 119 Infants completers 114 Pregnant age: Placebo: 32.7 DHA: 32.5 DHA+AA: 32.9 (Placebo: 5.1 DHA: 4.4 DHA+AA: 4.8) Infant age: 18 months Race of Mother: NR (100)	Exclusion Criteria: women with vegetarian or vegan diets; women with diabetes mellitus; birth complications	Mothers 33-39 weeks Infants NR Arm 1: placebo Description: Soy bean oil Brand name: none Arm 2: DHA Description: DHA plus soy bean oil Brand name: Marinol D40 Manufacturer: Lipid Nutrition B.V., Wormerveer, The Netherlands; AA: Dose: 1 capsule DHA and 1 capsule soy bean oil once a day ALA: 32 mg/d DHA: 220 mg/d EPA: 34 mg/d Arm 3: DHA+AA Description: DHA plus AA Brand name: AA: no brand name Manufacturer: Wuhan Alking Bioengeneering Co. Ltd., Wuhan, China Dose: 2 capsules once a day ALA: 7 mg/d DHA: 220 mg/d EPA: 36 mg/d AA: 220 mg per capsule	Arm 2: Sample size 41; mean 95.8; SD (11.4) Arm 3: Sample size 39; mean 92.4; SD (8.8) Outcome: fluency score (Unspecified) Follow-up time: 18 months Arm 1: Sample size 34; median 10.0; range Arm 2: Sample size 41; median 9.0; range Arm 3: Sample size 39; median 10.0; range Outcome: neurological optimality score (Unspecified) Follow-up time: 18 months Arm 1: Sample size 34; median 47.5; range Arm 2: Sample size 41; median 46.0; range Arm 3: Sample size 39; median 48.0; range Outcome: prevalence of complex minor neurological dysfunction (Unspecified) Follow-up time: 18 months Arm 1: 5/34 (14.7%) Arm 2: 3/41 (7.3%) Arm 3: 5/39 (12.8%) Outcome: prevalence of normal neurological condition (Unspecified) Follow-up time: 18 months Arm 1: 20/34 (58.8%) Arm 2: 24/41 (58.5%) Arm 3: 28/39 (71.8%) Outcome: prevalence of simple minor neurological dysfunction (Unspecified) Follow-up time: 18 months Arm 1: 9/34 (26.5%) Arm 2: 14/41 (34.1%) Arm 3: 6/39 (15.4%)
Gustafson et al., 2013[74] Study name: NR Study dates: May 2009 - July 2011 Study design: Trial randomized parallel	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 67 Pregnant withdrawals 12 Pregnant completers 52 Infants enrolled 44 Infants completers 41	Inclusion Criteria: between 16–35.9 years of age and carrying a singleton pregnancy between the 12th and 20th week of gestation Exclusion Criteria: any serious health condition likely to affect the growth	Start time: Pregnant 12-20 week gestation Infants birth Duration: Pregnancy to birth Arm 1: Placebo Description: g 50% soy and 50% corn oil Manufacturer: Martek Biosciences, now DSM Nutritional Products Dose: 3 capsule a day each 500 mg	Outcome: Neonatal Behavior Assessment: autonomic (Primary) Follow-up time: 7 days post-partum Arm 1: Sample size 12; mean 14.83; SD (16.9) Arm 2: Sample size 15; mean 18.13; SD (14.48) t_{25}=1.99, P=0.029 Outcome: Neonatal Behavior Assessment:

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Location: US Funding source / conflict: Government, Manufacturer supplied product	Pregnant age: placebo 25.6+; DHA 25.5 (placebo 4.8; DHA 4.3) Race of Mother: White European (46.3) Black (37.3) Asian (3) Hispanic (13.4) Baseline biomarker information: plasma DHA (wt% TFA) placebo group: 3.91 (3.15-4.21); DHA group: 3.94(3.39-4.72) RBC DHA (wt% TFA) placebo group 4.30(3.99-5.03); DHA group 4.50 (3.73-5.44)	and development of the fetus or health of the mother including cancer, lupus, hepatitis, diabetes mellitus (Type1, Type 2 or gestational) or HIV/AIDS at baseline or fetal cardiac structural or conduction defects. Women who self-reported illicit drug use or alcohol use during pregnancy and those with hypertension or BMI Z40 were excluded. Women who were taking more than 200 mg/day DHA in prenatal vitamins or over the counter supplements were excluded from participation	Blinding: Only members of the investigational pharmacy knew the subject allocation. Participants and all members of the investigational team were blinded to the intervention assignment. Participants were allocated to either group based on the simple randomization procedure using random numbers generated by SAS. All capsules were the same color, size, weight and the oils were orange-flavored to prevent investigator or subject bias. Arm 2: algal oil as a source of DHA (200 mg of DHA per capsule for a total of 600 mg DHA/day) Dose: 3 capsule of 200mg DHA total 600 mg DHA: 200 mg * 3	motor (Primary) Follow-up time: 7 days post-partum Arm 1: Sample size 12; mean 23.08; SD (11.4) Arm 2: Sample size 15; mean 26.07; SD (18.13) t_{25}=1.87, P=0.038)
Jensen et al., 2005[136] Study name: Unnamed Trial B Study dates: <2004 Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Government Original, same study, or follow-up studies: Jensen, 2010[135]	Study Population: Breast-feeding women Lactating enrolled 227 Lactating completers 174 Infants enrolled 230 Infants completers 177 Lactating enrolled 227 Lactating completers 174 Lactating age: 31.5 years (5 years) 18-40 Infant age: birth (NA) NA Race of Mother: NR	Inclusion Criteria: maternal age between 18 and 40 y, infant gestational age >=37 wk, infant birth weight between 2500 and 4200 g Exclusion Criteria: chronic maternal disorders, major congenital anomalies, obvious gastrointestinal or metabolic disorders of the infant	Start time: Lactating 5 days after delivery Infants 5 days after birth Duration: Lactating 4 months Infants 4 months Arm 1: placebo Description: capsule containing corn & soy oil Manufacturer: Martek Biosciences Purity Data: 15% saturated fatty acids, 23.5% monounsaturated fatty acids, 56.3% linoleic acid (18: 2n_x0001_6), and 3.9% _x0001_-linolenic acid (18:3n_x0001_3) Dose: 1 capsule Blinding: identical capsules ALA: 56.3% linoleic acid (18: 2n_x0001_6), 3.9% _x0001_-linolenic acid (18:3n_x0001_3) Total N-3: 57.2% Arm 2: DHA algal triacylglycerol (DHASCO) Description: DHA capsule Brand name: DHASCO	Outcome: Bayley Physical Developmental Index (Primary) Follow-up time: 30 months Arm 1: Sample size 65; mean 108.4; SD (13.8) Arm 2: Sample size 68; mean 116.8; SD (15.2) Outcome: Clinical Linguistic and Auditory Milestone Scale (CLAMS) (Secondary) Follow-up time: 30 months Arm 1: Sample size 72; mean 106.6; SD (14.9) Arm 2: Sample size 75; mean 106.8; SD (15.2) Follow-up time: 12 months Arm 1: Sample size 76; mean 102.5; SD (13.2) Arm 2: Sample size 86; mean 100.6; SD (14.6) Outcome: Clinical adaptive test development quotient (CAT DQ)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			Manufacturer: Martek Biosciences Purity Data: 44%saturatedfattyacids, 13.6% monounsaturated fatty acids, 0.8% linoleic acid (18:2n _x0001_ 6), and 41.7% DHA (22:6n-3) by weight Dose: 1 capsule ALA: 0.8% (18:2n-6) DHA: 200 mg, 41.7% (22:6n-3) Total N-3: 42.5%	(Secondary) Follow-up time: 30 months Arm 1: Sample size 72; mean 98.3; SD (8.7) Arm 2: Sample size 75; mean 98.1; SD (9) Follow-up time: 12 months Arm 1: Sample size 76; mean 110.0; SD (10.8) Arm 2: Sample size 86; mean 109.0; SD (10) Outcome: Gesell Gross Motor development quotient (DQ) (Secondary) Follow-up time: 30 months Arm 1: Sample size 72; mean 102.4; SD (10.2) Arm 2: Sample size 75; mean 100.8; SD (11.4) Follow-up time: 12 months Arm 1: Sample size 76; mean 99.5; SD (13.3) Arm 2: Sample size 86; mean 101.8; SD (13.8)
Jensen et al., 2010[135] Study name: Unnamed Trial B Study dates: NR (<2010) Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Government Study follow-up: 5 years Original, same study, or follow-up studies: Jensen, 2005[136]	Study Population: Breast-feeding women Lactating enrolled 227 Infants enrolled 230 Infants completers 119 Lactating enrolled 227 Lactating age: 31.5 years (5 years) 18 to 40 Infant age: birth (NA) NA Race of Mother: NR (NR)	Inclusion Criteria: maternal age between 18 and 40 y, infant gestational age >=37 wk, infant birth weight between 2500 and 4200 g Exclusion Criteria: chronic maternal disorders, major congenital anomalies, obvious gastrointestinal or metabolic disorders of the infant	Start time: Infants birth Duration: Infants 4 months Arm 1: placebo Description: capsule containing corn & soy oil Manufacturer: Martek Biosciences Purity Data: 50:50 mixture of soy and corn oils consisting, by weight, of 15% saturated fatty acids, 23.5% monounsaturated fatty acids, 56.3% linoleic acid (18:2 n-6) and 3.9% a-linolenic acid (18:3 n-3) Dose: 1 capsule Blinding: capsules were identical ALA: 3.9% Arm 2: omega 3 capsule Description: high-DHA algal triglyceride capsule Brand name: DHASCO Manufacturer: Martek Purity Data: by weight, 44% saturated fatty acids, 13.6% monounsaturated fatty acids, 0.8% linoleic	Outcome: Development test of Visual-Motor Integration (Secondary) Follow-up time: 5 years Arm 1: Sample size 56; mean 11.8; SD (1.8) Arm 2: Sample size 57; mean 11.6; SD (1.9) Outcome: Kaufman Assessment Battery for Children: hand movement (Secondary) Follow-up time: 5 years Arm 1: Sample size 56; mean 9.02; SD (2.84) Arm 2: Sample size 59; mean 8.39; SD (2.55) Outcome: McCarthy (leg coordination) (Secondary) Follow-up time: 5 years Arm 1: Sample size 56; mean 10.7; SD (1.9) Arm 2: Sample size 59; mean 10.6; SD (1.5)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			acid (18:2n-6) and 41.7% DHA (22:6n-3) Dose: 1 capsule DHA: 200 mg	Outcome: Purdue pegboard test (dominant hand) (Secondary) Follow-up time: 5 years Arm 1: Sample size 57; mean 9.8; SD (2.7) Arm 2: Sample size 59; mean 9.6; SD (1.7) Outcome: Purdue pegboard test (non-dominant hand) (Secondary) Follow-up time: 5 years Arm 1: Sample size 57; mean 8.9; SD (2.7) Arm 2: Sample size 59; mean 8.9; SD (1.6)
Judge et al., 2012[40] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: US Funding source / conflict: Multiple foundations and Societies	Study Population: Healthy pregnant women Pregnant enrolled 48 Pregnant age: Treatment group: 23.93 Placebo: 23.86 (Treatment group: 4.32 Placebo: 4.53) Race of Mother: White European (Treatment: 11.1%, Placebo: 0%) Black (Treatment: 18.5%, Placebo: 4.8%) Asian (Treatment: 3.7%, Placebo: 0%) Hispanic (Treatment: 59.3%, Placebo: 80.9%) NR (Treatment: 7.4%, 3 (14.3%)) Baseline biomarker information: Maternal plasma phospholipid (PL) fatty acids (FA): 2.85 +/- .87 % in treatment group and 2.95 +/- .91% in placebo group. Infant RBC PL FA: 7.55 +/- 1.61% in treatment group and 7.07 +/- 1.25% in placebo group.	Inclusion Criteria: The women were either primiparous or had not been pregnant for the past 2 years. Exclusion Criteria: parity greater than 5, history of chronic hypertension, hyperlipidemia, renal, liver or heart disease, thyroid disorder, multiple gestations or pregnancy induced complications including hypertension, preeclampsia or preterm labor, smoking and psychiatric disorders. Women who were treated during labor with analgesics such as Stadol (butorphanol tartrate), that may cause infant respiratory distress were also excluded. In addition, infants born preterm and infants with less than 4 h of crib time in the first and second days postpartum were excluded from the analyses.	Start time: Pregnant 24 weeks gestation Duration: Pregnant until delivery Arm 1: Placebo Description: Control group Manufacturer: Nestec, S.A., Switzerland Blinding: The total macronutrient content was the same in both the DHA and placebo bars with respect to carbohydrate, protein and fat, how- ever, the DHA bars contained fish oil (300 mg DHA) and the placebo bars contained corn oil. Arm 2: DHA Description: Intervention group Manufacturer: Nestec, S.A., Switzerland Dose: average of 5 bars weekly DHA: 300 mg EPA-DHA: 8:1 ratio of DHA to EPA	Outcome: Infant sleep: Active Sleep (AS, %) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 51.81; SD (10.43) Arm 2: Sample size 27; mean 49.39; SD (10.32) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 51.7; SD (11.13) Arm 2: Sample size 24; mean 51.57; SD (14.54) Outcome: Infant sleep: Active–Quiet Sleep Transition (AQST, %) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 0.53; SD (0.23) Arm 2: Sample size 27; mean 0.59; SD (0.37) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 0.41; SD (0.27) Arm 2: Sample size 24; mean 0.47; SD (0.3) Outcome: Infant sleep: Arousals in AS (Ar/AS) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 20.41; SD (4.39) Arm 2: Sample size 27; mean 17.41; SD (4.71) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 24.67; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(6.82) Arm 2: Sample size 24; mean 24.04; SD (7.04) Outcome: Infant sleep: Arousals in QS (Ar/QS) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 5.89; SD (6.01) Arm 2: Sample size 27; mean 2.7; SD (2.65) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 5.44; SD (4.07) Arm 2: Sample size 24; mean 3.55; SD (3.98) Outcome: Infant sleep: Mean Sleep Period (LSP, min) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 185.95; SD (79.75) Arm 2: Sample size 27; mean 228.19; SD (104.89) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 202.6; SD (123.18) Arm 2: Sample size 24; mean 190.75; SD (102.75) Outcome: Infant sleep: Mean Sleep Period (MSP, min) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 46.09; SD (17.6) Arm 2: Sample size 27; mean 48.03; SD (17.55) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 48.85; SD (29.99) Arm 2: Sample size 24; mean 48.67; SD (21.18) Outcome: Infant sleep: Wakefulness (W, %) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 27.59; SD (11.54)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 2: Sample size 27; mean 29.57; SD (13.56) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 28.95; SD (12.14) Arm 2: Sample size 24; mean 30.71; SD (18.92) Outcome: Infant sleep: quiet sleep (QS,%) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 15.14; SD (4.26) Arm 2: Sample size 27; mean 15.88; SD (5.1) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 13.7; SD (4.76) Arm 2: Sample size 24; mean 12.7; SD (5.85) Outcome: Infant sleep: Active sleep bout length (ASBL, min) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 28.93; SD (9.67) Arm 2: Sample size 27; mean 29.0; SD (7.07) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 29.81; SD (12.5) Arm 2: Sample size 24; mean 30.48; SD (9.14) Outcome: Infant sleep: Active/Quiet Sleep Ratio(AS:QS) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 3.83; SD (2.15) Arm 2: Sample size 27; mean 3.38; SD (1.1) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 4.56; SD (3.13) Arm 2: Sample size 24; mean 4.46; SD (2.14) Outcome: Infant sleep: Quiet sleep bout

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				length (QSBL, min) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 21.81; SD (4.93) Arm 2: Sample size 27; mean 22.74; SD (5.73) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 20.59; SD (4.98) Arm 2: Sample size 24; mean 18.75; SD (6.86) Outcome: Infant sleep: Sleep–Wake Transition (T, %) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 4.92; SD (1.48) Arm 2: Sample size 27; mean 4.57; SD (1.33) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 5.23; SD (1.88) Arm 2: Sample size 24; mean 4.5; SD (1.39) Outcome: Infant sleep: Sleep–Wake Transition (T, %) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 4.92; SD (1.48) Arm 2: Sample size 27; mean 4.57; SD (1.33) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 5.23; SD (1.88) Arm 2: Sample size 24; mean 4.5; SD (1.39)
Makrides et al., 2009[116] Study name: DINO Study dates: Enrollment April 2001 to October 2005	Study Population: Preterm infants Breast-feeding women Pregnant enrolled 545 Infants enrolled 657 Infants completers 614	Inclusion Criteria: infants born at < 33 wk of gestation Exclusion Criteria: Infants born with major congenital or chromosomal	Start time: Infants 4 days after birth Duration: Infants until infants reached their "expected" date of delivery Arm 1: Placebo Description: Soy oil capsules or regular preterm formula	Outcome: Bayley psychomotor development index (Secondary) Follow-up time: 18 months Arm 1: Sample size 335; mean 92.1; SD (16.3) Arm 2: Sample size 322; mean 93.1; SD (16.1)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies, Manufacturer supplied product, Some authors serve on scientific advisory boards for corporations, Some authors have received research funding from infant formula manufacturers Study follow-up: 18 months Original, same study, or follow-up studies: Smithers, 2008[104]; Smithers, 2010[117]; Manley, 2011[118]; Collins, 2011[105]; Atwell, 2013[119]; Collins, 2015[120]	Lactating age: 30 years (5.5 years) NR Infant age: 4 days after birth (29 weeks gestation) 2 to 6 days after birth Race of Mother: White European (90%)	abnormalities, lactating women for whom tuna oil was contraindicated(women with bleeding disorders or taking anticoagulants)	Manufacturer: Clover Corporation Dose: six 500-mg soy oil capsules Blinding: all capsules were similar in size, shape, and color Maternal conditions Infant conditions Current smoker 25.1% during pregnancy Pre-term birth 100% Low birth weight 44.5% Other conditions 1 SGA 18.6% Arm 2: tuna oil capsules Description: DHA-rich tuna oil capsules or high-DHA formula Manufacturer: Clover Corporation Dose: 6 500 mg capsules Maternal conditions Infant conditions DHA: Capsules: Intended to achieve breast milk concentration of 1.0%.Formula: 1.0% AA: Capsules: not intended to alter AA levels. Formula: 0.6% Current smoker 25.6% during pregnancy Pre-term birth 100% Low birth weight 45.7% Other conditions 1 SGA 18.9%	
Meldrum et al., 2012[140] Study name: Infant FishOil Supplementation Study (IFOS) Study dates: Recruitment from June 2005 through October 2008 Study design: Trial randomized parallel Location: Australia	Study Population: Pregnant women with allergies Pregnant enrolled 420 Infants enrolled 420 Infants completers 287 Mother age: NR (NR) NR Infant age: Birth (NA) NA Race of Mother: NR	Inclusion Criteria: allergic pregnant women were recruited as their infants are at a higher risk of developing allergic disease. Maternal atopy was defined by at least one positive skin prick test to at least one of a defined panel of allergens. Exclusion Criteria: maternal smoking, a pre-existing medical	Start time: Infants birth Duration: Infants 6 months Arm 1: placebo Description: olive oil capsule Manufacturer: Ocean Nutrition, Canada Active ingredients: 66·6 % n-9 oleic acid Viability: he composition was regularly tested by an independent laboratory during the trial Dose: one 650 mg capsule Blinding: image and scent matched Arm 2: fish oil capsule Manufacturer: Ocean Nutrition, Canada	Outcome: Categorical Child Behavior Checklist: Sleep problems - number with t-score>59 (Primary) Follow-up time: 18 months Arm 1: 56/144 (39.0%) Arm 2: 54/125 (43.5%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Funding source / conflict: Government, None, Manufacturer supplied product Original, same study, or follow-up studies: D'Vaz, 2012[142]	Baseline biomarker information: Cord blood data Fish oil group LA, linoleic acid 3.71 ALA, a-linolenic acid 0·496 EPA 0·334 DHA 7·36 DPA 0·700 AA, arachidonic acid 15·76 Olive oil group LA, linoleic acid 3.81 ALA, a-linolenic acid 0·513 EPA 0·308 DHA 7·44 DPA 0·673 AA, arachidonic acid 15·54 Baseline Omega-3 intake: From maternal food questionnaire, while pregnant Fish oil group LA, linoleic acid 10·59 ALA, a-linolenic acid 0·87 EPA 0·07 DHA 0·09 AA, arachidonic acid 0·87 Olive oil group LA, linoleic acid 9·90 ALA, a-linolenic acid 0·89 EPA 0.06 DHA 0·08 AA, arachidonic acid 0·84	condition or high-risk pregnancy, more than three fish meals consumed per week or fish oil intake during pregnancy in excess of 1000 mg/d, preterm delivery, and infants with significant congenital abnormalities or medical conditions.	Viability: he composition was regularly tested by an independent laboratory during the trial. Dose: one 650 mg capsule DHA: 280 mg EPA: 110 mg	
Meldrum et al., 2015[51] Study name: Dunstan Study dates: 10/2012-12/2013 for 12-year followup Study design: Trial randomized parallel Location: Australia Funding source / conflict: Multiple foundations and Societies, None	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 98 Pregnant completers 82 Infants enrolled 82 Infants completers 50 Pregnant age: Fish oil 30.9 Control 32.6 (Fish oil: 3.7 Control: 3.6) Infant age: NR (NR)	Inclusion Criteria: Pregnant women with allergies Exclusion Criteria: Women were ineligible for the study if they smoked, had medical problems, a complicated pregnancy, seafood allergy, or if their normal dietary intake exceeded two meals of fish per week. Children were excluded from the study if they were born before	Start time: Pregnant 20 weeks gestation Duration: Pregnant to birth Arm 1: Placebo Description: Olive oil capsules Manufacturer: Pan Laboratories Dose: 4 1g capsules per day Blinding: Randomization and allocation of capsules was carried out in a blinded manner, and capsules in the two groups were image matched Arm 2: Fish oil Manufacturer: Ocean Nutrition Active ingredients: 3–4 mg/g oil a-tocopherol (vitamin E)	Outcome: Beery-Buktenica Development Test of Visual-Motor Integration (TVMI) (Secondary) Follow-up time: 12 years Arm 1: Sample size 23; mean 103.2; SD (9.9) Arm 2: Sample size 24; mean 104.4; SD (9)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study follow-up: 12 years Original, same study, or follow-up studies: Dunstan, 2003[50]; Dunstan, 2008[44];	Race of Mother: NR (100)	36 weeks' gestation or with major disease (to avoid the confounding effects on immune response) or if cord blood was not collected	Dose: 4 1g capsules per day DHA: 2.2g EPA: 1.1g	
Mulder et al., 2014[75] Study name: NR Study dates: 2004 to 2008 Study design: Trial randomized parallel Location: Canada Funding source / conflict: Government Study follow-up: 18 months	Study Population: Healthy pregnant women Pregnant enrolled 271 Pregnant completers 200 Pregnant age: 33 years (4 years) NR Race of Mother: White European (73%) Other race/ethnicity (27%) Baseline biomarker information: maternal RBC Phusphatidylethanolamine DHA: placebo group 6.25 (1.60) g/ 100g DHA group 6.36 (1.62) g/ 100g Baseline Omega-3 intake: median (2.5 to 97.5th percentile range) intake: placebo group 80.0 (0.00-334) mg/day, DHA group 90.0 (6.00-472) mg/d	Inclusion Criteria: at least 16 wk gestation, not taking any lipid or fatty acid supplement, and were expected to deliver one infant at full-term gestation, with no maternal or fetal complications Exclusion Criteria: NR	Start time: Pregnant 16 weeks gestation Duration: Pregnant Until birth Arm 1: placebo Description: corn and soybean oil supplement Manufacturer: Martek Biosciences Blinding: supplements were identical in appearance, contained an orange flavor mask Arm 2: DHA supplement Description: algal oil DHA supplement Manufacturer: Martek Biosciences DHA: 400 mg	Outcome: Number in highest quartile of Bayley Scales of Infant Development III: fine motor (Unspecified) Follow-up time: 18 months Arm 1: 20/80 (25.6%) Arm 2: 22/74 (30.1%) Outcome: Number in highest quartile of Bayley Scales of Infant Development III: gross motor (Unspecified) Follow-up time: 18 months Arm 1: 21/80 (26.6%) Arm 2: 22/74 (29.7%)
Ramakrishnan et al., 2015[61] Study name: POSGRAD Study dates: 2005-2009 Study design: Trial	Study Population: Healthy pregnant women Pregnant enrolled 1094 Pregnant completers 968 Infants enrolled 973 Infants completers 730	Inclusion Criteria: Women who were in gestation week 18–22, age 18–35 years, planned to deliver at the IMSS General Hospital and to remain in the area for the next 2 years, and	Start time: Pregnant 18-22 weeks gestation Duration: Pregnant 18-22 weeks gestation until delivery Arm 1: Control Description: Corn and soy oils with no added antioxidants	Outcome: Bayley PDI (Primary) Follow-up time: 18 months Arm 1: Sample size 365; mean 93.3; SD (9.8) Arm 2: Sample size 365; mean 93.0; SD (8.9)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
randomized parallel Location: Mexico Funding source / conflict: Government, None, March of Dimes Study follow-up: 18 months Original, same study, or follow-up studies: Ramakrishnan, 2010[32]; Stein, 2012[33]; Imhoff-Kunsch, 2011[58]; Escamilla-Nunez, 2014[59]; Gonzalez-Casanova, 2015[60]; Ramakrishnan, 2015[61]	Pregnant age: Placebo: 26.3 Intervention: 26.5 (Placebo: 4.6 Intervention: 4.9) Infant age: Placebo: 20.5 weeks gestation Intervention: 20.6 weeks gestation (Placebo: 2.1 weeks Intervention: 2.0 weeks) Race of Mother: NR (NR) Baseline Omega-3 intake: From original study ref 3364 mg/day for all: LA: 17,846 in controls, 17,645 in DHA AA: 137 in controls, 140 in DHA ALA: 1,488 in controls, 1,477 in DHA EPA: 18 in controls, 18 in DHA DHA: 54 in controls, 56 in DHA	planned predominant breastfeeding for at least 3 months Exclusion Criteria: High risk pregnancy, had any lipid metabolism/absorption conditions, regularly took DHA or fish oil supplements, or used certain chronic medications (such as antiepileptic drugs)	Dose: 2 capsules/day Blinding: Similar in appearance and taste to the DHA capsules Arm 2: Intervention Description: Algal-sourced DHA capsule Manufacturer: Martek Biosciences Dose: 2 capsules/day DHA: 200 mg * 2 = 400 mg/d	
Stein et al., 2012[33] Study name: POSGRAD Study dates: Feb 2005-Feb 2007 Study design: Trial randomized parallel Location: NR Funding source / conflict: Government Original, same study, or follow-up studies:	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 1094 Pregnant withdrawals 63 Pregnant completers 900 Pregnant age: 26.3 (4.6-4.8) Infant age: 39.1 (1.7-1.8) Race of Mother: NR (NR)	Inclusion Criteria: Singleton live births without congenital anomalies Exclusion Criteria: 3364: high risk pregnancy, (history and prevalence of pregnancy complications, including abruption placentae, preeclampsia, pregnancy-induced hypertension, any serious bleeding episode in the current pregnancy, and physician referral);	Start time: Pregnant 18-22 wk Duration: Pregnant to birth Arm 1: Placebo Description: A mixture of corn and soy oil Manufacturer: Martek Biosciences Blinding: "Participants and members of the study team were unaware of the treatment scheme throughout the intervention period of the study" Arm 2: DHA Description: DHA 400 mg/d Manufacturer: Martek Biosciences Dose: 2 capsule per day DHA: 2*200mg	Outcome: auditory evoked responses: latency 1 (ms) (Primary) Follow-up time: 1 month Arm 1: Sample size 377; mean 1.63; SD (0.14) Arm 2: Sample size 372; mean 1.62; SD (0.16) Follow-up time: 3 months Arm 1: Sample size 334; mean 1.58; SD (0.15) Arm 2: Sample size 330; mean 1.58; SD (0.15) Outcome: auditory evoked responses: latency 1-3 (ms) (Primary) Follow-up time: 1 month Arm 1: Sample size 377; mean 2.57; SD (0.36)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Ramakrishnan, 2010[32]; Imhoff-Kunsch, 2011[58]; Escamilla-Nunez, 2014[59]; Gonzalez-Casanova, 2015[60]; Ramakrishnan, 2015[61]		lipid metabolism or absorption disorders, regular intake of fish oil or DHA supplement, or chronic use of certain medication(e.g. epilepsy medications)		Arm 2: Sample size 372; mean 2.56; SD (0.27) Follow-up time: 3 months Arm 1: Sample size 334; mean 2.44; SD (0.28) Arm 2: Sample size 330; mean 2.45; SD (0.28) Outcome: auditory evoked responses: latency 1-5 (ms) (Primary) Follow-up time: 1 month Arm 1: Sample size 377; mean 4.93; SD (0.36) Arm 2: Sample size 372; mean 4.91; SD (0.39) Follow-up time: 3 months Arm 1: Sample size 334; mean 4.75; SD (0.39) Arm 2: Sample size 330; mean 4.72; SD (0.39) Outcome: auditory evoked responses: latency 3 (ms) (Primary) Follow-up time: 1 month Arm 1: Sample size 377; mean 4.19; SD (0.33) Arm 2: Sample size 372; mean 4.18; SD (0.32) Follow-up time: 3 months Arm 1: Sample size 334; mean 4.02; SD (0.32) Arm 2: Sample size 330; mean 4.03; SD (0.33) Outcome: auditory evoked responses: latency 3-5 (ms) (Primary) Follow-up time: 1 month Arm 1: Sample size 377; mean 2.37; SD (0.3) Arm 2: Sample size 372; mean 2.37; SD (0.34) Follow-up time: 3 months Arm 1: Sample size 334; mean 2.31; SD (0.35) Arm 2: Sample size 330; mean 2.28; SD (0.33) Outcome: auditory evoked responses:

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				latency 5 (ms) (Primary) Follow-up time: 1 month Arm 1: Sample size 377; mean 6.55; SD (0.42) Arm 2: Sample size 372; mean 6.52; SD (0.48) Follow-up time: 3 months Arm 1: Sample size 334; mean 6.33; SD (0.4) Arm 2: Sample size 330; mean 6.29; SD (0.42)
Tofail et al., 2006[77] Study name: NR Study dates: Enrollment January to March 2000 Study design: Trial randomized parallel Location: Bangladesh Funding source / conflict: Government Study follow-up: 10 months	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 400 Pregnant completers 151 Pregnant age: 22.7 years (4.35 years) NR Race of Mother: Asian (100%)	Inclusion Criteria: seems as if all pregnant women at 25 weeks gestation were enrolled, no inclusion criteria specified Exclusion Criteria: NR	Start time: Pregnant 25 weeks gestation Duration: Pregnant until birth Arm 1: placebo Description: soy oil capsule Dose: 4 one gram capsules per day Blinding: capsules were identical in appearance Other dose 1: LNA 0.27 g Other dose 2: linoleic acid 2.25 g Arm 2: DHA supplement Description: fish oil capsules Dose: 4 one gram capsules per day DHA: 1.2 g EPA: 1.8 g	Outcome: Bayley Scale of Infant Development (Psychomotor developmental index) (Unspecified) Follow-up time: 10 months Arm 1: Sample size 124; mean 100.5; SD (10.1) Arm 2: Sample size 125; mean 101.7; SD (10.9)
Unay et al., 2004[138] Study name: NR Study dates: 2000-2001 Study design: Trial randomized parallel Location: Turkey Funding source / conflict: NR	Study Population: Healthy infants Infants enrolled 54 Infants completers 44 Infant age: NR (term) Race of Mother: NR (NR)	Inclusion Criteria: healthy, full term newborns of appropriate size for gestational age, who were not going to be breast fed because that was the mother’s wish or because of maternal illness or medication incompatible with breast feeding just after birth Exclusion Criteria: Perinatal asphyxia, central nervous system	Start time: Infants week 1 Duration: Infants 16 weeks Arm 1: Formula B Description: Infant formula without added DHA Brand name: Nutrilon I Manufacturer: NV Nutricia Netherlands Active ingredients: Linoleic acid 11.2gm/100gm fat ALA: 2.2g/100g fat AA: Trace Arm 2: Formula A Description: DHA-containing formula Brand name: Farley's First Milk	Outcome: brainstem auditory evoked potentials: interpeak latency I-III (Unspecified) Follow-up time: 16 weeks Arm 1: Sample size 22; mean decrease 0.25; SD (0.14) Arm 2: Sample size 22; mean decrease 0.34; SD (0.16) Outcome: brainstem auditory evoked potentials: interpeak latency I-V (Unspecified) Follow-up time: 16 weeks Arm 1: Sample size 22; mean decrease 0.33; SD (0.16) Arm 2: Sample size 22; mean decrease

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		infection, congenital malformation, or significant hyperbilirubinaemia	Manufacturer: HJ Heinz UK Blinding: not reported ALA: 1.2g/100gm DHA: 0.5g/100gm AA: Trace Arm 3: Human milk Description: Breast milk Active ingredients: Linoleic acid: 10.85 gm/100gm fat ALA: 1.03gm/100g fat DHA: 0.25 gm/100gm fat AA: 0.46 gm/100g fat	0.47; SD (0.2) Outcome: brainstem auditory evoked potentials: interpeak latency III-V (Unspecified) Follow-up time: 16 weeks Arm 1: Sample size 22; mean decrease 0.08; SD (0.07) Arm 2: Sample size 22; mean decrease 0.14; SD (0.1) Outcome: brainstem auditory evoked potentials: wave I (Unspecified) Follow-up time: 16 weeks Arm 1: Sample size 22; mean decrease 0.27; SD (0.14) Arm 2: Sample size 22; mean decrease 0.35; SD (0.13) Outcome: brainstem auditory evoked potentials: wave III (Unspecified) Follow-up time: 16 weeks Arm 1: Sample size 22; mean decrease 0.52; SD (0.15) Arm 2: Sample size 22; mean decrease 0.69; SD (0.16) Outcome: brainstem auditory evoked potentials: wave V (Unspecified) Follow-up time: 16 weeks Arm 1: Sample size 22; mean decrease 0.6; SD (0.11) Arm 2: Sample size 22; mean decrease 0.83; SD (0.18)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
de Jong et al., 2010[64] Study name: Groningen LCPUFA study Study dates: 1997-2008 Study design: Trial randomized parallel Location: Netherlands Funding source / conflict: Government Study follow-up: 9 years Original, same study, or follow-up studies: Bouwstra, 2003[62]; Bouwstra, 2005[63]; de Jong, 2012[65]; van Goor, 2010[36]; van Goor, 2011[66]	Study Population: Healthy infants Infants enrolled 474 Infants completers 341 Infant age: Gestational age 39.6 wk (1.3 weeks) NR Race of Mother: White European (100)	Inclusion Criteria: healthy term infants Exclusion Criteria: Infants who had a congenital disorder that interfered with adequate functioning in daily life, infants from multiple births, infants whose mothers did not have mastery of the Dutch language or suffered from significant illness or disability, adopted and foster infants, and formula-fed infants who had received human milk for >5 d.	Start time: Infants birth Duration: NR Arm 1: control group Description: standard formula Manufacturer: Zoetermeer, Netherlands Active ingredients: linoleic acid (11mol%); ALA 1.27 mol% Blinding: NR Arm 2: Omega 3 group Description: LCPUFA formula Brand name: Nutrilon Premium Manufacturer: Nutricia, Zoetermeer, The Netherlands Dose: NR DHA: 0·30 % (by weight) AA: 0·45 % (by weight) Arm 3: Breast fed group Description: Breast feeding only - no formula	Outcome: Touwen examination: neurologically normal (Unspecified) Follow-up time: 9 years Arm 1: 56/123 (46.0%) Arm 2: 44/91 (48.0%)
van Goor et al., 2010[36] Study name: Groningen LCPUFA study Study dates: Enrollment from December 2004 until December 2006 Study design: Trial randomized parallel Location: Netherlands Funding source / conflict: Industry, Government Study follow-up: 12 weeks	Study Population: Healthy pregnant women Breast-feeding women Pregnant enrolled 183 Pregnant completers 125 Infants completers 119 Pregnant age: 32 years (5 years) Infant age: 14 to 20 weeks gestation Race of Mother: NR (100)	Inclusion Criteria: healthy women with a first or second low-risk singleton pregnancy Exclusion Criteria: women with vegetarian or vegan diets and women with diabetes mellitus	Start time: Pregnant 14 to 20 weeks gestation Infants 14 to 20 weeks gestation Duration: Pregnant until 3 months after delivery Infants until 3 months of age Arm 1: placebo Description: soybean oil capsule Manufacturer: Wuhan Alking Bioengineering Active ingredients: standard dose vitamins and minerals Dose: 2 capsules Maternal conditions ALA: 60 mg DHA: 0 EPA: 0 AA: 0 Other dose 1: LA 535 mg Current smoker 2%	Outcome: general movements: number definitely abnormal (Secondary) Follow-up time: 12 weeks Arm 1: 0/36 (0.0%) Arm 2: 1/42 (2.38%) Arm 3: 0/41 (0.0%) Follow-up time: 2 weeks Arm 1: 1/36 (2.78%) Arm 2: 0/42 (0.0%) Arm 3: 0/41 (0.0%) Outcome: general movements: number mildly abnormal (Secondary) Follow-up time: 12 weeks Arm 1: 11/36 (30.56%) Arm 2: 25/42 (59.52%) Arm 3: 14/41 (34.15%) Follow-up time: 2 weeks Arm 1: 11/36 (30.56%) Arm 2: 20/42 (47.62%) Arm 3: 15/41 (36.59%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Original, same study, or follow-up studies: Bouwstra, 2003[62]; Bouwstra, 2005[63]; de Jong, 2010[64]; de Jong, 2012[65]; van Goor, 2011[66]			Arm 2: DHA group Description: DHA fish oil capsule Manufacturer: Wuhan Alking Bioengineering Active ingredients: standard dose vitamins and minerals Dose: 2 capsules Maternal conditions ALA: 32 mg DHA: 220 mg EPA: 34 mg AA: 15 mg Other dose 2: LA 274 mg Current smoker 2% Arm 3: DHA + AA group Description: DHA + AA capsule Brand name: Marinol D40 Manufacturer: Lipid Nutrition B.V., Wormerveer, The Netherlands Active ingredients: standard dose vitamins and minerals Dose: 2 capsules Maternal conditions ALA: 7 mg DHA: 220 mg EPA: 36 mg AA: 220 mg Other dose 2: LA 46 mg Current smoker 3%	Outcome: general movements: number normal optimal (Secondary) Follow-up time: 12 weeks Arm 1: 2/36 (5.56%) Arm 2: 0/42 (0.0%) Arm 3: 1/41 (2.44%) Follow-up time: 2 weeks Arm 1: 1/36 (2.78%) Arm 2: 0/42 (0.0%) Arm 3: 1/41 (2.44%) Outcome: general movements: number normal suboptimal (Secondary) Follow-up time: 12 weeks Arm 1: 23/36 (63.89%) Arm 2: 16/42 (38.1%) Arm 3: 26/41 (63.41%) Follow-up time: 2 weeks Arm 1: 19/36 (52.78%) Arm 2: 17/42 (40.48%) Arm 3: 22/41 (53.66%) Outcome: neonatal neurological classification: number definitely abnormal (Secondary) Follow-up time: 2 weeks Arm 1: 0/36 (0.0%) Arm 2: 0/42 (0.0%) Arm 3: 0/41 (0.0%) Outcome: neonatal neurological classification: number mildly abnormal (Secondary) Follow-up time: 2 weeks Arm 1: 7/36 (19.44%) Arm 2: 6/42 (14.29%) Arm 3: 8/41 (19.51%) Outcome: neonatal neurological classification: number normal (Secondary) Follow-up time: 2 weeks Arm 1: 28/36 (77.78%) Arm 2: 35/42 (83.33%) Arm 3: 33/41 (80.49%)

Table 15. Observational studies for neurological development

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Bakker, et al., 2009[134] Outcome domain: Neurological Study dates: 12/90-1/94 Study design: Observational prospective Location: Netherlands Funding source / conflict: Government Follow-up: 7 years Original, same study, or follow-up studies: Bakker, 2003[80] and two articles in original report: Ghys, 2002 and Al, 1995	Study Population: Healthy infants Infants enrolled 750 Infants withdrawals 444 Infants completers 306 Pregnant age: 29.8 (4.1) Infant age: gestational age: boys: 39.8; girls 40.0 (boys 1.7; girls 1.4) Race of Mother: White European (100)	Inclusion Criteria: 750 Caucasian children of 7 y old, born between December 1990 and January 1994 in the course of an earlier study on maternal and neonatal LCPUFA status and pregnancy outcome Exclusion Criteria: Not reported	Adjustments: Gender, cognitive function, gestational age, age at measurement
Bernard, et al., 2013[89] Outcome domain: Neurological Study name: EDEN Study dates: Recruitment 2003 to 2005 Study design: Observational prospective Location: NR Funding source / conflict: Industry, Government Follow-up: 2 and 3 years Original, same study, or follow-up studies: Drouillet, 2009[80]	Study Population: Healthy pregnant women Pregnant enrolled 2,002 Pregnant completers 1,882 Infants enrolled 1.882 Infants completers 1,510 Pregnant age: 29.2 years (at conception) (4.8 years) NR Infant age: < 24 weeks gestation (NR) NR Race of Mother: NR (100)	Inclusion Criteria: < 24 weeks amenorrhea Exclusion Criteria: multiple pregnancies, known diabetes before pregnancy, illiteracy, and intention to move outside the region in the next 3 years	Adjustments: Center, child gender & age, gestational age, maternal age, obesity, energy intake, tobacco & alcohol consumption, parental education & income, first born, main daytime caregiver, and frequency of maternal stimulations
Bouwstra, et al., 2006[133] Outcome domain: Neurological Study dates: 1997-1999	Study Population: Healthy infants Infants enrolled 317 Infants completers 269 Pregnant age: 30 (4.3)	Inclusion Criteria: All infants were born at 37–42 wk of gestation, had a native West European origin, and were born between February 1997 and October 1999. Exclusion Criteria: children with a congenital	Adjustments: Type of postnatal feeding and potential confounders such as the postnatal age of the infant at GM assessment, paternal smoking, and the total

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Study design: NR Location: Netherlands Funding source / conflict: Industry Follow-up: 3 months Original, same study, or follow-up studies: Bouwstra, 2003[62]	Infant age: 3 months (NR) Race of Mother: White European (100)	disorder interfering with adequate functioning in daily life, children from multiple births, children whose mother did not master the Dutch language or had significant illness or disability, and adopted and fostered children	Obstetric Optimality Score
Jordi Julvez, et al., 2014[143] Outcome domain: Neurological Study name: INMA Study dates: Enrollment conducted July 2004 to July 2006 Followup: 4 years Study design: Observational prospective Location: Spain Funding source / conflict: Government, Multiple foundations and Societies Follow-up: 4 years Original, same study, or follow-up studies: Guxens, 2011[144]	Study Population: Breast-feeding women Pregnant enrolled 657 Pregnant completers 622 Lactating enrolled 622 Lactating completers 582 Infants enrolled 622 Infants completers 434 Lactating enrolled 622 Lactating completers 582 Lactating age: 31.6 years (4.2 years) Infant age: 2 to 5 days after birth Race of Mother: NR (NR)	Inclusion Criteria: age older than 16 years, intent to deliver at the reference hospital, singleton pregnancy Exclusion Criteria: no problems with communication, no assisted conception	Adjustments: Test conditions, child age & sex, parental age, parity, alcohol consumption and smoking during pregnancy, day care attendance, country of birth, maternal education, social class, mental health, attachment to child, and perceptive performance IQ at 14 months, maternal psych symptoms, verbal IQ at 4 years, pollutant exposure during pregnancy.

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Sun, et al., 2010[131] Outcome domain: Neurological Study name: Danish National Birth Cohort Study dates: Recruitment March 1996 to November 2002 Study design: Observational prospective Location: Denmark Funding source / conflict: Government Follow-up: 10.8 years (median 7.8 years)	Study Population: Healthy infants Infants enrolled 65,754 Infants completers 65754 Infant age: birth Race of Mother: NR (NR)	Inclusion Criteria: live-born singletons whose mothers provided information on fish intake from food frequency questionnaire Exclusion Criteria: children with missing information on maternal smoking and parity, children who died during the neonatal period, and children born to mothers with an unlikely high (>16,700 kJ/day) or low (<4200 kJ/day) intake of energy during pregnancy	Adjustments: Energy intake, sex, gestational age, parity, time breastfeeding, maternal age, SES, pre-pregnancy BMI, smoking status at recruitment, maternal history of epilepsy
Valent, et al., 2013[132] Outcome domain: Neurological Study dates: 2007-2011 Study design: Observational prospective Location: Italy Funding source / conflict: Government	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 900 Pregnant completers 767 Infants enrolled 767 Infants completers 632 Pregnant age: 33.3 (4.3) Infant age: Birth Race of Mother: NR (100)	Inclusion Criteria: Permanent residents of the study areas for at least 2 years, at least 18 years of age, and had no absence from the study area for more than 6 weeks during pregnancy, no history of drug abuse, no serious health problems or complications of pregnancy, and no twin gestation Exclusion Criteria: Preterm births (<37 weeks of gestational age), babies with congenital malformations or severe perinatal problems, and those with severe health problems that presented postnatally and potentially compromised their neurological development	Adjustments: Fish intake, fatty acids in maternal serum and proportion of PUFAs, sex, birth weight, maternal IQ, weight gain during pregnancy, marital status at delivery, SES index, number of children living in home, alcohol intake during pregnancy, breastfeeding history, child intake of fish until age 18 months, and daycare attendance at age 18 months

Development of Visual Function (Acuity)

Key Points

- Prenatal Supplementation: Four RCTs found no effects of prenatal supplemental DHA on infant visual acuity, measured behaviorally or using VEP, at follow-up times ranging from 1 week to 6 months. (Studies were too dissimilar to pool).
  - Assessment of the associations between maternal and infant biomarkers following prenatal supplementation and visual acuity showed no association with maternal red blood cell DHA levels or maternal breast milk DHA but a significant association of earlier VEP development with cord blood DHA (p=0.003) .
  - No prospective cohort studies were identified that assessed associations with visual function.
- Postpartum maternal supplementation: Four RCTs (two described in the original report) found no effect of postpartum maternal supplementation (of mothers with healthy term infants) with DHA on any measure of infant visual acuity among breastfed infants at 4 or 8 months, except for one study (n=230) that found a significant improvement in transient VEP amplitude at both time points, favoring DHA (p<0.03); this improvement was not seen at 5 years (n=117).
  - No association of infant plasma biomarkers with visual acuity was seen in one study but an association between visual acuity at 4 months and infant RBC DHA was reported in another study. No studies assessed the association of maternal biomarkers.
  - No observational studies were identified that assessed associations of postpartum maternal exposures with infant visual function.
- Supplementation of preterm infants with any n-3 FA and its effects on infant visual acuity was assessed in 9 studies in the original report and three studies identified for the current report. Pooling five studies that assessed visual acuity using visually-evoked potentials (VEP) at 4 and 6 months of age showed an insignificant effect of n-3 FA supplementation on VEP compared with placebo.
- Supplementation of preterm infants with DHA and its effect on visual acuity was assessed in four RCTs (two in the original report and two identified for the current report; the intervention formula in two of the studies actually included small amounts of EPA). No differences were seen between groups at 2 months, but one study found a significant improvement in adjusted sweep VEP in boys (but not girls) at 4 months of age (p=0.017).

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- Supplementation of healthy term infants with any n-3 FA showed inconsistent effects on visual acuity. At two months' follow-up, the pooled effect size for behavioral measurements showed an insignificant effect of n-3 FA (WMD 0.07 [0.00, 0.14] six RCTs); the pooled effect size for VEP was insignificant (WMD 0.07[-0.03, 0.17], six RCTs). At 4 months' follow-up, the pooled effect size for behavioral measurements was significant in favor of placebo treatment (WMD -0.05 [-0.08, -0.01], six RCTs); the pooled effect size for VEP was significant in favor of n-3 FA (WMD 0.10[0.07, 0.13], eight RCTs). At 12 months follow-up, the pooled effect size for behavioral measures was insignificant (WMD -0.01[-0.04, 0.01]); the pooled effect size for VEP was significant in favor of n-3 FA (WMD 0.14 [0.11, 0.16]).

- Supplementation of healthy term infants with DHA+AA also showed inconsistent results. Eight studies identified for the original report showed no differences at 2, 4, 6, 8 and 9 months; however four studies that assessed VEP at 12 months showed a significant pooled effect size in favor of DHA+AA (p=0.01). Two new studies were identified for the current report that assessed VEP at 4 and 12 months. At 4 months, the pooled effect size for VEP was significant in favor of DHA+AA (WMD -0.10 [-0.14, -0.07], five RCTs). At 12 months follow-up, the pooled effect size for VEP was significant in favor of DHA+AA (WMD -0.14 [-0.17, -0.12] six RCTs).
- Only one study assessed the association between infant biomarkers and visual acuity: This study found mixed associations between term infant red blood cell DHA, and subsequent visual acuity; however better visual acuity was associated with lower n-6 FA to n-3 FA ratios at 4, 9, and 12 months of age.
- No prospective observational studies assessed the association of infant n-3FA exposures and visual acuity development.

Description of Included Studies

Visual acuity in the developing infant and child is assessed using two types of methods. Behavioral methods assess eye movement and head turning in response to the presentation of infants' preferred visual stimuli (patterns); visual acuity is defined as the highest spatial frequency that is distinguishable by the infant (according to the examiner). Electrophysiological methods include the measurement of visual evoked potentials (VEPs), which are physiological responses to these stimuli.

This section reports the findings of studies that assessed the effects of prenatal, postnatal maternal (breast milk), or postnatal infant PUFA supplementation or exposure on visual acuity development. Studies identified for this report are summarized in Table 16 and briefly summarized below.

Antepartum Maternal Supplementation with n-3 Fatty Acids and Infant Visual Acuity

The original report identified one RCT that assessed the effects of administering fish oil to pregnant women on infant photoreceptor function (by electroretinogram) at 1 week of age; this study found no effect.

DHA Versus Placebo

For the current report, we identified four articles reporting on four RCTs that assessed the effect of supplementation of pregnant women with n-3 FA on infant visual acuity:[33, 53, 100, 145] one article[100] reported on the same study in the original report that found no effect of DHA supplementation on photoreceptor function at 1 week. Enrollments ranged from 100 [100] to 900.[33] Studies were conducted in the UK, Canada, Australia, and Mexico.

All four studies administered supplemental DHA, two in the form of DHA-enriched fish oil,[53, 100] and two from algal sources[33, 145] Concentrations ranged from 0.2g/d to 1 gm/d. One study commenced supplementation at 15 weeks,[100] one began at 16 weeks,[145] and the two remaining studies began at midterm: all four continued supplementation until term.

Behavioral Measures

One study employed a BM, Teller visual acuity cards, to assess visual acuity in term infants at 60 days of age.[145]

This study was not powered or designed to assess the effects of maternal DHA supplementation on infant visual acuity but to establish a range of visual acuity scores for infants born to women whose DHA intake was considered to be above requirements.[145] Visual acuity scores did not differ significantly between groups (p=0.3), however, in multivariate analysis, visual acuity scores were related only to sex and DHA intervention group.

Electrophysiological Measures

The remaining three studies employed various VEP measures to assess visual acuity at 0.25, 2.5, and 4 months,[100] 4 months,[53] and 3 and 6 months.[33] The study by Malcolm and colleagues (2003) found no difference between intervention groups in any VEP measure at birth or at 2.5 months and 4 months.[100] The study by Smithers and colleagues (2011) found no difference between intervention groups in mean sweep VEP acuity at 4 months in healthy full-term infants.[53] The study by Stein and colleagues (2012) found no difference between intervention groups in any measure of VEPs at 3 and 6 months.[33]

Maternal and Infant Biomarkers

Two of the four RCTs that assessed the effects of antepartum maternal supplementation with n-3 FA on children's visual acuity also assessed the association between biomarkers of exposure and visual acuity outcomes.

Innis and Friesen assessed the association between maternal red blood cell (RBC) ethanolamine phosphoglyceride (EPG) concentrations of DHA and infant visual acuity at 2 months of age. No difference was seen in Spearman rank correlation coefficients for either the DHA-supplemented or placebo groups, for girls (ρ =0.18, 0.10) or boys (ρ=-0.06, 0.07).[145]

Malcolm and colleagues assessed the association between cord RBC DHA maternal breast milk DHA, and VEP. They found a significant association between higher cord blood DHA at birth and earlier VEP development (pattern reversal peak latencies) (p=0.03 for absolute levels and 0.004 for RBC DHA as a percent of total fatty acids). They observed no association between maternal breast milk DHA levels and VEPs.[100]

No prospective cohort studies that assessed the association between maternal or infant biomarkers of n-3 FA status and visual acuity met our inclusion criteria.

Postpartum Maternal Supplementation with n-3 FA and Infant Visual Acuity

The original report identified two RCTs (one reported in an abstract) that examined the effects of postpartum maternal supplementation with increasing doses of n-3 FA (DHA) on the visual acuity of healthy term infants who were breastfed for at least 4 months (follow-up time). Doses ranged from 0.2g/d to 1.3g/d. Neither study showed a significant effect of DHA.

For the current report, we identified two new RCTs that examined the effects of supplementing lactating mothers with n-3 FA on infant visual acuity.

Fish Oil Versus Placebo

We identified one 2004 RCT not included in the original report that examined the effects of postpartum maternal fish oil supplementation on visual acuity in 97 healthy term infants using sweep VEP at 2 and 4 months of age.[127] Mothers in the Danish National Birth Cohort with low habitual fish intake were supplemented beginning within one week of birth to microencapsulated

FO (1.3g per day) or olive oil. Supplementation resulted in significant increases in the n-3 FA content of breastmilk and infant erythrocytes at 4 months. No difference was seen in mean visual acuity measures between the infants of women who received FO (0.62±0.08), those of mothers who received olive oil 0.64±0.09), and those of mothers with high fish intake (0.63±0.09). Bivariate analysis showed that across treatment groups, visual acuity was not significantly associated with infant erythrocyte n-3 FA (p=0.117); however, multivariate analysis that controlled for gestational age and parity showed that infant RBC DHA was significantly associated with visual acuity at 4 months (p=0.008).

DHA Versus Placebo

We identified two new articles reporting on one RCT that examined the effects of postpartum maternal DHA supplementation on infant visual acuity.[135, 136]

Jensen and colleagues (the authors of the abstract summarized in the original report) randomly assigned 227 pregnant U.S. women who planned to breastfeed for at least 4 months to either algal DHA (approximately 0.2g/d) or placebo, to begin at 5 days postpartum and continue for 4 months.[136] Mothers of preterm or low birth weight infants were excluded. Compliance with the supplement was 95 percent to 100 percent. Visual acuity was assessed at 4 and 8 months of age in the 230 infants (including 3 twin pairs) as a secondary variable, using both BM and VEP. No significant differences were seen in visual acuity as assessed by BM at 4 (5.6±0.71 vs. 5.3±0.56 cycles/degree) or 8 months of age (12.3±0.53 vs. 13.5±0.57 cycles/degree) or sweep VEP at 4 months (9.4±0.23 vs. 9.4±0.21 cycles/degree). Transient VEP latency also did not differ between groups at 4 (124.8±11.7 vs. 123.9±0.10.6 milliseconds) or 8 months (115.1±8.1 vs. 115.3±10.5 milliseconds). Transient VEP amplitude was significantly lower in the infants of DHA-treated mothers than in the infants of placebo-treated mothers at both 4 (28.9±12.1 vs. 33.3±12.4 μVolts, p<0.03) and 8 months (24.3±8.9 vs. 27.9±11.0 μV, p<0.03).

A subsequent article reported on visual acuity at 5 years of age in the same population (n=60 children of DHA-supplemented mothers and 57 children of placebo mothers).[135] No differences were seen in visual acuity as measured by BM (Bailey Lovie visual acuity for both right and left eyes) between the groups (52.6±4.6 vs. 51.6 ±5.6 letters correct and 53.1±4.7 vs. 52.1± 4.9, respectively). VEP latency, amplitude, and sweep VEP acuity also showed no significant differences between treatment groups (110.3±8.1 vs. 108.0 ±6.5 msec; 39.6 ±13.7 vs. 45.3 ±18.0 μVolts; 11.9 cycles/degree ±0.3 octaves vs. 11.8 ±0.3 octaves, respectively).

Maternal and Infant Biomarkers

Jensen and colleagues assessed the association between infant plasma phospholipid DHA and visual acuity and found no association (data not reported).[136]

As described above, in an RCT by Lauritzen and colleagues, bivariate analysis showed that across treatment groups, visual acuity was not significantly associated with infant erythrocyte n-3 FA (p=0.117); however, multivariate analysis that controlled for gestational age and parity showed that infant RBC DHA was significantly associated with visual acuity at 4 months (p=0.008).[127]

Infant Formula Supplementation with n-3 FA and Visual Acuity in Preterm Infants

The original report identified nine RCTs that examined the effects of supplementing preterm or term formula with n-3 FA with or without breast feeding on visual acuity in preterm infants; the studies dated from 1992 to 2002. Duration of supplementation ranged from ¾ month to 12 months. Follow-ups ranged from 2 months to 12 months: in some studies, the intervention ended several months before follow-up assessment. Two RCTs assessed the use of formula supplemented with DHA alone, 5 RCTs assessed the use of formula supplemented with DHA plus AA (or DHA plus AA plus a very small quantity of EPA), and the remainder used some combination of DHA, EPA, and ALA. Seven of the RCTs assessed visual acuity using BM, five employed VEP or flash VEP, and three RCTs employed both. Across the nine studies, outcomes were mixed: five studies reported a positive effect of some combination of n-3 FA on a visual acuity outcome, whereas four reported no effects (the intervention in three of these four studies was 2 months or less).

The searches for the current report identified three new studies on the effects of supplementing preterm infants with n-3 FA on visual acuity. One study supplemented infant formula given to large preterm infants with DHA and AA for 6 months and assessed visual acuity at 4 and 6 months using BM and VEP.[137] A second study supplemented breastfeeding mothers of preterm infants or formula fed infants from birth with DHA and assessed visual acuity using sweep VEP (primary) and VEP latency (secondary) at 2 and 4 months (supplementation duration was until expected due date).[104] The third study, DINO, also supplemented breastfeeding mothers of preterm infants or supplemented the formula of formula-fed infants from birth with DHA and conducted tests of visual perception skills at 7 years of age.[120. 121, 146]

Any Omega-3 Fatty Acid vs. Placebo

We were able to pool one of the studies identified for the current report[137] with three studies identified for the original report,[147-149] all measuring visual acuity using VEP at 4 months and 6 months corrected age (one of the studies in the original report stratified participant responses by diagnosis of bronchopulmonary dysplasia)(Figures 16 and 17). At 4 months, the pooled analysis showed an insignificant effect of the intervention on VEP (WMD -0.06 [−0.12; 0.01]; I^2=1.7%). At 6 months corrected age, the pooled analysis showed a similarly insignificant effect (WMD -0.04[-0.09, 0.01] I^2=0%).

Figure 16. Visual function in preterm infants at 4-months corrected age

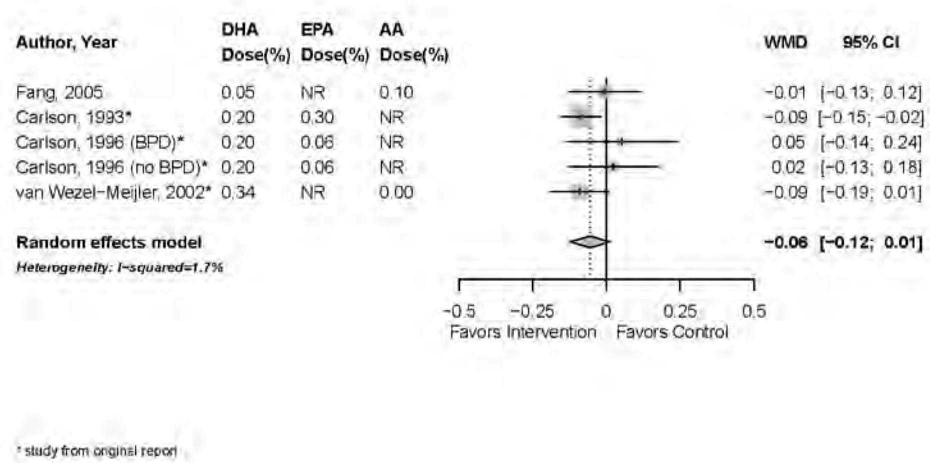
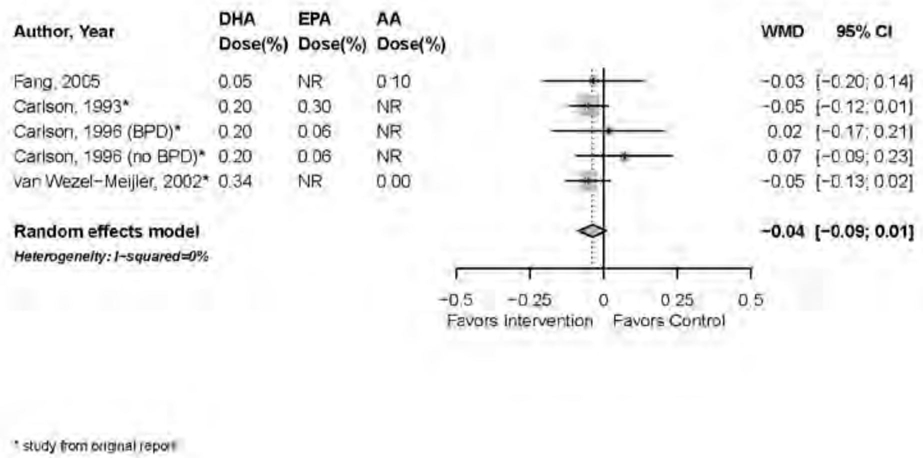


Figure 17. Visual function in preterm infants at 6-months corrected age



DHA Versus Placebo

The original report identified two RCTs that compared the effects of supplementing preterm or term infant formula with DHA vs. placebo on visual acuity outcomes of healthy preterm infants, as assessed using BM. One RCT assessed acuity at 0, 2, 4, 6, and 9 months, and the other at 2 and 4 months. The formula employed in one of the two RCTs actually contained more EPA than DHA and the intervention duration was 9 months; the formula employed in the other intervention appears to have contained only DHA, but the intervention duration was only 1 month. No differences in visual acuity between treatment groups were observed at any time (effect sizes were pooled at 2 and 4 months).

One RCT identified for the current report randomized 143 preterm Australian infants (born at less than 33 weeks gestation) and their mothers to a supplement that contained DHA (29.5 percent of total fatty acids), EPA (6.5 percent), and a small amount of AA (1.8%) in the form of tuna fish oil or to a preterm formula that contained soy oil; the concentration of DHA was intended to mimic that provided in utero.[104] Breastfeeding mothers consumed the oil for the group to which they were assigned (the proportion of infants who received some breastmilk did not differ significantly between groups). The intervention duration was from birth to the expected delivery data. Visual acuity was assessed by sweep VEP at 4 months corrected age (the primary outcome) and VEP latency at 2 and 4 months corrected age. Adjusted sweep VEP was significantly higher at 4 months in the group that received the fish oil-supplemented formula (-1.4[-2.6,-0.2] p=0.017). The effect was significant in boys (-2.1[-3.4, -0.9]) but it was not significant in girls (-0.8[-1.9, 0.4). No differences were observed in visual acuity latency at 2 or 4 months. Use of n-3 FA supplements prenatally was similar across both groups.

A second RCT identified for the current report, the DINO Trial, randomized 657 preterm infants to receive high-dose DHA (or lactating mothers of preterm infants to receive DHA-rich tuna oil capsules) or standard-DHA infant formula (lactating mothers received soy oil capsules).[116, 120] At 7 years corrected age, 604 children were tested on a battery of neurodevelopmental tests, including the Test of Visual Perception Skills. No difference was seen between treatment groups in any of the standard scores.

DHA plus AA Versus Placebo

The original report identified five RCTs that compared the effects of infant formula supplemented with DHA and AA to a control formula. Pooled analysis of studies that measured visual acuity using BM found no differences between groups at 0, 2, 3, 4, or 6 months. Two studies employed VEP to measure visual acuity: One of the studies reported significantly improved visual acuity at 6 months, and pooled assessment of the outcomes of the two studies at 4 months showed no difference.

One RCT identified for the current report randomized 27 preterm infants (30 to 37 weeks gestation, >2000g birth weight) in Taiwan to a DHA (0.05%)- and AA(0.1%)-supplemented infant formula or the same formula without LC-PUFA.[137] The intervention duration was 6 months. No significant differences were observed in visual acuity between the intervention and control groups, measured by VEP or BM, at 4 or 6 months. The VEP outcomes were included in the pooled analyses described above.

Infant Formula Supplementation with n-3 FA and Visual Acuity in Term Infants

The original report identified 13 RCTs that examined the effects of supplementing infant formula with various combinations of n-3 and n-6 FA on visual acuity of term infants. Across the 13 RCTs, effects of supplementation on visual acuity were mixed. For the current report, we identified two new RCTs that examined the effect of supplementing infant formula with n-3 FA on visual acuity in term infants. We were able to pool the results of these studies with those of studies identified for the original report for both BM and VEP at follow-up times of 2, 4, and 12 months of age. At 2 months follow-up time, the pooled effect size for BM of acuity was significant in favor of n-3 FA (WMD 0.07 [0.00, 0.14] I^2=20.2%). The pooled effect size for sweep VEP/VEP was not significant and studies were highly heterogeneous (WMD 0.07 [-0.03, 0.17] I^2=88.3%). At 4 months follow-up time, the pooled effect size for BM of acuity was significant in favor of the placebo (WMD -0.05 [-0.08, -0.01] I^2=0%), whereas the pooled effect size for sweep VEP/VEP was significant in favor of n-3 FA supplementation (WMD 0.10 [0.07, 0.13] I^2=9.1%). No evidence of publication bias was seen (Begg's and Egger's p values were 0.652 and 0.663, respectively) At 12 months follow-up time, the pooled effect size for BM of acuity showed no difference (WMD -0.01 [-0.04, -0.01] I^2=0%), whereas the pooled effect size for sweep VEP/VEP was significant in favor of n-3 FA supplementation (WMD -0.14 [-0.16, -0.11] I^2=18.1%). Again, no evidence of publication bias was seen (Begg's and Egger's p values were 0.188, 0.189, respectively)

DHA Versus Placebo

The original report conducted a pooled analysis of two studies that compared infant formula supplemented with DHA on BM of visual acuity and found no significant benefit at 2, 4, 6, 9, or 12 months. Pooled analysis of three RCTs that used VEP to assess visual acuity also showed no effects at 2, 4, 6, 8, 9, or 12 months.

We identified one RCT[121] that was not included in the original report.[146] A 2007 article reported on a 4-year follow-up to a 1993-1995 RCT that randomized 79 healthy term U.S. infants within the first 5 days of life to 4 months of microalgal DHA, DHA plus microfungal AA, or a control formula.[150] At 1.5, 4 and 12 months of age follow-up, infants supplemented with DHA had shown significantly better visual acuity than the control group (as measured by sweep VEP), but not at 6 months.[150] Of the 79, 52 were available for follow-up visual acuity assessment at 4 years using a BM. At 4 years, the DHA group showed significantly better right-eye visual acuity than did the controls; the DHA group did not differ significantly from the DHA plus AA group or from a breast fed reference standard group. Left-eye visual acuity did not differ significantly among the groups. This follow-up could not be pooled with those of any other studies.

DHA plus AA Versus Placebo

The original report pooled the results of three RCTs, which showed a significant improvement in visual acuity with DHA plus AA supplementation at 2 months, as measured using BM ($p<0.01$) but not at 4 months or older (outcomes at 6, 9, and12 months were reported in only one or two studies each). The original report also pooled eight RCTs that assessed visual acuity using VEP and found no effects of n-3 FA and AA at 2, 4, 6, 8, and 9 months; however pooling four studies that reported VEP outcomes at 12 months showed significant improvement ($p=0.01$). Three new RCTs were identified for the current report. These studies are described briefly below. One of the studies identified for the current report[121] was pooled with three studies from the original report[150-152] that assessed the effects of supplementation with DHA+AA on sweep VEP/VEP at 2 months of age; the pooled effect size showed no significant difference (WMD -0.06 [−0.22; 0.10] I^2=92%).(Figure 18) Two of the studies identified for the current report[111, 121] were pooled with three studies from the original report[150-152] that assessed the effects of supplementation with DHA+AA on sweep VEP/VEP at 4 months of age. The pooled effect size was significant in favor of DHA+AA (WMD -0.10 [-0.14, -0.07] I^2=31.8%)(Figure 19). The two new studies were also pooled with four studies from the original report[150-153] that assessed the effects of supplementation with DHA+AA on sweep/VEP at 12 months (Figure 20); the pooled effect size was significant in favor of DHA+AA (WMD -0.14 [-0.17, -0.12]I^2=6.9%)%)(Figures 21-23).

Figure 18. Visual function in term infants at 2-months follow-up, behavior methods

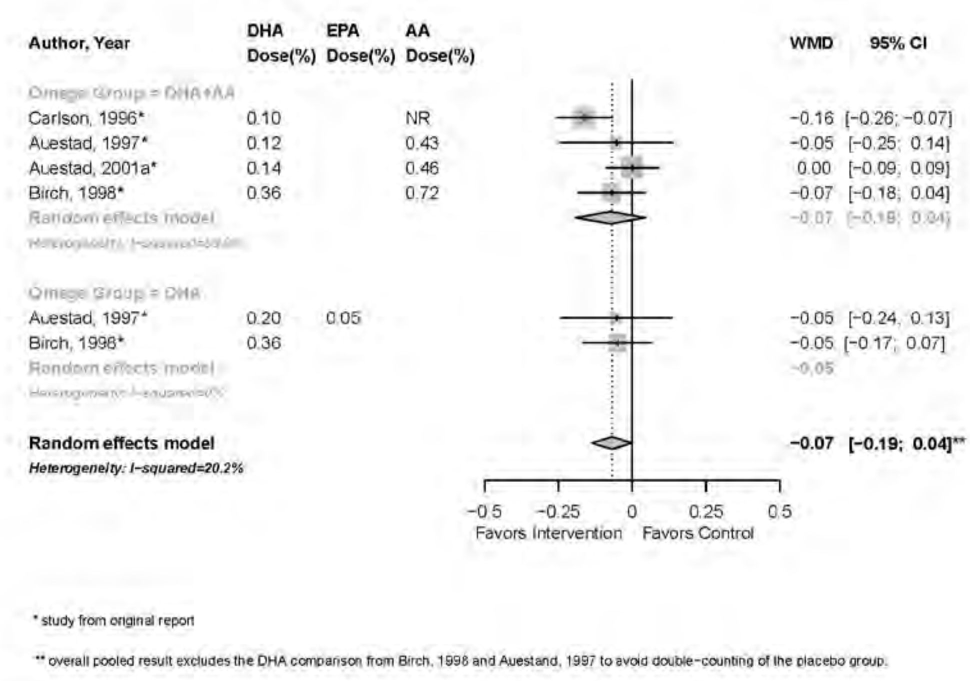


Figure 19. Visual function in term infants at 4-months follow-up, behavioral methods

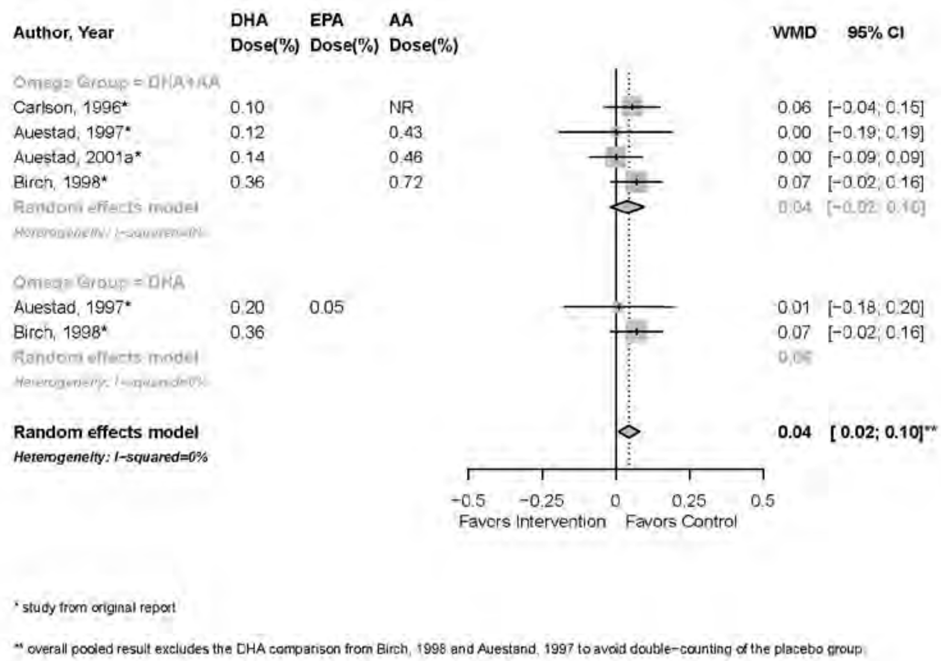


Figure 20. Visual function in term infants at 12-months follow-up, behavioral methods

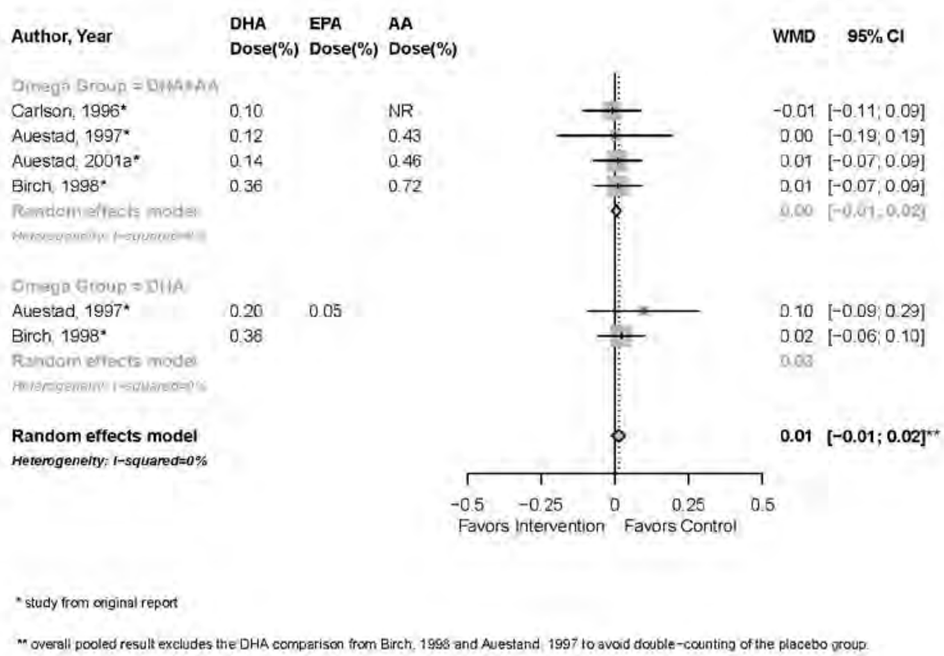


Figure 21. Visual function in term Infants at 2-months follow-up, Sweep Visual Evoked Potential

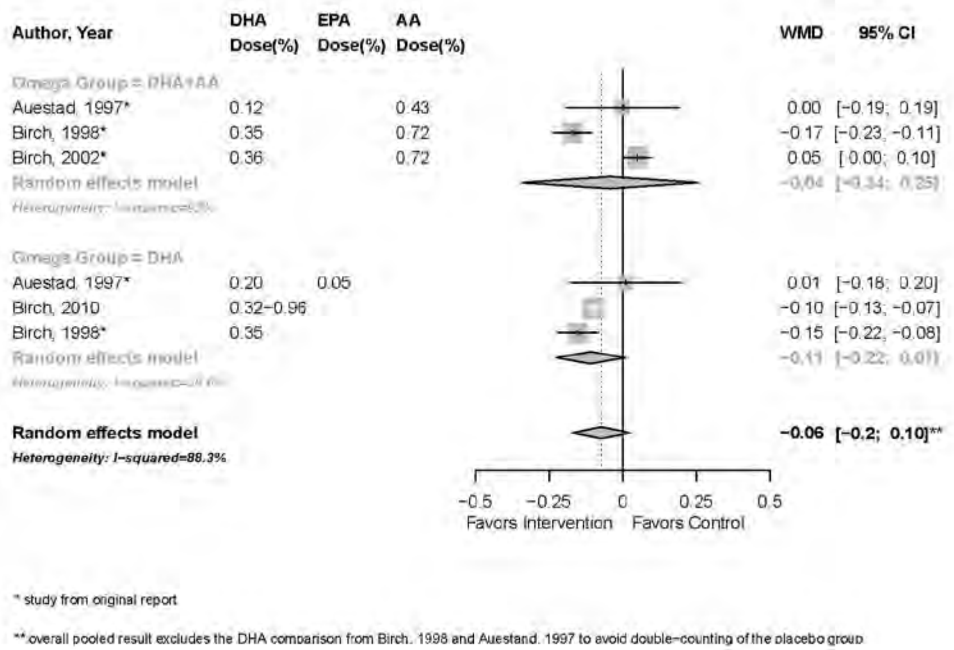


Figure 22. Visual function in term infants at 4-months follow-up, Sweep Visual Evoked Potential

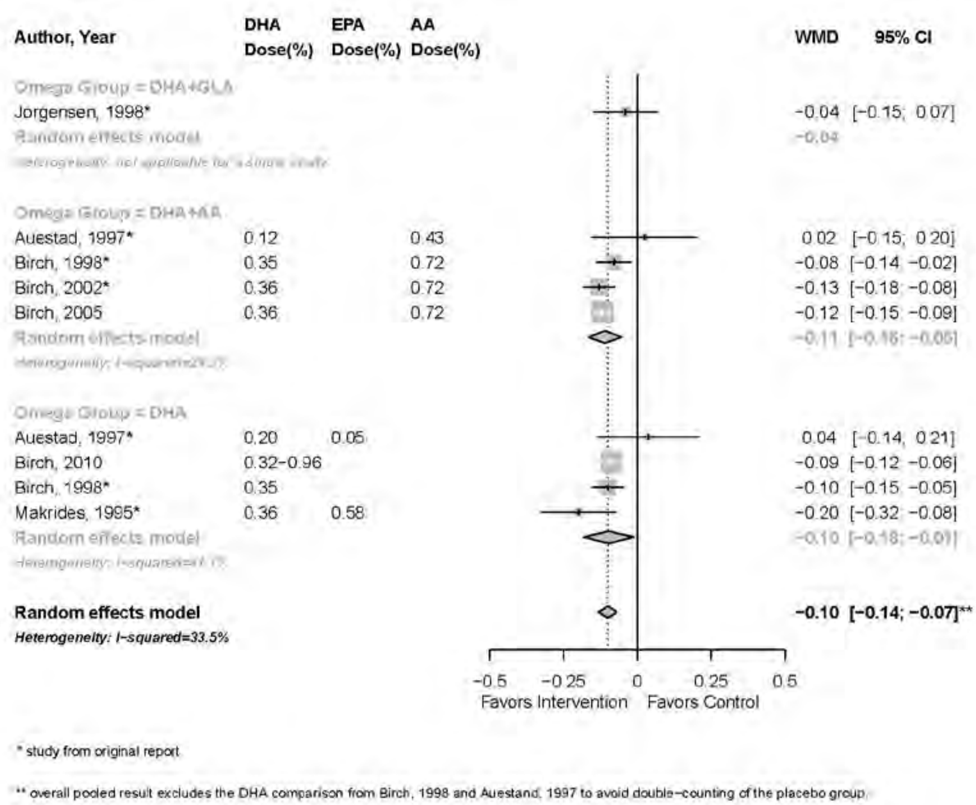
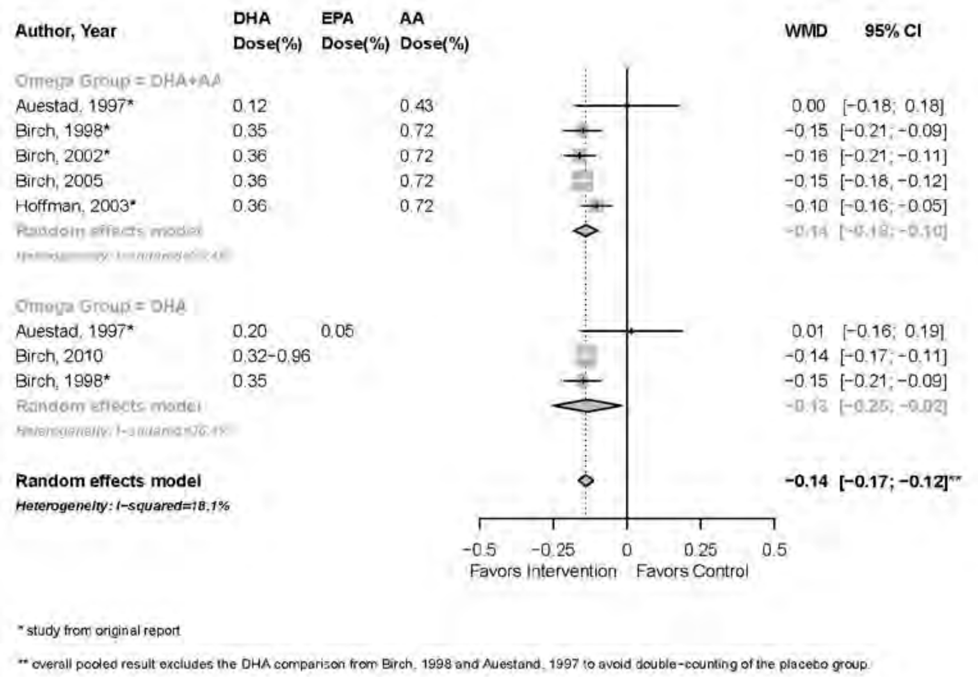


Figure 23. Visual function in term infants at 12-months follow-up, Sweep Visual Evoked Potential



The 2005 RCT by Birch and colleagues randomized103 healthy term U.S. infants in the first 5 days of life to a standard infant formula or a formula fortified with DHA (0.36% of total fatty acids) and AA (0.72% of total fatty acids).[111] The experimental diets were given through 12 months and solid foods were not introduced before 4 months. Visual function was assessed by sweep VEP, random dot stereoacuity, and electroretinography at 1.5 months, 4 months, 9 months, and 12 months. VEP acuity was significantly greater in the intervention group at all time-points, with the overall differences corresponding to slightly more than a one-line difference in reading a standard eye chart.

A 2010 RCT by the same researchers, the DIAMOND Study, randomized healthy term U.S. infants born at one of 7 hospitals at two study sites to one of four intervention groups within 9 days of birth (study sites differed significantly by race, ethnicity, parental education, and gestational length).[121] Children who had received breast milk were excluded. Three of the intervention groups received a standard formula fortified with 0.32% DHA (0.017g/100kcal), 0.64% DHA (0.034g/100 kcal), or 0.96% DHA; all intervention formulae also included 0.64% fatty acids as AA (0.034 g/100kcal). The control group received the standard formula with no DHA or AA. As in the 2005 study, the intervention was continued for 12 months and no other foods were introduced prior to 4 months of age. Visual acuity was assessed by sweep VEP at 1.5, 4, 6, 9 and 12 months. Control infants had poorer visual acuity than the intervention groups at all time-points; visual acuity did not differ among the active intervention groups at any time, demonstrating no dose-response effect. Significant differences in acuity and response to the interventions were noted between study sites, with the control group at one site showing significantly worse visual acuity than the control group at the other site but the interventions groups at the first site showing significantly better response to the interventions than the intervention groups at the second site.

The 2007 4-year follow-up RCT described in the previous subsection on DHA-only interventions found that right-eye visual acuity in the children who received formula with DHA plus AA was better, but not significantly better, than that of the children who had received the control formula. Left-eye visual acuity did not differ significantly among the groups.[146] Infants treated with formula containing DHA plus AA had shown significantly better visual acuity than the control group (as measured by sweep VEP), at 1.5, 4 and 12 months of age but not at 6 months.[150]

Infant biomarkers

One RCT identified for the current study assessed the association between infant red blood cell lipids and sweep VEP acuity.[111] This study, which compared visual acuity over 12 months between infants who received a formula containing DHA plus AA and those receiving a control formula, found that at 4 months, better visual acuity was associated with higher DHA concentrations but not with AA, ALA, or LA concentrations. At 9 months, better visual acuity was associated with higher DHA and AA levels at both 4 months and 9 months. At 1 year, better visual acuity was associated with higher DHA at 4 months and 9 months and with higher AA at 9 months. At all time-points, better visual acuity was also associated with a lower n-6 to n-3 ratio and higher DHA to n-6 DPA.

Table 16. RCTs for visual function

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Birch et al., 2005[111] Study name: NR Study dates: Not reported Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product	Study Population: Healthy infants Infants enrolled 103 Infants completers 86 Pregnant age: 31 years (4 years) Infant age: 3.6 _x0004_days (1.3 days) 1-5 days Race of Mother: NR	Inclusion Criteria: All were born at 37– 40 wk after conception. Only singleton births with birth weight appropriate for gestational age Exclusion Criteria: Family history of milk protein allergy, genetic or familial eye disease, vegetarian or vegan maternal dietary patterns, maternal metabolic disease or infection, jaundice, perinatal asphyxia, meconium aspiration, or any perinatal event that resulted in placement of the infant in the neonatal intensive care unit.	Start time: Infants 1-5 days Duration: Infants 52 wks Arm 1: Control Description: Commercial infant formula Brand name: Enfamil with Iron Manufacturer: Mead Johnson Nutritionals, Evansville, IN Active ingredients: Linoleic acid-8.48g/L (14.6%); 14.7 g protein/L, 37.5 g fat/L, 69.0 g carbohydrate/L Blinding: Each diet was masked by 2 color and 2 number codes, for a total of 4 possible diet assignments. The randomization schedule had random-length blocks (block length varied from 6 to 12) and was provided in individual sealed envelopes to the study site. ALA: 1.5% of total fatty acids Arm 2: LCPUFA-supplemented formula Description: Commercial formula supplemented with LCPUFA Brand name: Enfamil with Iron plus DHASCO and ARASCO Manufacturer: Formula: Mead Johnson; DHA+ARA: Martek Biosciences Active ingredients: 15% linoleic acid,14.7 g /L protein, 37.5 g /L fat, 69.0 g /L carbohydrate ALA: 1.5% of total fatty acids DHA: 0.36% of total fatty acids AA: 0.72% of total fatty acids	data only reported on graph Outcome: (Primary)
Birch et al., 2007[146] Study name: Birch Study dates: 1993-1999 Study design: Trial randomized parallel Location: US	Study Population: Healthy infants, Pregnant women whose unborn children were at high risk of developing asthma Infants enrolled 79+40BF Infants completers 52+32BF	Inclusion Criteria: All participants were born at 37 to 40 weeks postmenstrual age. Only singleton births with birth weights appropriate for gestational age Exclusion Criteria: family history of milk-protein	Start time: Infants birth (0-5 days) Duration: Infants 17 weeks Arm 1: Control Description: standard infant formula without added n-3 FA Brand name: Enfamil with Iron Manufacturer: Mead Johnson Nutritionals Active ingredients: linoleic acid: 15% of total fats	Outcome: Visual acuity Left Eye (log minimum angle of resolution in minutes of arc) (Primary) Follow-up time: 4 years Arm 1: Sample size 19; mean 0.05; SE (0.016) Arm 2: Sample size 16; mean 0.02; SE (0.018) Arm 3: Sample size 17; mean 0.03; SE (0.017)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Funding source / conflict: Government, Manufacturer supplied product Study follow-up: 4 years	Infant age: birth (0-5 days) Race of Mother: NR	allergy, genetic or familial eye disease (e.g. hereditary retinal disease, strabismus), vegetarian or vegan maternal dietary patterns, maternal metabolic disease, anemia, or infection, presence of a congenital malformation or infection, jaundice, perinatal asphyxia, meconium aspiration, and any perinatal event which resulted in placement of the infant in the neonatal intensive care unit	ALA: 1.5% of total fats Arm 2: DHA Description: infant formula fortified with DHA Brand name: Enfamil with Iron, supplemented with DHASCO Manufacturer: Formula: Mead Johnson; DHA: Martek Biosciences Active ingredients: linoleic acid: 15% of total fats ALA: 1.5% DHA: 0.36% Arm 3: DHA+ARA Description: infant formula fortified with DHA and ARA Brand name: Enfamil with Iron, fortified with DHASCO and ARASCO Manufacturer: Formula: Mead-Johnson; DHA, ARA: Martek Biosciences Active ingredients: linoleic acid 15% ALA: 1.5% DHA: 0.36% AA: 0.72%	Outcome: Visual acuity Right Eye (log minimum angle of resolution in minutes of arc) (Primary) Follow-up time: 4 years Arm 1: Sample size 19; mean 0.08; SE (0.022) Arm 2: Sample size 16; mean 0.02; SE (0.019) Arm 3: Sample size 17; mean 0.03; SE (0.017)
Birch et al., 2010[121] Study name: Diamond Study dates: 2003-2006 Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Some authors employed by industry (companies that make the supplements) Original, same study, or follow-up studies: Drover, 2011[122]; Drover. 2012[123];	Study Population: Healthy infants Infants enrolled 343 Infants completers 244 Pregnant age: NR Mother age: NR Infant age: 1-9 days Race of Mother: NR	Inclusion Criteria: Healthy term formula-fed, singleton-birth infants born in any of 5 hospitals Exclusion Criteria: Infants who had received human milk within 24 h of randomization or who had diseases or congenital abnormalities likely to interfere with normal growth and development or with the normal maturation of visual or cognitive function, poor formula intake, or known or suspected intolerance to cow milk infant formula	Start time: Infants 4-9 days of age Duration: Infants 12 months Arm 1: Control Brand name: Enfamil with Iron Manufacturer: Mead-Johnson Nutrition, Evansville IN Arm 2: 0.32% DHA Brand name: Enfamil LIPIL Manufacturer: Mead-Johnson; DHA and ARA from algal and fungal oils manufactured by Martek Biosciences Dose: not specified Blinding: not specified DHA: 0.32% or 17mg/100kcal AA: 0.64% FA or 34mg/100kcal Arm 3: 0.64% DHA	data only reported on graph Outcome: (Primary)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Colombo, 2013[124]; Currie, 2015[115]		were excluded from the study. Also excluded were infants born to mothers with chronic illness, such as HIV disease, renal or hepatic disease, type 1 or type 2 diabetes, alcoholism, or substance abuse	Brand name: not specified Manufacturer: not specified DHA: 34mg/100kg AA: 0.64% FA or 34mg/100kcal Arm 4: 0.96% DHA Brand name: not specified Manufacturer: not specified DHA: 51mg/100kg AA: 0.64% FA or 34mg/100kcal	
Collins et al., 2015[120] Study name: DINO Study dates: 2001-2013 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Industry, Government Study follow-up: 7 years Original, same study, or follow-up studies: Smithers, 2008[104]; Makrides, 2009[116]; Smithers, 2010[117]; Manley, 2011[118]; Collins, 2011[105]; Atwell, 2013[119]; Collins, 2015[120]	Study Population: Preterm infants Infants enrolled 657 Infants completers 604 Infant age: median 30 weeks gestational age 28-31 weeks Race of Mother: NR (100)	Inclusion Criteria: infants born at <33 weeks' gestation from five Australian tertiary hospitals between 2001 and 2005 Exclusion Criteria: a major congenital or chromosomal abnormality, multiple birth in which not all live-born infants were eligible, enrollment in other trials of fatty acid supplementation, or if fish oil was contraindicated in the lactating mother	Start time: Infants within 5 days of 1st enteral feeding Duration: Infants to expected due date Arm 1: standard DHA Description: DHA supplementation of infant formula or breastfeeding mothers to achieve DHA concentrations of term formula fed infants DHA: ___20 mg/kg/ day of DHA Arm 2: High DHA Description: DHA supplementation of infant formula or breastfeeding mothers to achieve DHA concentration of breastmilk DHA: ___50 mg/kg/ day of DHA	Outcome: Test of visual perception skills: figure ground standard score (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 9.6; SD (4.3) Arm 2: Sample size 291; mean 9.4; SD (3.8) Outcome: Test of visual perception skills: visual closure standard score (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 8.0; SD (3.7) Arm 2: Sample size 291; mean 7.6; SD (3.6) Outcome: Test of visual perception skills: visual discrimination standard score (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 8.1; SD (3.6) Arm 2: Sample size 291; mean 8.1; SD (3.1)
Fang et al., 2005[137] Study name: NR Study dates: NR Study design: Trial randomized parallel	Study Population: Preterm infants Infants enrolled 28 Infants withdrawals 1 Infants completers 27 Infant age: 1 week (mean gestation age 33 weeks)	Inclusion Criteria: (1) A gestational age at birth between 30 and 37 weeks; (2) Normal fundus oculi; (3) Recruitment prior to commencement of feeding	Start time: Infants 1 week after birth Duration: Infants 24 weeks Arm 1: placebo Description: infant formula based on the composition of human milk Brand name: Neoangelac Manufacturer: Multipower Enterprise Corporation	Outcome: Hiding Heidi Analysis <100% (Primary) Follow-up time: 4 months Arm 1: 2/11 (18.0%) Arm 2: 5/16 (31.0%) Follow-up time: 6 months Arm 1: 10/11 (91.0%) Arm 2: 16/16 (100.0%) Outcome: Lea grating acuity card 1 or 2

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Location: Taiwan Funding source / conflict: Manufacturer supplied product	(0.5 week) NA Race of Mother: NR (100)	Exclusion Criteria: (1) Breast feeding; (2) A maternal history of infection, diabetes mellitus, gestational diabetes mellitus, cocaine or alcohol abuse, systemic diseases or if intrauterine growth retardation had been diagnosed during pregnancy; (3) Major congenital abnormality; (4) Severe intraventricular hemorrhage > grade 2; (5) Cystic periventricular leukomalacia; (6) Retinopathy of prematurity stage 2; (7) Bronchopulmonary dysplasia on radiographs or oxygen usage 28 days; (8) Body weight less than the third percentile; (9) Surgical intervention for necrotizing enterocolitis (10) Mechanical ventilation after achieving enteral intake > 110 kcal/kg per day; (11) A 5-min Apgar score < 7; (12) Administration of blood transfusion, blood products, or parenteral lipids with DHA or AA.	Dose: Babies were given more than 110 kcal/kg per day during the first 4 months and more than 70 kcal/kg per day from 4 to 6 months N-6 N-3: 10:1 linoleic:linolenic Arm 2: Neoangelac Plus Description: Neoangelac supplemented with Omega 3 Brand name: Neoangelac Plus Manufacturer: Multipower Enterprise Corporation Dose: Babies were given more than 110 kcal/kg per day during the first 4 months and more than 70 kcal/kg per day from 4 to 6 months DHA: 0.05% AA: 0.10%	cycles per degree (Primary) Follow-up time: 4 months Arm 1: 8/11 (72.0%) Arm 2: 16/16 (100.0%) Outcome: Lea grating acuity card 2 or4 cycles per degree (Primary) Follow-up time: 6 months Arm 1: 8/11 (73.0%) Arm 2: 15/16 (94.0%) Outcome: Visual evoked potential (log minimum angle of resolution in minutes of arc) (Primary) Follow-up time: 4 months Arm 1: Sample size 10; mean 0.36; SD (0.34) Arm 2: Sample size 14; mean 0.19; SD (0.27) Follow-up time: 6 months Arm 1: Sample size 10; mean 0.13; SD (0.22) Arm 2: Sample size 13; mean 0.1; SD (0.17)
Innis et al., 2008[145] Study name: NR Study dates: NR, <2008	Study Population: Healthy pregnant women Pregnant enrolled NR Pregnant completers 135	Inclusion Criteria: 14 –16 wk gestation, not taking any lipid supplement, no complications likely to affect maternal or fetal metabolism or fetal	Start time: Pregnant 16 weeks gestation Infants 16 weeks gestation Duration: Pregnant to birth Infants to birth Arm 1: placebo	Outcome: Teller Acuity Card procedure (visual acuity) (cyc/deg) (Secondary) Follow-up time: 60 days Arm 1: Sample size 68; mean 2.42; SD (0.63) Arm 2: Sample size 67; mean 2.6; SD (0.5)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study design: Trial randomized parallel Location: Canada Funding source / conflict: Government, None, Manufacturer supplied product Study follow-up: 60 days	Infants enrolled 135 Infants completers 134 Pregnant age: 33 years (0. 4 years) Infant age: 14 to 16 weeks gestation Race of Mother: White European (72%) Baseline biomarker information: 16 week gestation baseline values for both groups similar. Reported graphically, so approximations. 22:6n-3: 7 %wt of total FA 22:5n-3: 4 %wt of total FA 20:5n-3: 1 %wt of total FA 18:3n-3: 0.4 %wt of total FA Baseline Omega-3 intake: For mothers, at assignment: Linoleic acid (g) median 13.5 range 2.52–43 Alpha Linolenic acid (g) median 1.48 range 0.46–9.21 Arachidonic acid (mg) median 90 range 20–360 EPA (mg) median 70 range 10–280 DHA (mg) median 110 range 10–760	development, expected to deliver one full-term infant Exclusion Criteria: NR	Description: corn oil / soybean oil capsule Manufacturer: Martek Biosciences, Columbia, MD) Dose: 2 capsules Blinding: identical capsules, containing an orange flavor to assist in further blinding Maternal conditions ALA: 40 mg Other dose 1: LA 265 mg Current smoker 2/67 Arm 2: DHA supplement Description: capsule containing 200 mg DHA Manufacturer: Martek Biosciences, Columbia, MD) Dose: 2 capsules Maternal conditions DHA: 200 mg/g Current smoker 0/68	
Jensen et al., 2005[136] Study name: Unnamed Trial B Study dates: <2004	Study Population: Breast-feeding women Lactating enrolled 227 Lactating completers 174	Inclusion Criteria: maternal age between 18 and 40 y, infant gestational age >=37 wk, infant birth weight between 2500 and 4200	Start time: Lactating 5 days after delivery Infants 5 days after birth Duration: Lactating 4 months Infants 4 months Arm 1: placebo	Outcome: Sweep VEP (cyc/deg) (Secondary) Follow-up time: 4 months Arm 1: Sample size 79; mean 9.4; SD (0.21) Arm 2: Sample size 81; mean 9.4; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Government Original, same study, or follow-up studies: Jensen, 2010[135]	Infants enrolled 230 Infants completers 177 Lactating enrolled 227 Lactating completers 174 Lactating age: 31.5 years (5 years) 18-40 Infant age: birth (NA) NA Race of Mother: NR	g Exclusion Criteria: chronic maternal disorders, major congenital anomalies, obvious gastrointestinal or metabolic disorders of the infant	Description: capsule containing corn & soy oil Manufacturer: Martek Biosciences Purity Data: 15% saturated fatty acids, 23.5% monounsaturated fatty acids, 56.3% linoleic acid (18: 2n_x0001_6), and 3.9% _x0001_-linolenic acid (18:3n_x0001_3) Dose: 1 capsule Blinding: identical capsules ALA: 56.3% linoleic acid (18: 2n_x0001_6), 3.9% _x0001_-linolenic acid (18:3n_x0001_3) Total N-3: 57.2% Arm 2: DHA algal triacylglycerol (DHASCO) Description: DHA capsule Brand name: DHASCO Manufacturer: Martek Biosciences Purity Data: 44%saturatedfattyacids, 13.6% monounsaturated fatty acids, 0.8% linoleic acid (18:2n _x0001_ 6), and 41.7% DHA (22:6n-3) by weight Dose: 1 capsule ALA: 0.8% (18:2n-6) DHA: 200 mg, 41.7% (22:6n-3) Total N-3: 42.5%	(0.23) Outcome: Teller Acuity Card procedure (cyc/deg) (Secondary) Follow-up time: 4 months Arm 1: Sample size 77; mean 5.3; SD (0.56) Arm 2: Sample size 70; mean 5.6; SD (0.71) Follow-up time: 8 months Arm 1: Sample size 73; mean 13.5; SD (0.57) Arm 2: Sample size 74; mean 12.3; SD (0.53) Outcome: Visual evoked potential amplitude (mV) (Secondary) Follow-up time: 4 months Arm 1: Sample size 82; mean 33.3; SD (12.4) Arm 2: Sample size 86; mean 28.9; SD (12.1) Follow-up time: 8 months Arm 1: Sample size 74; mean 27.9; SD (11) Arm 2: Sample size 79; mean 24.3; SD (8.9) Outcome: Visual evoked potential latency (ms) (Secondary) Follow-up time: 4 months Arm 1: Sample size 82; mean 123.9; SD (10.6) Arm 2: Sample size 86; mean 124.8; SD (11.7) Follow-up time: 8 months Arm 1: Sample size 74; mean 115.3; SD (10.5) Arm 2: Sample size 79; mean 115.1; SD (8.1)
Jensen et al., 2010[135] Study name: Unnamed Trial B Study dates: NR (<2010)	Study Population: Breast-feeding women Lactating enrolled 227 Infants enrolled 230 Infants completers 119	Inclusion Criteria: maternal age between 18 and 40 y, infant gestational age >=37 wk, infant birth weight between 2500 and 4200 g	Start time: Infants birth Duration: Infants 4 months Arm 1: placebo Description: capsule containing corn & soy oil Manufacturer: Martek Biosciences	intervention first 4 months; same trial as 3433 (later followup) Outcome: Bailey Lovie Acuity - left eye (number of letters correct) (Secondary) Follow-up time: 5 years Arm 1: Sample size 57; mean 52.1; SD (4.9)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Government Study follow-up: 5 years Original, same study, or follow-up studies: Jensen, 2005[136]	Lactating enrolled 227 Lactating age: 31.5 years (5 years) 18 to 40 Infant age: birth (NA) NA Race of Mother: NR (NR)	Exclusion Criteria: chronic maternal disorders, major congenital anomalies, obvious gastrointestinal or metabolic disorders of the infant	Purity Data: 50:50 mixture of soy and corn oils consisting, by weight, of 15% saturated fatty acids, 23.5% monounsaturated fatty acids, 56.3% linoleic acid (18:2 n-6) and 3.9% a-linolenic acid (18:3 n-3) Dose: 1 capsule Blinding: capsules were identical ALA: 3.9% Arm 2: omega 3 capsule Description: high-DHA algal triglyceride capsule Brand name: DHASCO Manufacturer: Martek Purity Data: by weight, 44% saturated fatty acids, 13.6% monounsaturated fatty acids, 0.8% linoleic acid (18:2n-6) and 41.7% DHA (22:6n-3) Dose: 1 capsule DHA: 200 mg	Arm 2: Sample size 60; mean 53.1; SD (4.7) Outcome: Bailey Lovie Acuity - right eye (number of letters correct) (Secondary) Follow-up time: 5 years Arm 1: Sample size 58; mean 51.6; SD (5.6) Arm 2: Sample size 60; mean 52.6; SD (4.6) Outcome: Sweep VEP acuity (cyc/deg) (Secondary) Follow-up time: 5 years Arm 1: Sample size 55; mean 11.8; SD (0.3) Arm 2: Sample size 56; mean 11.9; SD (0.3) Outcome: VEP Amplitude (mV) (Secondary) Follow-up time: 5 years Arm 1: Sample size 56; mean 45.3; SD (18) Arm 2: Sample size 60; mean 39.6; SD (13.7) Outcome: VEP Latency (30' check sizes) (ms) (Secondary) Follow-up time: 5 years Arm 1: Sample size 56; mean 108.0; SD (6.5)
Lauritzen et al., 2004[127] Study name: Danish National Birth Cohort-Lactating Women Study dates: December 1998 to November 1999 Study design: Trial randomized parallel Location: Denmark Funding source / conflict: Industry, Government	Study Population: Breast-feeding mothers with lower than average fish intake Infants enrolled 175 Infants completers 149 Pregnant age: Olive oil 30.2 Fish oil 29.6 High fish 31.9 (Olive oil ± 4.1 Fish oil ± 4.3 High fish ± 4.1) Infant age: 40.1 weeks gestation (birth) (1.2	Inclusion Criteria: pregnant Danish women living in the greater Copenhagen area who had a fish intake below the 50th percentile of the DNBC population; an uncomplicated pregnancy, prepregnancy body mass index (BMI) < 30 kg/m2 , and an absence of metabolic disorders; intention to breast-feed for at least 4 mon at the time of recruiting; newborns had	Start time: NR Duration: NR Arm 1: Placebo Blinding: Intervention fish oil was deodorized Arm 2: FO Intervention Description: Fish oil powder baked into cookies Other dose 1: 17 g/d of deodorized microencapsulated FO powder, containing 4.5 g of FO and 1.5 g of n-3 LCPUF	Outcome: swept visual evoked potential (SWEEP-VEP) (Primary) Follow-up time: 2 months Arm 1: Sample size 46; mean 0.84; SD (0.08) Arm 2: Sample size 42; mean 0.84; SD (0.09) Follow-up time: 4 months Arm 1: Sample size 45; mean 0.64; SD (0.09) Arm 2: Sample size 52; mean 0.62; SD (0.08)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study follow-up: 2 and 4 months Original, same study, or follow-up studies: Lauritzen, 2005[102]; Lauritzen, 2005[128]; Cheatham, 2011[129];	weeks) Race of Mother: NR (100) Baseline Omega-3 intake: Habitual n-3 LCPUFA intake (g/d) Olive oil: 0.3 ± 0.3 Fish oil: 0.3 ± 0.3 High fish: 1.1 ± 0.6	to be healthy (no admission to a neonatal department), term (37–43 wks of gestation), singleton infants with normal weight for gestation (20) and an Apgar score >7 at 5 min after delivery. Willingness to start on the supplements within 2 wks after birth; no use of other types of oil supplements Exclusion Criteria: BMI >= 30 kg/m2		
Malcolm et al., 2003[100] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: NR Funding source / conflict: NR	Study Population: NR Pregnant enrolled 100 Pregnant withdrawals 37 Pregnant completers 63 Infants enrolled 60 Infants withdrawals 5 Infants completers 55 Infant age: 279.6 (8.5) Race of Mother: NR (NR) Baseline biomarker information: Only reported: "The fish oil and placebo groups did not differ in maternal RBC and plasma fatty acid composition at enrollment"	Inclusion Criteria: d women who were expected to deliver their infants at term and planned to feed them on breast and/or formula milk Exclusion Criteria: diabetes, twin pregnancies, pre-eclamptic toxaemia, a past history of abruption or postpartum haemorrhage, allergy to fish products, a thrombophilic tendency, or who were receiving drugs that affect thrombocyte function (non-steroidal anti-inflammatories)	Start time: Pregnant week 15 Infants birth Duration: Pregnant birth Arm 1: Placebo Description: contained 323 mg sunflower oil with high levels of oleic acid and was free of any significant amounts of LCPUFAs or their precursors Manufacturer: R P Scherer Limited (Swindon, Wiltshire, UK) Dose: 323 mg per capsule * 2 Blinding: e identical in appearance and could not be identified on the basis of scent or taste Total N-3: 0 Arm 2: DHA Description: f a blended fish oil, Marinol D40, and contained 100 mg DHA in 323 mg oil per capsule Manufacturer: R P Scherer Limited (Swindon, Wiltshire, UK) Dose: 323 mg capsule * 2 DHA: 200 mg EPA: .64 mg (estimated based on the FA composition)	Outcome: Peak latencies of major components of the transient flash visual evoked potential waveform: N1 (Primary) Follow-up time: 50 weeks (corrected age) Arm 1: Sample size 18; mean 58.1; SD (21.4) Arm 2: Sample size 19; mean 54.7; SD (16.2) Follow-up time: 66 weeks (corrected age) Arm 1: Sample size 24; mean 57.3; SD (10.7) Arm 2: Sample size 23; mean 61.5; SD (5.4) Follow-up time: birth Arm 1: Sample size 4; mean 74.8; SD (16.8) Arm 2: Sample size 5; mean 62.2; SD (3.8) Outcome: Peak latencies of major components of the transient flash visual evoked potential waveform: N2 (Primary) Follow-up time: 50 weeks (corrected age) Arm 1: Sample size 28; mean 112.8; SD (46.5) Arm 2: Sample size 24; mean 128.9; SD (47.9) Follow-up time: 66 weeks (corrected age)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 1: Sample size 26; mean 122.1; SD (33.7) Arm 2: Sample size 25; mean 128.5; SD (30.3) Follow-up time: birth Arm 1: Sample size 22; mean 149.9; SD (28) Arm 2: Sample size 27; mean 153.5; SD (28.9) Outcome: Peak latencies of major components of the transient flash visual evoked potential waveform: N3 (Primary) Follow-up time: 50 weeks (corrected age) Arm 1: Sample size 20; mean 277.3; SD (49.4) Arm 2: Sample size 14; mean 241.8; SD (49.8) Follow-up time: 66 weeks (corrected age) Arm 1: Sample size 15; mean 209.2; SD (38.2) Arm 2: Sample size 11; mean 228.9; SD (55.9) Follow-up time: birth Arm 1: Sample size 27; mean 298.4; SD (52.8) Arm 2: Sample size 26; mean 292.2; SD (58.2) Outcome: Peak latencies of major components of the transient flash visual evoked potential waveform: P1 (Primary) Follow-up time: 50 weeks (corrected age) Arm 1: Sample size 22; mean 84.2; SD (22.5) Arm 2: Sample size 23; mean 80.3; SD (21.1) Follow-up time: 66 weeks (corrected age) Arm 1: Sample size 26; mean 76.5; SD (19.5) Arm 2: Sample size 25; mean 80.1; SD (15.8) Follow-up time: birth Arm 1: Sample size 5; mean 107.8; SD (11.8) Arm 2: Sample size 9; mean 101.0; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(13.6) Outcome: Peak latencies of major components of the transient flash visual evoked potential waveform: P2 (Primary) Follow-up time: 50 weeks (corrected age) Arm 1: Sample size 26; mean 162.5; SD (26.5) Arm 2: Sample size 21; mean 164.2; SD (29.9) Follow-up time: 66 weeks (corrected age) Arm 1: Sample size 19; mean 152.5; SD (43.6) Arm 2: Sample size 12; mean 150.6; SD (33) Follow-up time: birth Arm 1: Sample size 27; mean 201.8; SD (33.3) Arm 2: Sample size 28; mean 201.9; SD (28.4)
Mulder et al., 2014[75] Study name: NR Study dates: 2004 to 2008 Study design: Trial randomized parallel Location: Canada Funding source / conflict: Government Study follow-up: 18 months	Study Population: Healthy pregnant women Pregnant enrolled 271 Pregnant completers 200 Pregnant age: 33 years (4 years) NR Race of Mother: White European (73%) Other race/ethnicity (27%) Baseline biomarker information: maternal RBC Phusphatidylethanolamine DHA: placebo group 6.25 (1.60) g/ 100g DHA group 6.36 (1.62) g/ 100g Baseline Omega-3 intake: median (2.5 to 97.5th percentile range)	Inclusion Criteria: at least 16 wk gestation, not taking any lipid or fatty acid supplement, and were expected to deliver one infant at full-term gestation, with no maternal or fetal complications Exclusion Criteria: NR	Start time: Pregnant 16 weeks gestation Duration: Pregnant Until birth Arm 1: placebo Description: corn and soybean oil supplement Manufacturer: Martek Biosciences Blinding: supplements were identical in appearance, contained an orange flavor mask Arm 2: DHA supplement Description: algal oil DHA supplement Manufacturer: Martek Biosciences DHA: 400 mg	Outcome: number with visual acuity>==13 cycles/degree (Unspecified) Follow-up time: 12 months Arm 1: 20/95 (21.1%) Arm 2: 20/81 (24.7%) Outcome: number with visual acuity>==3.3 cycles/degree (Unspecified) Follow-up time: 2 months Arm 1: 8/94 (8.51%) Arm 2: 17/90 (18.9%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	intake: placebo group 80.0 (0.00-334) mg/day, DHA group 90.0 (6.00-472) mg/d			
Smithers et al., 2008[104] Study name: DINO Study dates: 2001-2004 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Manufacturer supplied product Study follow-up: 2 months, 4 months Original, same study, or follow-up studies: Makrides, 2009[116]; Smithers, 2010[117]; Manley, 2011[118]; Collins, 2011[105]; Atwell, 2013[119]; Collins, 2015[120]	Study Population: Preterm infants Lactating enrolled unclear Infants enrolled 143 Infants completers 125 Lactating enrolled unclear Mother age: Control: 31 Treatment: 29 (Control: 6 Treatment: 6) Infant age: 5 days (control) (mean gestational age at birth 29.4 weeks) 6 days (Treatment) (3) Race of Mother: NR (NR) Baseline Omega-3 intake: Intervention begun at birth: see below	Inclusion Criteria: infants born_x0001_33 wk gestation at the Women's and Children's Hospital of the Child, Youth, and Women's Health Service, Adelaide, Australia, between April 2001 and September 2003 Exclusion Criteria: Infants with major congenital or chromosomal abnormalities, lactating mothers for whom tuna oil was contraindicated (women with blood-thinning disorders or currently taking anticoagulants)	Start time: Lactating approximately 5 days after birth Infants approximately 5 days after birth Duration: Lactating to estimated due date Infants to estimated due date Arm 1: Control group Description: Placebo capsules and/or formula Active ingredients: Linoleic acid 53.4% of fatty acids Dose: 6 500-mg capsules per day to mothers Blinding: The soy and tuna oil capsules were identical in size, color, and shape ALA: 5.9% of total fatty acids Arm 2: Treatment Description: DHA supplemented breastfeeding mothers and/or formula Active ingredients: Linoleic acid 2.7% of fatty acids Dose: 6 capsules or formula ad lib ALA: 0.4% total FA DHA: 29.5% total FA EPA: 6.5% total FA AA: 1.8% total FA	Outcome: Visual evoked potential acuity (cyc/deg) (Primary) Follow-up time: 2 months (corrected age) Arm 1: Sample size 61; mean 5.6; SD (2.4) Arm 2: Sample size 54; mean 5.6; SD (2.4) Follow-up time: 4 months (corrected age) Arm 1: Sample size 51; mean 8.2; SD (1.8) Arm 2: Sample size 44; mean 9.6; SD (3.7) Outcome: Visual evoked potential latency: 48 min of arc (ms) (Secondary) Follow-up time: 4 months (corrected age) Arm 1: Sample size 67; mean 138.0; SD (23) Arm 2: Sample size 58; mean 135.0; SD (23) Outcome: Visual evoked potential latency: 69 min of arc (ms) (Secondary) Follow-up time: 2 months (corrected age) Arm 1: Sample size 66; mean 200.0; SD (29) Arm 2: Sample size 58; mean 193.0; SD (27) Follow-up time: 4 months (corrected age) Arm 1: Sample size 67; mean 131.0; SD (21) Arm 2: Sample size 58; mean 129.0; SD (20) Outcome: Visual evoked potential latency: 96 min of arc (ms) (Secondary) Follow-up time: 2 months (corrected age) Arm 1: Sample size 66; mean 188.0; SD (27) Arm 2: Sample size 58; mean 182.0; SD (24)
Smithers et al., 2011[53] Study name: DOMInO Study dates: Enrollment	Study Population: Healthy infants Healthy pregnant women Infants enrolled 185	Inclusion Criteria: singleton pregnancies at less than 21 weeks' gestation	Start time: Pregnant 18 to 21 weeks gestation Duration: Pregnant until birth Arm 1: placebo	Outcome: VEP Latency: 20 min of arc (ms) (Secondary) Follow-up time: 4 months Arm 1: Sample size 93; mean 133.0; SD (14)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
from June 2007 to August 2008 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Manufacturer supplied product, Some authors serve on scientific advisory boards for corporations, Some authors have received research funding from infant formula manufacturers Study follow-up: 4 months Original, same study, or follow-up studies: Makrides, 2010[35]; Palmer, 2012[54]; Zhou, 2012[55]; Palmer, 2013[56]; Makrides, 2014 [57]	Infants completers 182 Pregnant age: Tx = 29.5 years, Placebo = 28.7 years (Tx = 5.5 years, Placebo = 5.4 years) NR Infant age: (NA) NA Race of Mother: NR (NR)	Exclusion Criteria: already taking a prenatal supplement with DHA, fetus had a known major abnormality, mother had a bleeding disorder in which tuna oil was contraindicated, taking anticoagulant therapy, history of drug or alcohol abuse, participating in another fatty acid trial, unable to give written informed consent, or English was not the main language spoken at home	Description: vegetable oil capsule Manufacturer: Efamol Dose: 3 500 mg capsules Blinding: similar in size, shape, and color Arm 2: Omega 3 supplement Description: fish oil capsule Brand name: Incromega Manufacturer: Croda Chemicals Dose: 3 500 mg capsules DHA: 800/3 mg EPA: 100/3 mg	Arm 2: Sample size 89; mean 133.0; SD (15) Outcome: VEP Latency: 48 min of arc (ms) (Secondary) Follow-up time: 4 months Arm 1: Sample size 93; mean 121.0; SD (12) Arm 2: Sample size 89; mean 121.0; SD (10) Outcome: VEP Latency: 69 min of arc (ms) (Secondary) Follow-up time: 4 months Arm 1: Sample size 93; mean 116.0; SD (9) Arm 2: Sample size 89; mean 115.0; SD (8) Outcome: VEP acuity (adjusted) (cyc/deg) (Primary) Follow-up time: 4 months Arm 1: Sample size 93; mean 8.55; SD (1.97) Arm 2: Sample size 89; mean 8.37; SD (1.97) Outcome: VEP acuity (unadjusted) (cyc/deg) (Primary) Follow-up time: 4 months Arm 1: Sample size 93; mean 8.55; SD (1.86) Arm 2: Sample size 89; mean 8.37; SD (2.11)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Stein et al., 2012[33] Study name: POSGRAD Study dates: Feb 2005-Feb 2007 Study design: Trial randomized parallel Location: NR Funding source / conflict: Government Original, same study, or follow-up studies: Ramakrishnan, 2010[32]; Imhoff-Kunsch, 2011[58]; Escamilla-Nunez, 2014[59]; Gonzalez-Casanova, 2015[60]; Ramakrishnan, 2015[61]	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 1094 Pregnant withdrawals 63 Pregnant completers 900 Pregnant age: 26.3 (4.6-4.8) Infant age: 39.1 (1.7-1.8) Race of Mother: NR (NR)	Inclusion Criteria: Singleton live births without congenital anomalies Exclusion Criteria: 3364: high risk pregnancy, (history and prevalence of pregnancy complications, including abruption placentae, preeclampsia, pregnancy-induced hypertension, any serious bleeding episode in the current pregnancy, and physician referral); lipid metabolism or absorption disorders, regular intake of fish oil or DHA supplement, or chronic use of certain medication(e.g. epilepsy medications)	Start time: Pregnant 18-22 wk Duration: Pregnant to birth Arm 1: Placebo Description: A mixture of corn and soy oil Manufacturer: Martek Biosciences Blinding: "Participants and members of the study team were unaware of the treatment scheme throughout the intervention period of the study" Arm 2: DHA Description: DHA 400 mg/d Manufacturer: Martek Biosciences Dose: 2 capsule per day DHA: 2*200mg	Outcome: Visual evoked potential: Amplitude P (mV) (Primary) Follow-up time: 3 months Arm 1: Sample size 342; mean 8.14; SD (6.04) Arm 2: Sample size 337; mean 7.75; SD (5.97) Follow-up time: 6 months Arm 1: Sample size 342; mean 11.3; SD (6.9) Arm 2: Sample size 337; mean 11.2; SD (7.2) Outcome: Visual evoked potential: Latency N1 (ms) (Primary) Follow-up time: 3 months Arm 1: Sample size 342; mean 93.9; SD (17.1) Arm 2: Sample size 337; mean 94.2; SD (16.3) Follow-up time: 6 months Arm 1: Sample size 342; mean 91.9; SD (15.1) Arm 2: Sample size 337; mean 90.5; SD (14.6) Outcome: Visual evoked potential: Latency N3 (ms) (Primary) Follow-up time: 3 months Arm 1: Sample size 342; mean 157.1; SD (24.1) Arm 2: Sample size 337; mean 154.8; SD (23.8) Follow-up time: 6 months Arm 1: Sample size 342; mean 154.9; SD (20.2) Arm 2: Sample size 337; mean 154.2; SD (19.9) Outcome: Visual evoked potential: Latency P1 (ms) (Primary) Follow-up time: 3 months Arm 1: Sample size 342; mean 126.3; SD (18.3) Arm 2: Sample size 337; mean 125.8; SD (17.5) Follow-up time: 6 months

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 1: Sample size 342; mean 123.5; SD (14.3) Arm 2: Sample size 337; mean 122.7; SD (14.6)
Werkman et al., 1996[154] Study name: NR Study dates: 1987-1990 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product Study follow-up: 12 months	Study Population: Preterm infants Infants enrolled 67 Infants completers 64 Mother age: 23 y (6 y) Infant age: Born at 29 wks gestation (2 wks) Race of Mother: NR (100)	Inclusion Criteria: Preterm infants weighing between 748 and 1398 g at birth. They were eligible for this study when they had tolerated enteral intakes > 462 kJ/kg body weight/day for 5-7 days Exclusion Criteria: Need for mechanical ventilation at that time, intraventricular hemorrhage > grade 2, retinopathy of prematurity > stage 2, surgery for necrotizing enterocolitis, a weight less than the fifth percentile for gestational age, and a history of maternal substance abuse	Start time: Infants 25 days Duration: Infants 25 days - 9 months Arm 1: Placebo term and pre-term infant formulas Active ingredients: n-6: 19.1-33.2% of total FA Dose: Formula remained the infants' major source of nutrients and energy through at least 9 mo past expected term, but other foods were gradually added to the diet beginning at -4 mon past term Blinding: NR Total N-3: Preterm: 3% of total FA; term: 4.8% of total FA Arm 2: DHA-supplemented term and pre-term infant formulas Description: Marine oil replaced fat blend in commercial formulas Brand name: Similac Manufacturer: Ross Products Division Active ingredients: 18.7-32.6% of total FA Dose: Formula remained the infants' major source of nutrients and energy through at least 9 mo past expected term, but other foods were gradually added to the diet beginning at -4 mon past term ALA: Preterm: 3.1% of total FA; Term: 4.9% of total FA DHA: 0.2% of total FA EPA: 0.3% of total FA Other dose 1: Preterm: 3.6% of total FA; term: 5.4% of total FA	Outcome: number of total looks (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 38.4; SD (1.6) Arm 2: Sample size 33; mean 38.9; SD (1.7) Follow-up time: 6.5 months Arm 1: Sample size 34; mean 52.6; SD (2.1) Arm 2: Sample size 33; mean 56.3; SD (2) Follow-up time: 9 months Arm 1: Sample size 34; mean 39.1; SD (1.8) Arm 2: Sample size 33; mean 42.0; SD (1.8) Outcome: time/total looks (seconds) (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 1.39; SD (0.06) Arm 2: Sample size 33; mean 1.34; SD (0.06) Follow-up time: 6.5 months Arm 1: Sample size 34; mean 2.01; SD (0.08) Arm 2: Sample size 33; mean 1.84; SD (0.07) Follow-up time: 9 months Arm 1: Sample size 34; mean 1.49; SD (0.07) Arm 2: Sample size 33; mean 1.4; SD (0.06)

Cognitive Development

Key Points

- **Pregnant women.** One RCT on supplementation of pregnant women was included in the previous AHRQ systematic review; we identified nine additional RCTs. Due to heterogeneity of n-3 FA content and outcomes reported, meta-analysis was not possible. One study that assessed infants at 14 days reported significant associations between DHA supplementation and higher scores on two scales of the Neonatal Behavior Assessment in offspring. Another RCT reported that infants of mothers who received placebo were significantly less likely than those of mothers who received DHA to score in the highest quartile on the receptive language scale of the Bayley Scales of Infant Development (BSID) and words understood on the McArthur Communicative Developmental Inventory CDI at 18 months. All other RCTs reported insignificant results.
- **Breastfeeding women.** Six RCTs, including two from the previous AHRQ review, reported on supplementation for lactating women. Due to heterogeneity of n-3FA content and outcomes measured, meta-analysis was not possible. Associations between supplementation and cognitive outcomes in offspring were not significant in these studies.
- **Pre-term infants.** The previous AHRQ systematic review included six RCTs in preterm infants that reported cognitive outcomes, while the current one identified an additional six reports on five RCTs. Seven of these RCTs (identified by either the new or prior systematic review) reported the Bayley MDI score at 18 to 24 months of age; the pooled difference between the intervention and placebo groups was significant (WMD 2.24; 95% CI 0.05, 4.43). The other RCTs reported mixed results.
- **Full term infants.** The previous AHRQ systematic review reported that six of eight RCTs did not find a significant difference between intervention and placebo groups in Bayley MDI scores. The current review identified five additional reports on four RCTs that measured cognitive outcomes. One of the RCTs identified in the prior AHRQ review and two identified in the current systematic review reported Bayley MDI at 18 to 24 months of age; the pooled difference in MDI scores between the intervention and placebo groups was not significant (WMD 0.75, 95% CI -9.29, 10.79). The two new RCTs that could not be pooled reported insignificant results regarding cognitive outcomes.
- **Observational studies.** Seven reports on six observational studies investigated potential association of maternal or infant n-3 FA intake with childhood cognitive outcomes. Several assessed infant cognitive development using the BSID, whereas others conducted follow up at seven, eight, and eleven years of age. Only one study reported a significant association between n-3 FA intake and cognitive outcomes. Although that study was high quality in that in controlled for 18 important potential confounders, the authors caution that the effect sizes were small (approximately one-tenth of a standard deviation).

Description of Included Studies

Randomized Controlled Trials

Interventions with pregnant women

The prior AHRQ-funded systematic review included one RCT on maternal supplementation during pregnancy; no differences were observed between groups in the Fagan Test of Infant Intelligence at 6 and 9 months of age.[86]

For the current systematic review, nine additional RCTs of pregnant women that reported cognitive outcomes were identified (see Table 17).[35, 44, 66, 74, 76, 77, 141] Follow-up times were diverse; children ranged in age from 14 days to 7 years. Due to the heterogeneity of interventions, populations, outcome measures, and timing, meta-analysis was not conducted. Results are summarized below.

DHA Alone

In the US, Gustafson et al., 2013[74] randomized healthy pregnant women to capsules containing either vegetable oil or algal oil as a source of DHA (total of 0.600 g/d). The majority of enrollees were non-White (37.3% African American, 3.0% Asian, and 13.4% Hispanic). This study had a significantly lower rate of completion (78%) than other studies of pregnant women. Of 67 pregnant women enrolled, 52 completed the study through childbirth. Forty-one infants participated in the Neonatal Behavior Assessment at 14 days of age. Infants in the DHA group scored significantly higher on the autonomic and motor skills scales.

Mulder, 2014[75] enrolled 271 pregnant women in an RCT of supplements containing 400 mg DHA versus placebo conducted in Canada. At 18 months of age, 200 of their infants were assessed using the BSID (Version 3) and the McArthur Communicative Developmental Inventory (CDI). Infants in the placebo group were significantly less likely than those in the DHA group to score in the highest quartile on the receptive language scale of the BSID and words understood on the CDI.

Ramakrishnan, 2015[61] reported on the POSGRAD study conducted in Mexico. Over 1,000 pregnant women at 18 to 22 weeks gestation were randomized to placebo or capsule containing 200 mg DHA. There was no difference between groups in Bayley MDI score at 18 months; 730 children completed this follow-up.

DHA Plus EPA

Makrides, 2010[35] reported on the DOMInO trial conducted in Australia which randomized pregnant women to either capsules containing vegetable oil or fish oil (0.800 g DHA and 0.100 g/d EPA). The authors reported no difference in mean score on the cognitive component of the BSID (Version 3) at 18 months of age. Makrides, 2014[57] reported results of this study at four years. There were no significant differences between groups in any scales of the Behavior Rating Inventory of Executive Function (Preschool).

Dunstan et al., 2008[44] also conducted an RCT in Australia. Pregnant women with a history of allergy were randomized to olive oil capsule or fish oil capsule containing 2.2 g DHA and 1.1 g EPA. Children in the fish oil group scored significantly higher on the hand eye coordination component of the Griffith Mental Development Scale scores at 2.5 years of age. Differences were not statistically significant for the six other Griffith components.

Campoy et al., 2011[141] reported on the NUHEAL study conducted in Germany, Spain, and Hungary. Pregnant women in the second half of pregnancy were randomized to three groups who all received a milk based supplement containing vitamins and minerals in amounts meeting the recommended intakes for European women. One of the groups received the supplement containing additional n-3 FA (DHA 0.500 g, EPA 0.100 g), while another received a supplement containing additional folic acid. Children were followed up at 6.5 years of age; differences in the Kauffman Assessment Battery for Children (K-ABC) were insignificant for all scales.

Tofail et al., 2006[77] randomized pregnant women in Bangladesh to either soy oil capsules containing 0.27 g ALA and 2.25 g linoleic acid or fish oil capsules containing 1.2 g DHA and 1.8 g EPA. Only 151 of the 400 women enrolled (38%) completed the study. There were no significant differences in BSID II Mental Development Index (MDI) scores when infants were 10 months of age.

Helland et al., 2008[76] randomized pregnant women in Norway to 10 mL of either corn oil or cod liver oil (n-3 FA content not reported) from week 18 of pregnancy until 3 months after delivery. At 7 years of age, no significant differences were observed in scores on the Kaufman Assessment Battery for Children (K-ABC) test.

DHA Plus AA

Van Goor et al., 2011[66] reported on the Groningen LCPUFA study conducted in the Netherlands. One hundred and nineteen pregnant women were randomized to three groups who received soy oil capsules containing either no n-3 FA, DHA (0.220 g/d), or DHA (0.220 g) +AA (0.220 g). There were no differences between groups in the BSID MDI at 18 months of age.

Postpartum Maternal Supplementation

Two RCTs[86, 155] and one prospective cohort study[156] on maternal supplementation during breastfeeding were identified in the prior AHRQ systematic review. In these studies, supplementation with n-3 FA had no effect on cognition in offspring.

The current systematic review identified four new RCTs of lactating women that reported cognitive outcomes.[76, 116, 128, 135] All were conducted in Western countries; most primarily enrolled white women. Sample sizes ranged from 89 to 545 women. Enrollment took place between 1995 and 2012. Follow up timing ranged from 9 months of age to 7 years. Due to heterogeneity of interventions, populations, outcome measures, and timing, meta-analysis was not conducted. Results are summarized below.

DHA Plus EPA

Makrides et al., 2009[116] reported on the DINO trial, conducted in Australia. Breast-feeding mothers of pre-term children were randomized to soy capsules or tuna oil capsules (0.500 g/d DHA) and instructed to take them daily until the infant reached "expected" date of delivery. When children were 18 months old, no difference was observed between groups in mean BSID MDI scores. However, for infants born weighing less than 1250g, the MDI in the high-DHA group was higher than with standard DHA in the unadjusted comparison (mean difference, 4.7; 95% CI, 0.2-9.2) but did not reach statistical significance following adjustment for gestational age, sex, maternal education, and birth order (mean difference, 3.8; 95% CI, −0.5 to 8.0).

Lauritzen et al., 2005[128] randomized pregnant Danish women with a fish intake below the population median (< 0.4 g n-3 LCPUFA·d–1) and an intention to breastfeed for at least four months to muesli bars containing either olive oil or 4.5 g fish oil (DHA 60%). At one year of age, infants were assessed with the MacArthur CDI Linguistic Development instrument. No significant differences were seen between groups.

In the U.S., Jensen et al., 2010[135] randomized breast feeding women to receive either vegetable oil capsule or high-DHA (0.200 g/d) algal triglyceride capsules for the first four months of lactation. At five years of age, children were assessed with the Wechsler Primary and Preschool Scale of Intelligence – Revised. No significant differences were observed between groups. The results for Helland et al., 2008,[76] which randomized pregnant and breastfeeding women to cod liver oil or vegetable oil, are described above in the section on pregnant women. This trial included supplementation during both pregnancy and lactation. No significant results were found for cognitive outcomes.

Infant Formula Supplementation with n-3 FA and Cognitive Function in Preterm infants

The previous AHRQ systematic review identified six RCTs in pre-term infants. Four of the five trials that reported the Bayley MDI score at various follow-up times found no significant difference between the placebo and intervention groups.[149, 157-159] Two studies[154, 160] found a significant difference between the supplementation group and the placebo group on some scales of the Fagan Test of Infant Intelligence. One RCT that reported Bayley scores also found no significant differences between groups in the Infant version of the MacArthur Communicative Development Inventories (MCDI).[157]

Five RCTs identified for the current report (described in six publications) assessed the effects of supplementing pre-term infants with n-3 FA on cognitive outcomes.[99, 107, 108, 116, 125, 137] Studies were conducted in Taiwan, the UK, Norway, Canada, and Australia. Follow up timing ranged from 6 months to 10 years. Using studies from both the prior and current systematic reviews, we were able to pool seven studies of n-3 supplemented formulas that reported the Bayley's MDI at 18 to 24 months of age. Four of these studies were reported in the previous AHRQ systematic review,[157, 159 158 149] while three were newly identified in the current review.[108, 116, 125] All supplements were categorized as DHA plus AA. Three of the formulas included some EPA; however, the proportion was too small to have clinical significance. The pooled difference in MDI scores between the intervention and placebo groups was significant (WMD 2.24; 95% CI 0.05, 4.43), as displayed in Figure 24. There was low heterogeneity ($I^2 = 23.2\%$) and no evidence of publication bias (Begg's p=0.293; Egger's p=0.388).

Results of new studies that could not be pooled, due to heterogeneity of intervention, outcome, or follow-up, are described below.

DHA Plus AA

We identified two studies of supplements containing DHA plus AA for pre-term infants not included in the prior systematic review that we did not pool due to follow-up timing. We also identified one long-term follow-up of a study included in the pooled analysis.

Fang (2005)[137] conducted an RCT in Taiwan that randomized preterm infants to either standard formula or formula supplemented with DHA (0.05%) and AA (0.10%) for 24 weeks. Infants were assessed at 6 months and 1 year of age using the Bayley MDI. Infants who received supplemented formula scored significantly higher at both time points.

Isaacs (2011)[99] randomized preterm infants in the UK to nine months of either standard formula or formula supplemented with DHA (0.5 g /100g fat), EPA (0.1 g/100g fat) and AA (0.04 g /100g fat). At 10 years of age, children were assessed with the Wechsler Abbreviated Scale of Intelligence, Wechsler Individual Achievement Test, and the CMS Word Pairs instrument. Differences between groups were not statistically significant.

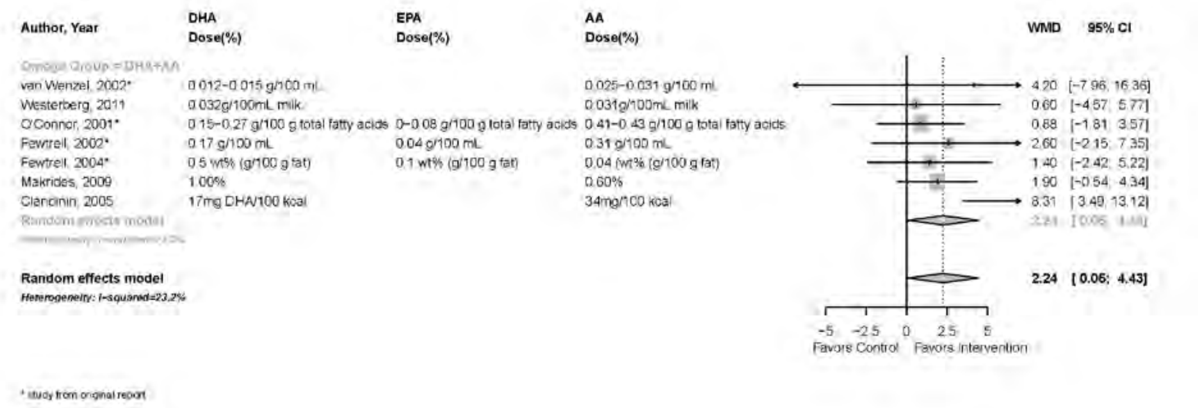
Almaas, 2015[126] reported on a long term follow-up of an RCT that was included in the meta-analysis described above.[125] At 8 years, children completed the Wechsler Abbreviated Scale of

Intelligence, Wechsler Intelligence Scale for Children III Digit Span, and the California Verbal Learning Test II. No significant differences were observed between the intervention group and the control group on any of these outcomes.

DHA Plus EPA Plus AA

One study identified for the current report that administered formula supplemented with DHA+EPA+AA could not be pooled with the other studies. Isaacs et al., 2011[99] randomized preterm infants in the UK to nine months of either standard formula or formula supplemented with DHA (0.5 g /100g fat), EPA (0.1 g/100g fat) and AA (0.04 g /100g fat). At 10 years of age, children were assessed with the Wechsler Abbreviated Scale of Intelligence, Wechsler Individual Achievement Test, and the CMS Word Pairs instrument. Differences between groups were not statistically significant.

Figure 24. Preterm cognitive



Infant Formula Supplementation with n-3 FA and Cognitive Function in Full Term infants

The original report identified eight RCTs that assessed the effect of supplementing term infants with n-3 FA on cognitive outcomes; six of the eight studies found no significant difference between intervention and placebo groups in the Bayley MDI score at any follow-up point. A meta-analysis of 3 RCTs reporting the Bayley MDI score at 12 months showed no significant difference between intervention and placebo groups.

The current review identified five additional reports on four RCTs of full term infants that measured cognitive outcomes.[63, 65, 122, 140, 146] With the exception of a study conducted in Bangladesh, the studies were conducted in Western countries with primarily Caucasian samples. Follow-up timing ranged from 10 months to 9 years. One of the RCTs[161] identified in the prior AHRQ review and two identified in the current systematic review[63, 122] reported Bayley's MDI at 18 to 24 months of age, and used supplements containing DHA + AA; thus we pooled these three studies. The pooled difference in MDI scores between the intervention and placebo groups was not significant (WMD 0.75, 95% CI -9.29, 10.79), as displayed in Figure 25. Considerable heterogeneity was detected (I^2 = 70.3%).

Results of the two new studies that could not be pooled, due to heterogeneity of intervention, outcome, or follow-up timing, are described below.

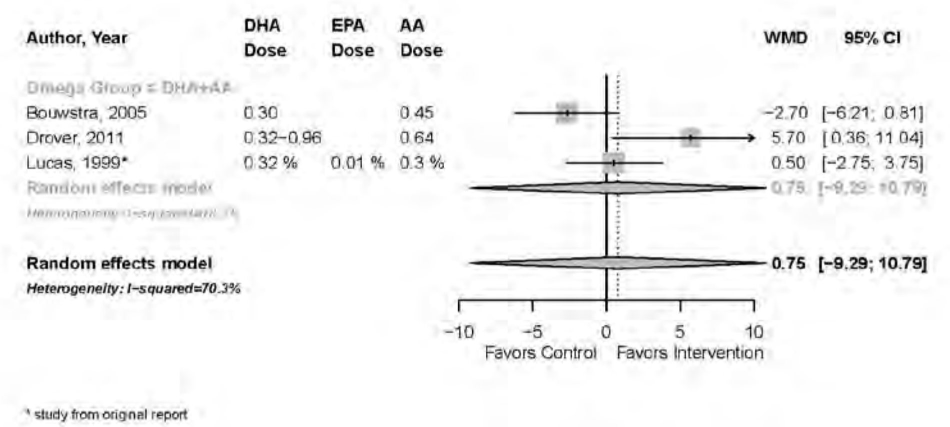
DHA Plus AA

Birch et al., 2007[146]randomized healthy full term infants in the US to 17 weeks of either standard formula, formula supplemented with DHA (0.36%), or formula supplemented with DHA (0.36%) plus AA (0.72%). A breast fed group served as an additional comparison. At four years of age, the control and DHA-supplemented groups had significantly lower verbal IQ scores than the breast fed group (the group that received DHA plus AA had an insignificantly lower score than the breastfed group). However, no differences were observed between any of the formula-fed groups and the breast-fed group in performance IQ or full scale IQ.

DHA Plus EPA

A newly identified study, Meldrum et al., 2012[140] was not pooled due to heterogeneity of population and intervention. Researchers randomized healthy Australian full term infants of women with allergies to six months of either olive oil or fish oil (0.250 g/d DHA, 0.060 g/d EPA) supplements. At 18 months of age, infants were assessed using the cognitive component of the BSID (Version 3); differences between the groups were not significant.

Figure 25. Full term cognitive



Observational Studies

Seven reports on six observational studies that investigated potential associations of maternal or infant n-3 FA intake with childhood cognitive outcomes were identified for the current report (see Table 18).[89, 132, 143, 144, 162-164] All were conducted in the U.S. or Europe. Two studies collected diet information via food frequency questionnaires (FFQ) and five collected biomarker data. Several assessed infant cognitive development using the Bayley Scales of Infant Development (BSID), while others conducted follow up at seven, eight, and eleven years of age.

Valent, et al.[132] recruited pregnant women at 20 to 22 weeks gestation from a hospital in northern Italy. The primary purpose of the study was to assess the potential association between maternal mercury exposure and neurodevelopment outcomes in offspring. Information on maternal fish intake was collected by FFQ and levels of PUFAs were measured via maternal serum at week 32 of gestation. (Mercury levels were obtained from cord blood; it is unclear why PUFAs were not measured in the cord blood samples.) Of 900 women recruited, 767 (85%) completed the study through childbirth. At 18 months, 632 children were assessed using the BSID III. Mothers of children lost to follow-up were of lower socio-economic status and had lower median IQ than those who participated. The authors developed a model that adjusted for maternal factors (concentration of mercury in hair during pregnancy, fish intake, weight gain during pregnancy, marital status, SES, number of children living at home, alcohol intake during pregnancy, breastfeeding history) and child factors (sex, birth weight, intake of fish, day care attendance) to assess whether concentration of ALA, EPA, DHA, LA, or ARA (mg/ml) were associated with BSID III scores. No statistically significant associations were found. However, child duration of fresh fish intake was associated with increased score on the cognitive component of the BSID III.

Keim, et al.[162] analyzed data from the Pregnancy, Infection, and Nutrition Study. This prospective cohort study enrolled pregnant women from North Carolina hospitals; 1,169 were eligible for post-partum follow-up. At four months post-partum, the study analyzed n-3 FA content of mothers' breast milk samples and also collected data on n-3 FA content of any infant formula utilized. At 12 months of age, offspring cognition was assessed using the Mullen Scales of Early Learning. When controlling for infant sex, pre-term status, race/ethnicity, mother's education, and parity, no statistically significant associations between scores and AA, DHA, or total LCPUFA were identified.

Julvez et al.[143] and Guxens, et al.[144] reported on the INMA (Infancia Y Medio Ambiete) prospective cohort study conducted in Catalonia, Spain. Pregnant women (N = 657) were recruited from a public health center. Colostrum was collected two to four days after childbirth to measure LCPUFA content for a sub-sample of women (N = 277). Breastfeeding information was collected by questionnaire from all women when the offspring were 6 and 14 months of age. At 14 months of age, 504 infants were assessed using the BSID; in a model adjusted for child's age, maternal and paternal factors (education, social class, attachment to the child, IQ, mental health) and maternal smoking and alcohol use, PUFA levels in colostrum were not associated with scores. At four years of age, cognition was assessed in 434 children using the McCarthy Scales of Children's Abilities (MSCA). No association was seen between n-3 FA intake during infancy and MSCA scores[143] when adjusting for child (age, sex, day care attendance) and parental (age, parity, alcohol and smoking during pregnancy, education, social class, mental health, attachment with child) characteristics.

Bernard et al.[89] reported on the EDEN prospective cohort study conducted in France. Using data on diet during last trimester of pregnancy collected via FFQ and a booklet displaying portion sizes, the researchers estimated intake of LA, AA, ALA, EPA, DHA, total n-6, total n-3, and total LCPUFAs for 1,585 women. At two years of age, 1,215 of their children were assessed using the Communicative Development Inventory (CDI). At three years of age 1,185 children were assessed using the Ages and Stages Questionnaire (ASQ), and Peg Moving Task Version 5. Among never breastfed children, a significant inverse relationship between maternal n6:n3 ratio and CDI and ASQ scores was reported. No significant associations were seen among scores of breastfed children and maternal intakes. Models were adjusted for child factors (gender, age, gestational age, firstborn, and main daytime caregiver) and parental factors (maternal age, obesity, energy intake, smoking and alcohol consumption during pregnancy, education, income, and maternal attachment).

Bakker, et al.[163] conducted a prospective cohort study that enrolled 750 pregnant women in the Netherlands. At childbirth, cord plasma was collected and analyzed for LCPUFA content. At 7 years of age, 306 children were assessed using the Kaufman Assessment Battery for Children (K-ABC). Baseline characteristics of participating and non-participating children were not significantly different. Backward stepwise multiple linear regression analyses found no association between cord plasma AA or DHA and K-ABC scores.

Finally, Steer, et al.[164] analyzed data from the Avon Longitudinal Study Of Parents in Children, conducted in the UK. Blood samples from 5,222 pregnant women were analyzed for LCPUFA content. At 8 years of age, 2,839 of their children were assessed using the Wechsler Intelligence Scale for Children (WISC). In a model that controlled for 18 potential confounders, low levels of AA were associated with lower performance IQ, high levels of adrenic acid were associated with lower verbal IQ, and low levels of DHA were associated with lower verbal and full scale IQ scores. The authors caution that the effect sizes were small (approximately one-tenth of a standard deviation.

Table 17. RCTs for cognitive development

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Almaas et al., 2015[126] Study name: Unnamed Trial D Study dates: 2003-2014 Study design: Trial randomized parallel Location: Norway Funding source / conflict: Government, None Study follow-up: 8 years Original, same study, or follow-up studies: Henriksen, 20008[107]; Westerberg, 2011[125]	Study Population: Preterm infants Low birth weight infants Infants enrolled 129 Infants completers 98 Mother age: Median: Intervention: 31 years Control: 32 years 28-35 years Infant age: Median Gestational age: Control: 28.9 weeks Intervention: 28.4 weeks Gestational age: 26.6-30.9 weeks Race of Mother: NR	Inclusion Criteria: Very low birth weight infants (birth weight <1500 g) Exclusion Criteria: Major congenital abnormalities and cerebral hemorrhage	Start time: Infants (intervention began when the infant received most of his nutrients enterally: >100ml human milk/kg body weight/day Duration: Infants Until discharge or bottle of study oil was empty (average 63 days of age) Arm 1: Control Description: Study oil: soy oil and medium chain triglycerides Active ingredients: 127mg linolenic acid/100 ml milk(27.1% total fatty acids) Dose: 0.5 ml study oil/100 ml human milk Blinding: Study oils packed in numbered bottles in hospital pharmacy Maternal conditions Infant conditions ALA: 16mg/100 ml milk; 3.4% total fatty acids Current smoker 15% Low birth weight 100% Other conditions 1 Small for gestational age: 30% Arm 2: Intervention Description: DHA and AA-containing oil Manufacturer: Martek Biosciences Active ingredients: 88mg/100 ml linoleic acid per 100 ml milk (18.8%) Dose: 0.5 ml study oil per 100 ml milk, ad lib Maternal conditions Infant conditions DHA: 32mg/100ml milk (6.9%) AA: 31 mg/100 ml milk (6.7% total fatty acids Current smoker 19% Low birth weight 100% Other conditions 1 Small for gestational age: 29%	Outcome: Wechsler Abbreviated Scale of Intelligence: Full Scale IQ (Secondary) Follow-up time: 8 years Arm 1: Sample size 52; mean 93.9; SD (10) Arm 2: Sample size 45; mean 92.7; SD (8.8) Outcome: Wechsler Abbreviated Scale of Intelligence: Verbal IQ (Secondary) Follow-up time: 8 years Arm 1: Sample size 52; mean 90.3; SD (12.5) Arm 2: Sample size 45; mean 88.8; SD (10.3) Outcome: Wechsler Abbreviated Scale of Intelligence: performance IQ (Secondary) Follow-up time: 8 years Arm 1: Sample size 52; mean 95.9; SD (14.4) Arm 2: Sample size 45; mean 95.0; SD (12.6)
Westerberg et al., 2011[125] Study name: Unnamed Trial D Study dates: Enrollment:	Study Population: Preterm infants Infants enrolled 141 Infants completers 92	Inclusion Criteria: All VLBW infants (<1500g) born between December 2003 and November 2005 at Rikshospitalet-Radiumhospitalet	Start time: Infants at start of enteral feeding Duration: Infants until discharge or until the study oil bottle was empty (mean duration of supplementation was 63 days)	Outcome: Bayley Mental Development Index (MDI) (Secondary) Follow-up time: 20 months Arm 1: Sample size 42; mean 82.9; SD (13.3) Arm 2: Sample size 40; mean 83.5; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
December 2003 and October 2005 Study design: Trial randomized parallel Location: Norway Funding source / conflict: Multiple foundations and Societies, Manufacturer supplied product Study follow-up: 20 months	Mother age: Intervention: 30.8 years Control: 31.7 years (Intervention: 4.9 years Control: 5.0 years) 28-35 years Infant age: Mean Gestational age: Intervention: 28.7 weeks Control: 28.9 weeks (Intervention: 2.9 weeks Control: 2.7 weeks) Gestational age: 26.6-30.9 weeks Race of Mother: NR Baseline biomarker information: DHA: intervention[64.2 (23.5) mg/mL] and control group [61.3 (18.7)mg / mL], AA: intervention[205.6 (52.8) mg/mL] and control group [199.6 (48.7)mg / mL],	Medical Center, Akershus University Hospital, Buskerud Hospital, and Vestfold Hospital in Norway Exclusion Criteria: Major congenital abnormalities or cerebral hemorrhage (grade 3 or 4) as determined through ultrasonography	Arm 1: Placebo Description: Soy oil Active ingredients: 127mg linolenic acid/100 ml milk(27.1% total fatty acids) Dose: 0.5 ml study oil/100 ml human milk Blinding: Study oils packed in numbered bottles in hospital pharmacy ALA: 16mg/100 ml milk; 3.4% total fatty acids Arm 2: DHA + AA group Description: DHA and AA-containing oil Manufacturer: Martek Active ingredients: 88mg/100 ml linoleic acid per 100 ml milk (18.8%) Dose: 0.5 ml study oil per 100 ml milk, ad lib Maternal conditions ALA: 11mg/100 ml milk; 3.4% total fatty acids DHA: 32mg/100ml milk (6.9%) AA: 31 mg/100 ml milk (6.7% total fatty acids Current smoker 22% during pregnancy	(10.5)
Birch et al., 2007[146] Study name: Birch Study dates: 1993-1999 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product	Study Population: Healthy infants, Pregnant women whose unborn children were at high risk of developing asthma Infants enrolled 79+40BF Infants completers 52+32BF Infant age: birth (0-5 days) Race of Mother: NR	Inclusion Criteria: All participants were born at 37 to 40 weeks postmenstrual age. Only singleton births with birth weights appropriate for gestational age Exclusion Criteria: family history of milk-protein allergy, genetic or familial eye disease (e.g. hereditary retinal disease, strabismus), vegetarian or vegan maternal dietary patterns,	Start time: Infants birth (0-5 days) Duration: Infants 17 weeks Arm 1: Control Description: standard infant formula without added n-3 FA Brand name: Enfamil with Iron Manufacturer: Mead Johnson Nutritionals Active ingredients: linoleic acid: 15% of total fats ALA: 1.5% of total fats Arm 2: DHA Description: infant formula fortified with DHA Brand name: Enfamil with Iron, supplemented with DHASCO	Outcome: Wechsler Preschool and Primary Scale of Intelligence: Full-Scale IQ (Secondary) Follow-up time: 4 years Arm 1: Sample size 19; mean 101.0; SE (2.6) Arm 2: Sample size 16; mean 105.9; SE (3.9) Arm 3: Sample size 32; mean 107.5; SE (3.1) Outcome: Wechsler Preschool and Primary Scale of Intelligence: Performance IQ (Secondary) Follow-up time: 4 years Arm 1: Sample size 19; mean 104.2; SE (2.7)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study follow-up: 4 years		maternal metabolic disease, anemia, or infection, presence of a congenital malformation or infection, jaundice, perinatal asphyxia, meconium aspiration, and any perinatal event which resulted in placement of the infant in the neonatal intensive care unit	Manufacturer: Formula: Mead Johnson; DHA: Martek Biosciences Active ingredients: linoleic acid: 15% of total fats ALA: 1.5% DHA: 0.36% Arm 3: DHA+ARA Description: infant formula fortified with DHA and ARA Brand name: Enfamil with Iron, fortified with DHASCO and ARASCO Manufacturer: Formula: Mead-Johnson; DHA, ARA: Martek Biosciences Active ingredients: linoleic acid 15% ALA: 1.5% DHA: 0.36% AA: 0.72%	Arm 2: Sample size 16; mean 108.1; SE (3.8) Arm 3: Sample size 32; mean 108.6; SE (3.3) Outcome: Wechsler Preschool and Primary Scale of Intelligence: Verbal IQ (Secondary) Follow-up time: 4 years Arm 1: Sample size 19; mean 98.8; SE (2.6) Arm 2: Sample size 16; mean 102.7; SE (4.1) Arm 3: Sample size 32; mean 104.5; SE (2.9)
Bouwstra et al., 2005[63] Study name: Groningen LCPUFA study Study dates: 1997-2002 Study design: Trial randomized parallel Location: Netherlands Funding source / conflict: Industry Study follow-up: 18 months Original, same study, or follow-up studies: Bouwstra, 2003[62]; de Jong, 2010[64]; de Jong, 2012[65]; van Goor, 2010[36]; van Goor, 2011[66]	Study Population: Healthy infants Infants enrolled 472 Infants completers 446 Mother age: 31 years (5 years) NR Infant age: birth Race of Mother: White European (100%)	Inclusion Criteria: healthy term infants Exclusion Criteria: infants who had a congenital disorder that interfered with adequate functioning in daily life, infants from multiple births, infants whose mothers did not have mastery of the Dutch language or suffered from significant illness or disability, adopted and foster infants, and formula-fed infants who had received human milk for >5 d.	Start time: Infants Birth Duration: Infants 2 months Arm 1: Control group Description: Standard formula Brand name: Nutrilon premium Manufacturer: Zoetermeer, Netherlands Active ingredients: linoleic acid (11mol%); ALA 1.27 mol% Dose: ad lib Maternal conditions Current smoker 31% during pregnancy Maternal abuse of alcohol/psychotropic drugs Alcohol USE during pregnancy 8% Arm 2: LCPUFA formula Description: LCPUFA formula Dose: ad lib Maternal conditions DHA: 0.30% DHA AA: 0.45% AA Current smoker 31% during pregnancy Maternal abuse of alcohol/psychotropic drugs 9% used alcohol during pregnancy	Outcome: Bayley Scales of Infant Development (Mental Development Index) (Secondary) Follow-up time: 18 months Arm 1: Sample size 155; mean 105.4; SD (15) Arm 2: Sample size 135; mean 102.7; SD (15.4)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			Arm 3: breast feeding group Description: breast fed, no formula Maternal conditions Current smoker 19% smoked during pregnancy Maternal abuse of alcohol/psychotropic drugs 24% used alcohol during pregnancy	
Brew et al., 2015[165] Study name: CAPS Study dates: September 1997 to 1999-2008 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government Study follow-up: 3, 5, 7, and 9 years of school Original, same study, or follow-up studies: Mihrshahi, 2003[166]; Mihrshahi, 2004[167]; Mihrshahi, 2006[168]; Toelle, 2010[169]	Study Population: Healthy infants Infants enrolled 616 Infants completers 239 Pregnant age: 29.8 (4.90) Infant age: NR Race of Mother: NR (NR) Baseline biomarker information: Total n-3 PUFA (DHA+EPA+DPA+ALA) as % of total fatty acids at 4 ages (on a bar chart): 18 months: Intervention 72% Controls: 48% 3 years Intervention 64% Controls: 46% 5 years Intervention 62% Controls: 50% 8 years: Intervention 50% Controls: 45% Baseline Omega-3 intake: 500 mg of tuna fish oil, daily, which comprised 37% LCPUFA (including 135 mg of DHA and 32 mg of EPA per capsule) and 6% omega-6 PUFA (linoleic	Inclusion Criteria: parent or an older sibling had a history of asthma or recurrent wheezing, and that the child was born at 436 weeks of gestation Exclusion Criteria: NR	Start time: Infants Birth Duration: Infants 8 years Arm 1: Intervention Description: d 500 mg of tuna fish oil 37% LCPUFA Manufacturer: Nu-Mega Industries Pty Ltd, Brisbane, Australia DHA: 135 mg EPA: 32 mg AA: 6% of omega 3PUFA (linoleic acid, arachidonic acid, docosapentaenoic acid) Arm 2: Control Description: a daily Sunola oil capsule Manufacturer: Nu-Mega Industries ALA: 0.3%	Outcome: National Assessment Program Literacy and Numeracy (NAPLAN): numeracy score (difference in NAPLAN units) (Secondary) Follow-up time: 10-11 years 239; difference in means -13.7; 95% CI Follow-up time: 12-13 years 239; difference in means -11.7; 95% CI Follow-up time: 14-15 years 239; difference in means -24.1; 95% CI Follow-up time: 8-9 years 239; difference in means -25.4; 95% CI Outcome: National Assessment Program Literacy and Numeracy (NAPLAN): reading score (difference in NAPLAN units) (Secondary) Follow-up time: 10-11 years 239; difference in means -3.2; 95% CI Follow-up time: 12-13 years 239; difference in means -7.0; 95% CI Follow-up time: 14-15 years 239; difference in means -19.9; 95% CI Follow-up time: 8-9 years 239; difference in means -27.03; 95% CI

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	acid, arachidonic acid and docosapentaenoic acid)			
Campoy et al., 2011[141] Study name: NR Study dates: NR, <2011 Study design: Trial randomized factorial design Location: Germany, Spain, Hungary Funding source / conflict: Government, None Study follow-up: 6.5 years Original, same study, or follow-up studies: Escolano-Margarit, 2011[130]	Study Population: Healthy pregnant women Pregnant enrolled 315 Pregnant completers 154 Pregnant age: 31 years (NR) Race of Mother: White European (99%) Baseline biomarker information: From Krauss, 2007 mean DHA Placebo group 5.95 Fish oil group 5.75 5-MHTF (folic acid) group 5.68 Fish oil + 5-MHTF group 5.89 mean EPA Placebo group 0.28 Fish oil group 0.18 5-MHTF (folic acid) group 0.17 Fish oil + 5-MHTF group 0.22	Inclusion Criteria: health pregnant women, singleton pregnancy, gestation 20 week at enrollment, body weight between 50 and 92 kg at study entry, and intention to deliver in one of the obstetrical centers Exclusion Criteria: serious chronic illness (e.g., diabetes, hepatitis, or chronic enteric disease), use of FO supplements since the beginning of pregnancy or folate or vitamin B-12 supplements after gestation week 16	Start time: Pregnant 22 weeks gestation Infants 22 weeks gestation Duration: Pregnant until birth Infants until birth Arm 1: placebo Description: milk-based supplement Brand name: Blemil Plus Manufacturer: Ordesa Laboratorios, Barcelona, Spain) Active ingredients: vitamins and minerals in amounts meeting the recommended intakes during the second half of pregnancy for European women Dose: one daily dose of 15 g Blinding: supplements were not distinguishable with respect to the appearance of the sachets or to their contents Maternal conditions Current smoker during pregnancy 8.9% Arm 2: fish oil Description: fish oil in milk-based supplement Manufacturer: Pronova Biocare, Lysaker, Norway Active ingredients: vitamins and minerals in amounts meeting the recommended intakes during the second half of pregnancy for European women Dose: one 15 g dose Maternal conditions DHA: 500 mg EPA: 100 mg Current smoker during pregnancy 18.9% Arm 3: folic acid Description: 400 ug 5-MTHF Manufacturer: BASF, Ludwigshafen, Germany Active ingredients: vitamins and minerals in amounts meeting the recommended intakes during the second half of pregnancy for European women Dose: one 15 g dose Maternal conditions	Outcome: Kauffman Assessment Battery for Children: Mental Processing Composite (Secondary) Follow-up time: 6.5 years Arm 1: Sample size 45; median 110.0; IQR (14.5) Arm 2: Sample size 37; median 110.0; IQR (11) Arm 3: Sample size 35; median 108.0; IQR (12) Arm 4: Sample size 37; median 108.0; IQR (10.5) Outcome: Kauffman Assessment Battery for Children: Sequential Processing Scale (Secondary) Follow-up time: 6.5 years Arm 1: Sample size 45; median 106.0; IQR (19) Arm 2: Sample size 37; median 108.0; IQR (12) Arm 3: Sample size 35; median 104.0; IQR (14) Arm 4: Sample size 37; median 104.0; IQR (17) Outcome: Kauffman Assessment Battery for Children: Simultaneous Processing Scale (Secondary) Follow-up time: 6.5 years Arm 1: Sample size 45; median 112.0; IQR (11.5) Arm 2: Sample size 37; median 112.0; IQR (10.5) Arm 3: Sample size 35; median 109.0; IQR (14) Arm 4: Sample size 37; median 110.0; IQR (10.5)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			Current smoker during pregnancy 17.1% Arm 4: folic acid + fish oil Description: 400 _x0001_g 5-MTHF +fish oil Manufacturer: BASF, Ludwigshafen, Germany Active ingredients: vitamins and minerals in amounts meeting the recommended intakes during the second half of pregnancy for European women Dose: one 15 g dose Maternal conditions DHA: 500 mg EPA: 100 mg Current smoker during pregnancy 18.9%	
Carlson et al., 1996[160] Study name: NR Study dates: NR (<1995) Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product Study follow-up: 12 months	Study Population: Preterm infants Infants enrolled 59 Infants completers 27 Infant age: 3 days (NR) 2 to 5 days Race of Mother: NR (100)	Inclusion Criteria: infants weighing between 747 and 1275 g at birth who achieved full enteral feeding of 418 kJ (100 kcal)/kg/d by 6 wk of age and tolerated enteral feeding thereafter Exclusion Criteria: intraventricular or periventricular hemorrhage > grade 2, a history of maternal cocaine or alcohol abuse, congenital anomalies likely to affect long-term growth and development, or intrauterine growth retardation defined as a weight for gestational age below the 5th percentile	Start time: Infants 3 days after birth Duration: Infants 2 months Arm 1: Placebo Description: standard formula Brand name: Similac Special Care Manufacturer: Ross Products Division, Abbott Laboratories Infant conditions ALA: 2.4 g / 100 g Other dose 1: linolenic acid 21.2 g/ 100 g Pre-term birth 100% Other conditions 1 bronchopulmonary dysplasia (BPD) or chronic lung disease of % Arm 2: DHA supplement Description: formula supplemented with DHA from marine oil Brand name: Similac Special Care (plus marine oil) Manufacturer: Ross Products Division, Abbott Laboratories Infant conditions ALA: 2.4 g / 100 g DHA: 0.20 g / 100g EPA: 0.06 g / 100 g Other dose 1: linolenic acid 21.2 g/ 100 g Pre-term birth 100% Other conditions 1 bronchopulmonary dysplasia (BPD) or chronic lung disease of- %	Outcome: Fagan Test of Intelligence: time/look (seconds) (Secondary) Follow-up time: 12 months Arm 1: Sample size 12; mean 1.3; SD (0.1) Arm 2: Sample size 15; mean 1.13; SD (0.07) Outcome: Fagan Test of Intelligence: looks to familiar (number) (Secondary) Follow-up time: 12 months Arm 1: Sample size 12; mean 17.5; SD (1.4) Arm 2: Sample size 15; mean 21.5; SD (1.3) Outcome: Fagan Test of Intelligence: looks to novel (number) (Secondary) Follow-up time: 12 months Arm 1: Sample size 12; mean 22.9; SD (1.5) Arm 2: Sample size 15; mean 25.3; SD (1.6) Outcome: Fagan Test of Intelligence: novel time (% of total) (Secondary) Follow-up time: 12 months Arm 1: Sample size 12; mean 64.0; SD (1.9) Arm 2: Sample size 15; mean 59.7; SD (1.7) Outcome: Fagan Test of Intelligence: time to familiar (seconds) (Secondary) Follow-up time: 12 months

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 1: Sample size 12; mean 16.9; SD (1) Arm 2: Sample size 15; mean 19.3; SD (0.9) Outcome: Fagan Test of Intelligence: time to novel (seconds) (Secondary) Follow-up time: 12 months Arm 1: Sample size 12; mean 33.1; SD (1.4) Arm 2: Sample size 15; mean 31.5; SD (1.5) Outcome: Fagan Test of Intelligence: time/familiar look (seconds) (Secondary) Follow-up time: 12 months Arm 1: Sample size 12; mean 1.04; SD (0.11) Arm 2: Sample size 15; mean 0.95; SD (0.08) Outcome: Fagan Test of Intelligence: time/novel look (seconds) (Secondary) Follow-up time: 12 months Arm 1: Sample size 12; mean 1.49; SD (0.09) Arm 2: Sample size 15; mean 1.28; SD (0.06) Outcome: Fagan Test of Intelligence: total looks (number) (Secondary) Follow-up time: 12 months Arm 1: Sample size 12; mean 40.4; SD (2.7) Arm 2: Sample size 15; mean 46.8; SD (2.7) Outcome: Fagan Test of Intelligence: total time (seconds) (Secondary) Follow-up time: 12 months Arm 1: Sample size 12; mean 50.0; SD (1.6) Arm 2: Sample size 15; mean 50.8; SD (1.7)
Cheatham et al., 2011[129] Study name: Danish National Birth Cohort-Lactating Women	Study Population: Healthy infants Pregnant enrolled 150 Pregnant completers 98	Inclusion Criteria: Described in Ref. 26 All the children who participated in the 9 month followup visit (n =	Start time: Pregnant birth Duration: Pregnant 9 months Arm 1: Fish oil	Outcome: Stroop scores (Secondary) Follow-up time: 7.5 years Arm 1: Sample size 28; mean -0.21; SD (0.1) Arm 2: Sample size 35; mean -0.23; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study dates: 1998-2007 Study design: Observational prospective Location: Denmark Funding source / conflict: Government Study follow-up: 7 years Original, same study, or follow-up studies: Lauritzen, 2004[127]; Lauritzen, 2005[102]; Lauritzen, 2005[128]	Infants enrolled 98 Infants completers 92 Infant age: 7.5 Race of Mother: NR (100)	149) were invited to participate in the 7 year follow-up study. Exclusion Criteria: Living outside Zealand	Manufacturer: m BASF Health and Nutrition A/S, Ballerup, Denmark DHA: 0.62 g EPA: 0.79 g Total N-3: 1.5 g/d LCPUFA Arm 2: Olive oil Manufacturer: m BASF Health and Nutrition A/S, Ballerup, Denmark	(0.14) Outcome: Woodcock Johnson Test: Standardized speed of processing (Secondary) Follow-up time: 7.5 years Arm 1: Sample size 27; mean 1.02; SD (0.26) Arm 2: Sample size 36; mean 0.96; SD (0.26)
Clandinin et al., 2005[108] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: Canada Funding source / conflict: Industry	Study Population: Preterm infants Infants enrolled 361 preterm+105 term breastfed Infants completers 179 preterm and 76/105 term breastfed Infant age: 30.6 weeks postmenstrual age 24-36 weeks postmenstrual age Race of Mother: NR (100)	Inclusion Criteria: Phase I: gestational age <35 weeks PMA and received <10 total days of enteral feedings of >30 mL/kg per day. Infants initially fed human milk were not enrolled unless formula was started within 10 days after completing the first day of human milk feeding Phase II: completion of phase I and >=80% enteral intake from study formula during hospitalization and 100% of caloric intake from study formula at completion of phase 1. Birth weight<1500g Exclusion Criteria: congenital abnormalities of the gastrointestinal	Start time: Infants 10 days of age Duration: Infants 118 weeks Arm 1: Control Description: Non-supplemented premature, discharge, and term formula Dose: Ad lib Blinding: Not reported Infant conditions Pre-term birth 119 (100%) Arm 2: Algal-DHA Description: supplemented premature infant formula supplemented with DHA from algal oil Manufacturer: Martek Biosciences Dose: ad lib DHA: 17mg/100kcal (0.33% by weight) EPA: 0.1% by weight AA: 34mg/100kcal (0.67% by weight) Arm 3: Fish-DHA Description: Premature infant formula supplemented with DHA from tuna fish oil	Outcome: Bayley Scale of Infant Development II (Mental developmental index) (Unspecified) Follow-up time: 118 weeks Arm 1: Sample size 54; mean 77.0; SE (2) Arm 2: Sample size 44; mean 83.0; SE (2) Arm 3: Sample size 60; mean 87.0; SE (2) Arm 4: Sample size 58; mean 98.0; SE (2)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		tract, hepatitis, hepatic or biliary pathology, necrotizing enterocolitis confirmed before enrollment, or history of underlying disease or congenital malformation likely to interfere with evaluation	Manufacturer: Martek Biosciences Dose: ad lib DHA: 17mg DHA/100 kcal AA: 34mg/100 kcal Arm 4: Reference Description: Breast fed term infants	
Collins et al., 2015[120] Study name: DINO Study dates: 2001-2013 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Industry, Government Study follow-up: 7 years Original, same study, or follow-up studies: Smithers, 2008[104]; Makrides, 2009[116]; Smithers, 2010[117]; Manley, 2011[118]; Collins, 2011[105]; Atwell, 2013[119]; Collins, 2015[120]	Study Population: Preterm infants Infants enrolled 657 Infants completers 604 Infant age: median 30 weeks gestational age 28-31 weeks Race of Mother: NR (100)	Inclusion Criteria: infants born at <33 weeks' gestation from five Australian tertiary hospitals between 2001 and 2005 Exclusion Criteria: a major congenital or chromosomal abnormality, multiple birth in which not all live-born infants were eligible, enrollment in other trials of fatty acid supplementation, or if fish oil was contraindicated in the lactating mother	Start time: Infants within 5 days of 1st enteral feeding Duration: Infants to expected due date Arm 1: standard DHA Description: DHA supplementation of infant formula or breastfeeding mothers to achieve DHA concentrations of term formula fed infants DHA: ___20 mg/kg/ day of DHA Arm 2: High DHA Description: DHA supplementation of infant formula or breastfeeding mothers to achieve DHA concentration of breastmilk DHA: ___50 mg/kg/ day of DHA	Outcome: Wechsler Abbreviated Scale of Intelligence: Full Scale IQ (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 98.5; SD (14.9) Arm 2: Sample size 291; mean 98.3; SD (14) Outcome: Wechsler Abbreviated Scale of Intelligence: Performance IQ (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 98.5; SD (13.6) Arm 2: Sample size 291; mean 98.5; SD (14.5) Outcome: Wechsler Abbreviated Scale of Intelligence: Verbal IQ (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 98.8; SD (15.8) Arm 2: Sample size 291; mean 98.0; SD (14.2)
Colombo et al., 2013[124] Study name: Diamond Study dates: 09/03/03-09/25/05 Study design: Trial randomized parallel	Study Population: Healthy infants Infants enrolled 159 Infants completers 81 Pregnant age: 24.1 (5.1) Race of Mother: White European (34.9) Black	Inclusion Criteria: Healthy, full term formula-fed singleton infants, 37-42 weeks gestation, 2490-4200 g birth weight, born in Kansas City between 9/3/03 and 9/25/05 Exclusion Criteria:	Start time: Infants Birth Duration: Infants 12 months Arm 1: 0.00% Description: Control, no DHA or AA Blinding: NR Arm 2: 0.32% Description: 0.32% DHA	Outcome: Macarthur-Bates Communicative Development Inventory Follow-up time: 18 months Arm 1: Sample size 18; mean 71.0; SEM (20) Arm 2: Sample size 21; mean 55.0; SEM (15) Arm 3: Sample size 18; mean 97.0; SEM (20) Arm 4: Sample size 24; mean 73.0; SEM

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Location: US Funding source / conflict: Industry, Government, Manufacturer supplied product Study follow-up: 18 months-6 years Original, same study, or follow-up studies: Birch, 2010[121]; Drover, 2011[122]; Drover. 2012[123]; Currie, 2015[115]	(63.9) Other race/ethnicity (1.2)	Receipt of human milk within 24 h of randomization; maternal and newborn health conditions known to interfere with normal growth and development (e.g., intrauterine growth restriction) or with normal cognitive function (e.g., congenital anomalies or established genetic diagnoses associated with intellectual disability), poor formula intake, or intolerance to cow milk infant formula; mothers with physician-documented chronic illness (e.g., HIV, renal or hepatic disease, type 1 or type 2 diabetes, alcoholism, or substance abuse)	DHA: 17mg/100 kcal AA: 34 mg/100 kcal Arm 3: 0.64% DHA: 34mg/100 kcal AA: 34 mg/100 kcal Arm 4: 0.96% DHA: 51mg/100 kcal AA: 34 mg/100 kcal	(15) Outcome: Wechsler Primary Preschool Test of Intelligence: Full Scale IQ (Secondary) Follow-up time: 6 year 66; mean 96.2; SE (2) Arm 1: Sample size 18; mean 90.5; SE (3)
Drover et al., 2011[122] Study name: Diamond Study dates: 2003-2006 Study design: Trial randomized parallel Location: US Funding source / conflict: Industry Study follow-up: 18 months Original, same study, or follow-up studies: Birch,	Study Population: Healthy infants Infants enrolled 181 Infants withdrawals 64 Infants completers 117 Infant age: 18.1 month (0.2) Race of Mother: White European (70%) Minority (30%)	Inclusion Criteria: Children who had enrolled in the initial phase of the DIAMOND study at the Dallas site, and had completed the 12-month feeding protocol and the 12-month primary outcome visit (141 children) Exclusion Criteria: Infants who had diseases or congenital abnormalities known to affect growth, development, visual or cognitive maturation, or who had poor formula intake did not participate	Start time: Infants birth (1 9 days) Duration: Infants 1 year Arm 1: No DHA (Control) Description: Cow's milk-based infant formula without DHA or ARA Brand name: Enfamil® with iron Manufacturer: Mead Johnson & Co, Evansville, IN Blinding: After obtaining signed assent from a parent, the study coordinator opened the next sequentially-numbered opaque sealed envelope to determine the code of the study formula to be assigned to that infant. All recruiting personnel, parents or guardians, study monitors, researchers, and pediatricians were masked to the infant's assigned formula. Arm 2: 0.32% DHA	Outcome: Bayley Scale of Infant Development II (Mental developmental index) (Secondary) Follow-up time: 18 months Arm 1: Sample size 28; mean 98.4; SD (13.1) Arm 2: Sample size 29; mean 105.2; SD (10.7) Arm 3: Sample size 32; mean 104.2; SD (9.8) Arm 4: Sample size 28; mean 102.6; SD (11.9)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
2010[121]; Drover. 2012[123]; Colombo, 2013[124]; Currie, 2015[115]		in the study. Infants were also excluded if they had received human milk within 24 h of randomization, or if they were born to mothers with chronic illness such as HIV disease, renal or hepatic disease, type 1 or type 2 diabetes, alcoholism, or substance abuse	Description: 0.32% fatty acids from DHA & 0.64% ARA Brand name: Enfamil LIPIL®) Manufacturer: Enfamil LIPIL® DHA: 17mg/100 kcal, 0.32% DHA with 0.32% fatty acids from DHA AA: 34mg/100 kcal, 0.64% ARA Arm 3: 0.64% DHA Description: 0.64% DHA & 0.64% ARA Brand name: Enfamil LIPIL Manufacturer: Mead Johnson Nutrition DHA: 34 mg/100 kcal AA: 34mg/100 kcal, 0.64% ARA Arm 4: 0.96% DHA Description: 0.96% DHA & 0.64% ARA Brand name: Enfamil LIPIL Manufacturer: Mead Johnson Nutrition DHA: 54 mg/100 kcal; 0.96% DHA AA: 34 mg/100 kcal; 0.64% ARA	
Drover et al., 2012[123] Study name: Diamond Study dates: NR Study design: Trial randomized parallel Location: US Funding source / conflict: Industry Study follow-up: 3.5 years Original, same study, or follow-up studies: Birch, 2010[121]; Drover, 2011[122]; Colombo, 2013[124]; Currie, 2015[115]	Study Population: Healthy infants Infants enrolled 343 Infants completers 88 Pregnant age: 31 years (4 years) Infant age: <= 9 days 1 to 9 days Race of Mother: NR (100)	Inclusion Criteria: Healthy term singleton-birth infants born in any of 5 hospitals Exclusion Criteria: Infants who had diseases or congenital abnormalities known to affect growth, development, visual or cognitive maturation, Infants were also excluded if they had received human milk within 24 h of randomization, or if they were born to mothers with chronic illness such as HIV disease, renal or hepatic disease, type 1 or type 2 diabetes, alcoholism, or substance	Start time: Infants <=9 days after birth Duration: Infants 12 months Arm 1: Control group Description: Standard infant formula Brand name: Enfamil with Iron Manufacturer: Mead-Johnson Nutrition, Evansville IN Arm 2: 0.32% DHA formula Brand name: Enfamil LIPIL® Manufacturer: Mead-Johnson; DHA and ARA from algal and fungal oils manufactured by Martek Biosciences DHA: 0.32% or 17mg/100kcal AA: 0.64% FA or 34mg/100kcal Arm 3: 0.64% DHA formula Brand name: NR Manufacturer: NR DHA: 34mg/100kg	Outcome: School Readiness Composite (SRC) (Secondary) Follow-up time: 2.5 years Arm 1: Sample size 19; mean 9.79; SD (2.42) Arm 2: Sample size 23; mean 10.3; SD (1.92) Arm 3: Sample size 27; mean 10.63; SD (2.75) Arm 4: Sample size 24; mean 10.79; SD (2.62)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		abuse	AA: 0.64% FA or 34mg/100kcal Arm 4: 0.96% DHA formula Brand name: NR Manufacturer: NR DHA: 51mg/100kg AA: 0.64% FA or 34mg/100kcal	
Dunstan et al., 2008[44] Study name: Dunstan Study dates: 2000-2003 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Multiple foundations and Societies Original, same study, or follow-up studies: Dunstan, 2003[50]; Meldrum, 2015[51]	Study Population: Healthy infants Pregnant women with allergies Pregnant enrolled 98 Pregnant completers 83 Infants enrolled 83 Infants withdrawals 11 (7 FO, 4 control) Infants completers 72 Pregnant age: Fish oil: 30.9 Control: 32.6 (Fish oil: 3.7 Control: 3.6) Infant age: Term (mean gestational period 275 days) Race of Mother: NR (NR) Baseline biomarker information: Cord blood erythrocyte (as % total fatty acids) 20:4n-6 14.9 (1.4) 17.6 (1.0) ,0.001 20:5n-3 1.3 (0.5) 0.4 (0.3) ,0.001 22:3n-6 2.8 (0.5) 3.9 (0.5) ,0.001 22:4n-6 0.8 (0.2) 1.5 (0.3) ,0.001 22:5n-3 6.3 (0.8) 6.0 (0.5) 0.037 22:6n-3 10.3 (1.1) 7.4 (0.9) ,0.001 Total n-6 PUFAs* 25.0 (1.8) 29.6	Inclusion Criteria: Healthy term infants of pregnant women enrolled in RCT of gestational supplementation Exclusion Criteria: Women were ineligible for the study if they smoked, had medical problems, a complicated pregnancy, seafood allergy, or if their normal dietary intake exceeded two meals of fish per week. Children were excluded from the study if they were born before 36 weeks' gestation or with major disease (to avoid the confounding effects on immune response) or if cord blood was not collected	Start time: Pregnant 20 weeks gestation Duration: Pregnant to term Arm 1: Control Description: olive oil placebo Blinding: capsules image matched Maternal conditions Current smoker 0% Maternal allergies 100% Arm 2: Fish oil Description: same Manufacturer: Ocean Nutrition, Halifax Nova Scotia Active ingredients: 3-4mg/g vitamin E Viability: none reported Dose: 4 1-gm capsules fish oil per day Maternal conditions DHA: 2.2 EPA: 1.1 Other dose 1: fish oil supplying 2,2g/d DHA and 1.1g/day EPA Current smoker 0% Maternal allergies 100%	Outcome: Griffith Mental Development Scales: Eye and hand coordination (Secondary) Follow-up time: 2.5 years Arm 1: Sample size 39; mean 108.0; SD (11.3) Arm 2: Sample size 33; mean 114.0; SD (10.2) Outcome: Griffith Mental Development Scales: Performance (Secondary) Follow-up time: 2.5 years Arm 1: Sample size 39; mean 115.8; SD (13.7) Arm 2: Sample size 33; mean 120.9; SD (12.7) Outcome: Griffith Mental Development Scales: Practical reasoning (Secondary) Follow-up time: 2.5 years Arm 1: Sample size 39; mean 113.6; SD (15) Arm 2: Sample size 33; mean 114.3; SD (14.5) Outcome: Griffith Mental Development Scales: Speech and hearing (Secondary) Follow-up time: 2.5 years Arm 1: Sample size 39; mean 109.6; SD (14.9) Arm 2: Sample size 33; mean 112.0; SD (15) Outcome: Griffith Mental Development Scales: General quotient score (Secondary) Follow-up time: 2.5 years Arm 1: Sample size 39; mean 110.5; SD (10.6) Arm 2: Sample size 33; mean 114.2; SD (9.8)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	(1.1) ,0.001 Total n-3 PUFAs{ 17.9 (1.9) 13.7 (1.3) ,0.001 Total n-3 to n-6{ 0.8 (0.1) 0.5 (0.1) ,0.001			Outcome: Griffith Mental Development Scales: Personal social (Secondary) Follow-up time: 2.5 years Arm 1: Sample size 39; mean 109.4; SD (11.5) Arm 2: Sample size 33; mean 112.4; SD (11.9) Outcome: Griffith Mental Development Scales: Locomotor (Secondary) Follow-up time: 2.5 years Arm 1: Sample size 39; mean 107.9; SD (12.6) Arm 2: Sample size 33; mean 112.5; SD (12.2)
Fang et al., 2005[137] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: Taiwan Funding source / conflict: Manufacturer supplied product	Study Population: Preterm infants Infants enrolled 28 Infants withdrawals 1 Infants completers 27 Infant age: 1 week (mean gestation age 33 weeks) (0.5 week) NA Race of Mother: NR (100)	Inclusion Criteria: (1) A gestational age at birth between 30 and 37 weeks; (2) Normal fundus oculi; (3) Recruitment prior to commencement of feeding Exclusion Criteria: (1) Breast feeding; (2) A maternal history of infection, diabetes mellitus, gestational diabetes mellitus, cocaine or alcohol abuse, systemic diseases or if intrauterine growth retardation had been diagnosed during pregnancy; (3) Major congenital abnormality; (4) Severe intraventricular hemorrhage > grade 2; (5) Cystic periventricular leukomalacia; (6) Retinopathy of prematurity stage 2; (7)	Start time: Infants 1 week after birth Duration: Infants 24 weeks Arm 1: placebo Description: infant formula based on the composition of human milk Brand name: Neoangelac Manufacturer: Multipower Enterprise Corporation Dose: Babies were given more than 110 kcal/kg per day during the first 4 months and more than 70 kcal/kg per day from 4 to 6 months N-6 N-3: 10:1 linoleic:linolenic Arm 2: Neoangelac Plus Description: Neoangelac supplemented with Omega 3 Brand name: Neoangelac Plus Manufacturer: Multipower Enterprise Corporation Dose: Babies were given more than 110 kcal/kg per day during the first 4 months and more than 70 kcal/kg per day from 4 to 6 months DHA: 0.05% AA: 0.10%	Outcome: Bayley Mental Development Index (Primary) Follow-up time: 1 year Arm 1: Sample size 11; mean 90.5; SD (6.9) Arm 2: Sample size 16; mean 98.7; SD (8) Follow-up time: 6 months Arm 1: Sample size 11; mean 91.7; SD (10.4) Arm 2: Sample size 16; mean 96.1; SD (8.6)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		Bronchopulmonary dysplasia on radiographs or oxygen usage 28 days; (8) Body weight less than the third percentile; (9) Surgical intervention for necrotizing enterocolitis (10) Mechanical ventilation after achieving enteral intake > 110 kcal/kg per day; (11) A 5-min Apgar score < 7; (12) Administration of blood transfusion, blood products, or parenteral lipids with DHA or AA.		
van Goor et al., 2011[66] Study name: Groningen LCPUFA study Study dates: 2004-2009 Study design: Trial randomized parallel Location: Netherlands Funding source / conflict: Industry Study follow-up: 18 months Original, same study, or follow-up studies: Bouwstra, 2003[62]; Bouwstra, 2005[63]; de Jong, 2010[64]; de Jong, 2012[65]; van Goor, 2010[36]	Study Population: Healthy infants Pregnant enrolled 119 Infants enrolled 119 Infants completers 114 Pregnant age: Placebo: 32.7 DHA: 32.5 DHA+AA: 32.9 (Placebo: 5.1 DHA: 4.4 DHA+AA: 4.8) Infant age: 18 months Race of Mother: NR (100)	Inclusion Criteria: women with a first or second low-risk singleton pregnancy, between the 14th and 20th weeks of pregnancy Exclusion Criteria: women with vegetarian or vegan diets; women with diabetes mellitus; birth complications	Start time: Pregnant 14th-20th week pregnancy Lactating 3 months after delivery Mothers 3 months after delivery Infants NR Duration: Pregnant NR Lactating 33-39 weeks Mothers 33-39 weeks Infants NR Arm 1: placebo Description: Soy bean oil Brand name: none Arm 2: DHA Description: DHA plus soy bean oil Brand name: Marinol D40 Manufacturer: Lipid Nutrition B.V., Wormerveer, The Netherlands; AA: Dose: 1 capsule DHA and 1 capsule soy bean oil once a day ALA: 32 mg/d DHA: 220 mg/d EPA: 34 mg/d Arm 3: DHA+AA Description: DHA plus AA Brand name: AA: no brand name Manufacturer: Wuhan Alking Bioengeneering Co.	Outcome: Bayley Scale of Infant Development (Mental developmental index) (Unspecified) Follow-up time: 18 months Arm 1: Sample size 34; mean 115.2; SD (11.6) Arm 2: Sample size 41; mean 113.7; SD (13)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			Ltd., Wuhan, China Dose: 2 capsules once a day ALA: 7 mg/d DHA: 220 mg/d EPA: 36 mg/d AA: 220 mg per capsule	
Gustafson et al., 2013[74] Study name: NR Study dates: May 2009 - July 2011 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 67 Pregnant withdrawals 12 Pregnant completers 52 Infants enrolled 44 Infants completers 41 Pregnant age: placebo 25.6+; DHA 25.5 (placebo 4.8; DHA 4.3) Race of Mother: White European (46.3) Black (37.3) Asian (3) Hispanic (13.4) Baseline biomarker information: plasma DHA (wt% TFA) placebo group: 3.91 (3.15-4.21); DHA group: 3.94(3.39-4.72) RBC DHA (wt% TFA) placebo group 4.30(3.99-5.03); DHA group 4.50 (3.73-5.44)	Inclusion Criteria: between 16–35.9 years of age and carrying a singleton pregnancy between the 12th and 20th week of gestation Exclusion Criteria: any serious health condition likely to affect the growth and development of the fetus or health of the mother including cancer, lupus, hepatitis, diabetes mellitus (Type1, Type 2 or gestational) or HIV/AIDS at baseline or fetal cardiac structural or conduction defects. Women who self-reported illicit drug use or alcohol use during pregnancy and those with hypertension or BMI Z40 were excluded. Women who were taking more than 200 mg/day DHA in prenatal vitamins or over the counter supplements were excluded from participation	Start time: Pregnant 12-20 week gestation Infants birth Duration: Pregnant till birth Arm 1: Placebo Description: g 50% soy and 50% corn oil Manufacturer: Martek Biosciences, now DSM Nutritional Products Dose: 3 capsule a day each 500 mg Blinding: Only members of the investigational pharmacy knew the subject allocation. Participants and all members of the investigational team were blinded to the intervention assignment. Participants were allocated to either group based on the simple randomization procedure using random numbers generated by SAS. All capsules were the same color, size, weight and the oils were orange-flavored to prevent investigator or subject bias. Arm 2: algal oil as a source of DHA (200 mg of DHA per capsule for a total of 600 mg DHA/day) Dose: 3 capsule of 200mg DHA total 600 mg DHA: 200 mg * 3	Outcome: Neonatal Behavior Assessment: state organization (Primary) Follow-up time: 1-14 days post-partum Arm 1: Sample size 12; mean 13.5; SD (13.89) Arm 2: Sample size 15; mean 15.13; SD (8.02) Outcome: Neonatal Behavior Assessment: autonomic (Primary) Follow-up time: 1-14 days post-partum Arm 1: Sample size 12; mean 14.83; SD (16.9) Arm 2: Sample size 15; mean 18.13; SD (14.48) Outcome: Neonatal Behavior Assessment: reflexes (Primary) Follow-up time: 1-14 days post-partum Arm 1: Sample size 12; mean 21.92; SD (14.45) Arm 2: Sample size 15; mean 22.6; SD (14.33) Outcome: Neonatal Behavior Assessment: state regulation (Primary) Follow-up time: 1-14 days post-partum Arm 1: Sample size 12; mean 16.42; SD (20.02) Arm 2: Sample size 15; mean 16.93; SD (20.06) Outcome: Neonatal Behavior Assessment: habituation (Primary) Follow-up time: 1-14 days post-partum Arm 1: Sample size 12; mean 9.92; SD (9.28) Arm 2: Sample size 15; mean 8.47; SD (9.26) Outcome: Neonatal Behavior Assessment: orienting (Primary)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Follow-up time: 1-14 days post-partum Arm 1: Sample size 12; mean 19.75; SD (15.45) Arm 2: Sample size 15; mean 23.4; SD (18.32)
Helland et al., 2008[76] Study name: NR Study dates: 1994-2003 Study design: Trial randomized parallel Location: Norway Funding source / conflict: Industry, Government, Multiple foundations and Societies Study follow-up: 7 years Original, same study, or follow-up studies: Helland, 2001[86] and Helland, 2003[87] and which are both included in the original report	Study Population: Healthy infants Healthy pregnant women Breast-feeding women Infants enrolled 262 Infants completers 143 Pregnant age: cod oil 28.6 n=175 corn oil 27.6 n=166 (cod oil 3.4; corn oil 3.2) Race of Mother: NR (100) Baseline biomarker information: from id 10331 cod(n148) corn (n137) n-3 cod: 73.7 (30.0) corn 52.0 (14.9)*** 20:5n-3 cod: 10.8 (7.6) corn: 2.5 (1.8)*** 22:5n-3 cod: 5.0 (2.6) corn: 2.9 (1.3)*** 22:6n-3 cod: 55.8 (20.6) corn: 45.3 (12.8)*** Baseline Omega-3 intake: from 10331 cod n147 corn n159 18:3 n-3: cod: 1.3 (0.5) corn: 1.2 (0.5) 20:5 n-3 cod: 0.2 (0.2) corn:0.2 (0.2) 22:5 n-3 cod: 0.05 (0.03) corn: 0.05 (0.03) 22:6 n-3 cod: 0.3 (0.3) corn: 0.3 (0.3)	Inclusion Criteria: Healthy nulliparous or primiparous women, aged 19-35 with single pregnancies Exclusion Criteria: Unhealthy neonates	Start time: Pregnant week 18 of pregnancy Duration: NR Arm 1: Cod oil Manufacturer: NRActive ingredients: Vit 1: 117 ug/mL, Vit D3: 1 ug/mL, vit E: 1.4 mg/mL Viability: frozen at _x0003_ 70 ° C under nitrogen. Before storage, the samples were sonicated and ethylenediaminetetraacetic acid and butylated hydroxytoluene were added to a final concentration of 1.85 mg/mL and 75 _x0003_ g/mL, respectively DHA: 1183mg/10 mL EPA: 803 mg/10mL Total N-3: 2494 mg/10mL Arm 2: corn oil Active ingredients: Vit 1: 117 ug/mL, Vit D3: 1 ug/mL, vit E: 1.4 mg/mL Viability: frozen at _x0003_ 70 ° C under nitrogen. Before storage, the samples were sonicated and ethylenediaminetetraacetic acid and butylated hydroxytoluene were added to a final concentration of 1.85 mg/mL and 75 _x0003_ g/mL, respectively ALA: 92 mg/10mL	Outcome: Kaufman Assessment Battery for Children (K-ABC): mental processing composite (Secondary) Follow-up time: 4 years Arm 1: Sample size 28; mean 102.0 Arm 2: Sample size 30; mean 107.0 Follow-up time: 7 years Arm 1: Sample size 28; mean 108.0 Arm 2: Sample size 30; mean 110.0 Outcome: Kaufman Assessment Battery for Children (K-ABC): non-verbal abilities (Secondary) Follow-up time: 4 years Arm 1: Sample size 28; mean 102.0 Arm 2: Sample size 30; mean 107.0 Follow-up time: 7 years Arm 1: Sample size 28; mean 112.0 Arm 2: Sample size 30; mean 112.0 Outcome: Kaufman Assessment Battery for Children (K-ABC): sequential processing (Secondary) Follow-up time: 4 years Arm 1: Sample size 28; mean 107.0 Arm 2: Sample size 30; mean 109.0 Follow-up time: 7 years Arm 1: Sample size 28; mean 105.0 Arm 2: Sample size 30; mean 107.0 Outcome: Kaufman Assessment Battery for Children (K-ABC): simultaneous processing (Secondary) Follow-up time: 4 years Arm 1: Sample size 28; mean 98.0 Arm 2: Sample size 30; mean 102.0 Follow-up time: 7 years Arm 1: Sample size 28; mean 110.0 Arm 2: Sample size 30; mean 110.0
Henriksen et al., 2008[107]	Study Population:	Inclusion Criteria: All	Start time: Infants (intervention began when the	Outcome: Ages and Stages:

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study name: Unnamed Trial D Study dates: 2003-2006 Study design: Trial randomized parallel Location: Norway Funding source / conflict: Multiple foundations and Societies, Manufacturer supplied product Study follow-up: 6 months Original, same study, or follow-up studies: Westerberg, 2011[125]; Almaas, 2015[126]	Preterm infants Infants enrolled 141 Infants completers 129 Mother age: Median: Intervention: 31 years Control: 32 years 28-35 years Infant age: Median Gestational age: Control: 28.9 weeks Intervention: 28.4 weeks Gestational age: 26.6-30.9 weeks Race of Mother: White European (Intervention: 79%; Control 84%)	VLBW infants (<1500g) born between December 2003 and November 2005 at Rikshospitalet-Radiumhospitalet Medical Center, Akershus University Hospital, Buskerud Hospital, and Vestfold Hospital in Norway Exclusion Criteria: Major congenital abnormalities or cerebral hemorrhage (grade 3 or 4, as determined through ultrasonography)	infant received most of his nutrients enterally: >100ml human milk/kg body weight/day Duration: Infants Until discharge or bottle of study oil was empty (average 63 days of age) Arm 1: Control Description: Study oil: soy oil and medium chain triglycerides Active ingredients: 127mg linolenic acid/100 ml milk(27.1% total fatty acids) Dose: 0.5 ml study oil/100 ml human milk Blinding: Study oils packed in numbered bottles in hospital pharmacy ALA: 16mg/100 ml milk; 3.4% total fatty acids Arm 2: Intervention Description: DHA and AA-containing oil Manufacturer: Martek Biosciences Active ingredients: 88mg/100 ml linoleic acid per 100 ml milk (18.8%) Dose: 0.5 ml study oil per 100 ml milk, ad lib Maternal conditions Infant conditions DHA: 32mg/100ml milk (6.9%) AA: 31 mg/100 ml milk (6.7% total fatty acids Current smoker 22% during pregnancy Low birth weight 100% (median 1090 g)	Communication Follow-up time: 6 months Arm 1: Sample size 55; mean 46.6; SD (9.1) Arm 2: Sample size 50; mean 45.4; SD (7.9) Outcome: Ages and Stages: Fine motor Follow-up time: 6 months Arm 1: Sample size 55; mean 45.8; SD (14.3) Arm 2: Sample size 50; mean 45.2; SD (10.7) Outcome: Ages and Stages: Gross motor Follow-up time: 6 months Arm 1: Sample size 55; mean 30.9; SD (11.1) Arm 2: Sample size 50; mean 33.3; SD (11.5) Outcome: Ages and Stages: Personal-social Follow-up time: 6 months Arm 1: Sample size 55; mean 42.2; SD (12.3) Arm 2: Sample size 50; mean 43.2; SD (12.8) Outcome: Ages and Stages: Problem-solving Follow-up time: 6 months Arm 1: Sample size 55; mean 49.5; SD (9.5) Arm 2: Sample size 50; mean 53.4; SD (7) Outcome: Ages and Stages: Total Follow-up time: 6 months Arm 1: Sample size 55; mean 215.0; SD (39) Arm 2: Sample size 50; mean 221.0; SD (32)
Isaacs et al., 2011[99] Study name: Unnamed Trial A Study dates: Recruitment	Study Population: Preterm infants Infants enrolled 238 Infants completers 107	Inclusion Criteria: birth weight of < 2000 g, and gestational age of < 35 weeks Exclusion Criteria:	Start time: Infants at hospital discharge Duration: Infants 9 months Arm 1: control Description: control formula	Outcome: Wechsler Abbreviated Scale of Intelligence: FSIQ (Secondary) Follow-up time: 10 years Arm 1: Sample size 57; mean 92.7; SD (12.3) Arm 2: Sample size 50; mean 95.1; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
of infants from 1995 through 1997 with 10-year followup Study design: Trial randomized parallel Location: UK Funding source / conflict: Industry, Government, Some authors have received research funding from infant formula manufacturers Study follow-up: 10 years Original, same study, or follow-up studies: Fewtrell, 2002[158] is the original study; Llorente, 2003[98] reports post-partum depression	Infant age: birth (at < 35 weeks gestation) NA Race of Mother: NR (NR)	congenital malformations	Active ingredients: protein, minerals, vitamins A, E, K, D DHA: 0 EPA: 0 AA: 0 Other dose 1: C18:2, n-6, linoleic acid 11.5 g / 100g fat Other dose 2: C18:3, n-3, alpha_x0004_-linolenic acid 1.6 g / 100g fat Arm 2: Omega 3 supplemented formula Description: LCPUFA-Supplemented Formula Active ingredients: protein, minerals, vitamins A, E, K, D Infant conditions DHA: 0.5 g / 100g fat EPA: 0.1 g/ 100g fat AA: 0.04 g / 100g fat Other dose 1: C18:2, n-6, linoleic acid 12.3 g / 100g fat Other dose 2: C18:3, n-6, gamma-linoleic acid 0.9 g / 100g fat Other dose 3: C18:3, n-3, _x0004_alpha-linolenic acid 1.5 g / 100g fat Pre-term birth 100% Low birth weight 100%	(13.2) Outcome: Wechsler Abbreviated Scale of Intelligence: Performance IQ (Secondary) Follow-up time: 10 years Arm 1: Sample size 57; mean 94.5; SD (14.1) Arm 2: Sample size 50; mean 94.2; SD (12.7) Outcome: Wechsler Abbreviated Scale of Intelligence: VIQ (Secondary) Follow-up time: 10 years Arm 1: Sample size 57; mean 92.6; SD (12.6) Arm 2: Sample size 50; mean 96.7; SD (13.2)
Jensen et al., 2010[135] Study name: Unnamed Trial B Study dates: NR (<2010) Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Government Study follow-up: 5 years	Study Population: Breast-feeding women Lactating enrolled 227 Infants enrolled 230 Infants completers 119 Lactating enrolled 227 Lactating age: 31.5 years (5 years) 18 to 40 Infant age: birth (NA) NA Race of Mother: NR (NR)	Inclusion Criteria: maternal age between 18 and 40 y, infant gestational age >=37 wk, infant birth weight between 2500 and 4200 g Exclusion Criteria: chronic maternal disorders, major congenital anomalies, obvious gastrointestinal or metabolic disorders of the infant	Start time: Infants birth Duration: Infants 4 months Arm 1: placebo Description: capsule containing corn & soy oil Manufacturer: Martek Biosciences Purity Data: 50:50 mixture of soy and corn oils consisting, by weight, of 15% saturated fatty acids, 23.5% monounsaturated fatty acids, 56.3% linoleic acid (18:2 n-6) and 3.9% a-linolenic acid (18:3 n-3) Dose: 1 capsule Blinding: capsules were identical ALA: 3.9% Arm 2: omega 3 capsule Description: high-DHA algal triglyceride capsule	Outcome: Wechsler Primary and Preschool Scale of Intelligence - Revised : Vocabulary Subset (Secondary) Follow-up time: 5 years Arm 1: Sample size 57; mean 12.9; SD (2.4) Arm 2: Sample size 60; mean 12.3; SD (2.8) Outcome: Wechsler Primary and Preschool Scale of Intelligence - Revised : Animal Pegs Subset (Secondary) Follow-up time: 5 years Arm 1: Sample size 57; mean 12.2; SD (1.8) Arm 2: Sample size 60; mean 12.1; SD (2.4) Outcome: Wechsler Primary and Preschool

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Original, same study, or follow-up studies: Jensen, 2005[136]			Brand name: DHASCO Manufacturer: Martek Purity Data: by weight, 44% saturated fatty acids, 13.6% monounsaturated fatty acids, 0.8% linoleic acid (18:2n-6) and 41.7% DHA (22:6n-3) Dose: 1 capsule DHA: 200 mg	Scale of Intelligence - Revised : Block Design Subset (Secondary) Follow-up time: 5 years Arm 1: Sample size 57; mean 11.1; SD (2.2) Arm 2: Sample size 60; mean 11.3; SD (2.1) Outcome: Wechsler Primary and Preschool Scale of Intelligence - Revised : Information Subset (Secondary) Follow-up time: 5 years Arm 1: Sample size 57; mean 11.2; SD (2.6) Arm 2: Sample size 60; mean 10.8; SD (2.6)
Lauritzen et al., 2005[128] Study name: Danish National Birth Cohort-Lactating Women Study dates: Enrolled in 1999 Study design: Trial randomized parallel Location: Denmark Funding source / conflict: Industry, Government Study follow-up: 9 months, 1 year, 2 years Original, same study, or follow-up studies: Lauritzen, 2004[127]; Lauritzen, 2005[102]; Cheatham, 2011[129];	Study Population: Healthy infants Breast-feeding women Lactating enrolled 122 Lactating completers 89 Infants enrolled 122 Infants completers 89 Lactating enrolled 122 Lactating completers 89 Pregnant age: NR (NR) NR Infant age: 9 days (3 days) NA Race of Mother: NR (100%) Baseline Omega-3 intake: < 0.4 g n-3 LCPUFA/d	Inclusion Criteria: pregnant women with a fish intake below the population median (< 0.4 g n-3 LCPUFA·d–1), uncomplicated pregnancy, a normal prepregnancy body mass index (< 30 kg·m–2), no metabolic disorders, an intention to breastfeed for at least four months. Newborns had to be healthy, singleton, term infants with normal weight for gestation [33] and an Apgar score > 7 five minutes after delivery. Exclusion Criteria: NR	Start time: Lactating 9 days after birth Infants 9 days after birth Duration: Lactating 4 months Infants 4 months Arm 1: placebo group Description: olive oil in musli bars, cookies, or capsules Manufacturer: BASF Dose: one bar/cookie/capsule containing 4.5 g olive oil Blinding: identical bars/cookies/capsules Arm 2: fish oil Description: fish oil in musli bars, cookies, or capsules Manufacturer: BASF Dose: one bar/cookie/capsule containing 4.5 g fish oil DHA: 0.9 g Total N-3: Other FA (not DHA): 0.6 g Arm 3: high n-3 reference group Description: top quartile fish intake at baseline Dose: no supplementation, high fish intake Total N-3: > 0.8 n-3 LCPUFA/d	Outcome: Infant Planning Test (problem solving) (Secondary) Follow-up time: 9 months Arm 1: Sample size 38; mean 4.3; SD (3.6) Arm 2: Sample size 48; mean 4.5; SD (3.1) Arm 3: Sample size 42; mean 4.5; SD (3.3) Outcome: MacArthur Communicative Development Inventory Linguistic Development: late gestures (Secondary) Follow-up time: 1 year Arm 1: Sample size 37; mean 15.0; SD (7) Arm 2: Sample size 52; mean 14.0; SD (6) Arm 3: Sample size 42; mean 16.0; SD (7) Outcome: MacArthur Communicative Development Inventory Linguistic Development: number of irregular words (Secondary) Follow-up time: 2 years Arm 1: Sample size 31; median 3.0; IQR Arm 2: Sample size 40; median 3.0; IQR Arm 3: Sample size 40; median 4.0; IQR Outcome: MacArthur Communicative Development Inventory Linguistic Development: number of over regularized words (Secondary) Follow-up time: 2 years Arm 1: Sample size 31; median 1.0; IQR Arm 2: Sample size 40; median 1.0; IQR

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 3: Sample size 40; median 1.0; IQR Outcome: MacArthur Communicative Development Inventory Linguistic Development: early gestures (Secondary) Follow-up time: 1 year Arm 1: Sample size 37; median 11.0; IQR Arm 2: Sample size 52; median 11.0; IQR Arm 3: Sample size 42; median 12.0; IQR Outcome: MacArthur Communicative Development Inventory Linguistic Development: percent starting to talk (Secondary) Follow-up time: 1 year Arm 1: 6/37 (16.0%) Arm 2: 6/52 (12.0%) Arm 3: 7/42 (17.0%) Outcome: MacArthur Communicative Development Inventory Linguistic Development: phrases understood (Secondary) Follow-up time: 1 year Arm 1: Sample size 37; mean 11.0; SD (6) Arm 2: Sample size 52; mean 11.0; SD (5) Arm 3: Sample size 42; mean 11.0; SD (5) Outcome: MacArthur Communicative Development Inventory Linguistic Development: talk about abstract (Secondary) Follow-up time: 2 years Arm 1: 29/31 (94.0%) Arm 2: 30/40 (75.0%) Arm 3: 38/40 (95.0%) Outcome: MacArthur Communicative Development Inventory Linguistic Development: use grammar (Secondary) Follow-up time: 2 years Arm 1: 10/31 (32.0%) Arm 2: 10/40 (25.0%) Arm 3: 16/40 (40.0%) Outcome: MacArthur Communicative Development Inventory Linguistic Development: vocabulary comprehension (Secondary) Follow-up time: 1 year

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 1: Sample size 37; mean 71.0; SD (45) Arm 2: Sample size 52; mean 54.0; SD (37) Arm 3: Sample size 42; mean 65.0; SD (40) Outcome: MacArthur Communicative Development Inventory Linguistic Development: vocabulary production (Secondary) Follow-up time: 1 year Arm 1: Sample size 37; median 5.0; IQR Arm 2: Sample size 52; median 3.0; IQR Arm 3: Sample size 42; median 5.0; IQR Follow-up time: 2 years Arm 1: Sample size 31; mean 297.0; SD (147) Arm 2: Sample size 40; mean 242.0; SD (170) Arm 3: Sample size 40; mean 312.0; SD (146)
Makrides et al., 2009[116] Study name: DINO Study dates: Enrollment April 2001 to October 2005 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies, Manufacturer supplied product, Some authors serve on scientific advisory boards for corporations, Some authors have received research funding from infant formula manufacturers	Study Population: Preterm infants Breast-feeding women Pregnant enrolled 545 Infants enrolled 657 Infants completers 614 Lactating age: 30 years (5.5 years) NR Infant age: 4 days after birth (29 weeks gestation) 2 to 6 days after birth Race of Mother: White European (90%)	Inclusion Criteria: infants born at < 33 wk of gestation Exclusion Criteria: Infants born with major congenital or chromosomal abnormalities, lactating women for whom tuna oil was contraindicated(women with bleeding disorders or taking anticoagulants)	Start time: Infants 4 days after birth Duration: Infants until infants reached their "expected" date of delivery Arm 1: Placebo Description: Soy oil capsules or regular preterm formula Manufacturer: Clover Corporation Dose: six 500-mg soy oil capsules Blinding: all capsules were similar in size, shape, and color Maternal conditions Infant conditions Current smoker 25.1% during pregnancy Pre-term birth 100% Low birth weight 44.5% Other conditions 1 SGA 18.6% Arm 2: tuna oil capsules Description: DHA-rich tuna oil capsules or high-DHA formula Manufacturer: Clover Corporation Dose: 6 500 mg capsules Maternal conditions	Outcome: Bayley Scale of Infant Development (Mental developmental index) (Primary) Follow-up time: 18 months Arm 1: Sample size 335; mean 93.0; SD (17.3) Arm 2: Sample size 322; mean 94.9; SD (14.5)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study follow-up: 18 months Original, same study, or follow-up studies: Smithers, 2008[104]; Smithers, 2010[117]; Manley, 2011[118]; Collins, 2011[105]; Atwell, 2013[119]; Collins, 2015[120]			Infant conditions DHA: Capsules: Intended to achieve breast milk concentration of 1.0%.Formula: 1.0% AA: Capsules: not intended to alter AA levels. Formula: 0.6% Current smoker 25.6% during pregnancy Pre-term birth 100% Low birth weight 45.7% Other conditions 1 SGA 18.9%	
Makrides et al., 2010[35] Study name: DOMInO Study dates: 2005-2008 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Manufacturer supplied product Original, same study, or follow-up studies: Smithers, 2011[53]; Palmer, 2012[54]; Zhou, 2012[55]; Palmer, 2013[56]; Makrides, 2014 [57]	Study Population: Healthy pregnant women Pregnant enrolled 2399 Pregnant withdrawals 1 Infants enrolled 605 Infants withdrawals 32 Infants completers 726 Pregnant age: 28.9 (DHA5.7___ control5.6) Race of Mother: NR (NR)	Inclusion Criteria: with singleton pregnancies at less than 21 weeks' gestation were approached by study research assistants while attending routine antenatal appointments Exclusion Criteria: already taking a prenatal supplement with DHA, their fetus had a known major abnormality, they had a bleeding disorder in which tuna oil was contraindicated, were taking anticoagulant therapy, had a documented history of drug or alcohol abuse, were participating in another fatty acid trial, were unable to give written informed consent, or if English was not the main language spoken at home	Start time: Pregnant < 21 week's gestation Duration: NR Arm 1: vegetable oil capsules Description: a blend of 3 nongenetically modified oils (rapeseed, sunflower, and palm) in equal proportions Manufacturer: Efamol, Surrey, England. Dose: 3* 500mg capsule / day Blinding: All capsules were similar in size, shape, and color Arm 2: DHA Description: DHA-rich fish oil concentrate Manufacturer: ; Incromega 500 TG, Croda Chemicals, East Yorkshire, England Dose: 500mg capsule *3/day DHA: 800mg EPA: 100mg	Outcome: Bayley Scale of Infant Development III (Cognitive Component) (Primary) Follow-up time: 18 months Arm 1: Sample size 375; weighted mean 101.75; SD (12.56) Arm 2: Sample size 351; weighted mean 101.81; SD (11.05)
Makrides et al., 2014[57] Study name: DOMInO	Study Population: Healthy pregnant women Infants enrolled 726	Inclusion Criteria: Women with singleton pregnancies at less than 21 weeks' gestation	Start time: Pregnant <21 weeks gestation Duration: Pregnant <21 weeks gestation until birth	Outcome: Behavior Rating Inventory of Executive Function-Preschool: Emergent Meta-Cognition Index (Secondary) Follow-up time: 4 years

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study dates: October 31, 2005 to September 25, 2012 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Manufacturer supplied product, Some authors have received research funding from infant formula manufacturers Original, same study, or follow-up studies: Makrides, 2010 [35] Smithers, 2011[53]; Palmer, 2012[54]; Zhou, 2012[55]; Palmer, 2013[56]	Infants completers 646 Race of Mother: NR (100)	Exclusion Criteria: Already taking a prenatal supplement with DHA, fetus had a known major abnormality, had a bleeding disorder in which tuna oil was contraindicated, were taking anticoagulant therapy, had a documented history of drug or alcohol abuse, were participating in another fatty acid trial, were unable to give written informed consent, or if English was not the main language spoken at home	Arm 1: Placebo Description: rapeseed, sunflower, and palm oil capsules Manufacturer: Enfamol Dose: 3 500mg capsules/day Blinding: similar in size, shape, and color Arm 2: DHA supplement Description: DHA-rich fish oil capsules Manufacturer: Enfamol Dose: 3 500mg capsules/day DHA: 800 mg/d EPA: 100 mg/day	Arm 1: Sample size 333 Arm 2: Sample size 313 Outcome: Behavior Rating Inventory of Executive Function-Preschool: Emotional Control Scale (Secondary) Follow-up time: 4 years Arm 1: Sample size 333 Arm 2: Sample size 313 Outcome: Behavior Rating Inventory of Executive Function-Preschool: Flexibility Index (Secondary) Follow-up time: 4 years Arm 1: Sample size 333 Arm 2: Sample size 313 Outcome: Behavior Rating Inventory of Executive Function-Preschool: Global Executive Composite score (Secondary) Follow-up time: 4 years Arm 1: Sample size 333 Arm 2: Sample size 313 Outcome: Behavior Rating Inventory of Executive Function-Preschool: Inhibition Scale (Secondary) Follow-up time: 4 years Arm 1: Sample size 333 Arm 2: Sample size 313 Outcome: Behavior Rating Inventory of Executive Function-Preschool: Inhibitory Self-Control Index (Secondary) Follow-up time: 4 years Arm 1: Sample size 333 Arm 2: Sample size 313 Outcome: Behavior Rating Inventory of Executive Function-Preschool: Plan/Organize Scale (Secondary) Follow-up time: 4 years Arm 1: Sample size 333 Arm 2: Sample size 313 Outcome: Behavior Rating Inventory of Executive Function-Preschool: Shift Scale (Secondary) Follow-up time: 4 years Arm 1: Sample size 333 Arm 2: Sample size 313

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Outcome: Behavior Rating Inventory of Executive Function-Preschool: Working Memory Scale (Secondary) Follow-up time: 4 years Arm 1: Sample size 333 Arm 2: Sample size 313 Outcome: CELF-P2 Core Language Score (Secondary) Follow-up time: 4 years Arm 1: Sample size 333 Arm 2: Sample size 313 Outcome: Day-night Stroop (measure of efficiency) (Secondary) Follow-up time: 4 years Arm 1: Sample size 333 Arm 2: Sample size 313 Outcome: Differential Ability Scales, second edition (DAS II) score: General Conceptual Ability Score (Secondary) Follow-up time: 4 years Arm 1: Sample size 333 Arm 2: Sample size 313 Outcome: Differential Ability Scales, second edition (DAS II) score: General Conceptual Ability Score (Secondary) Follow-up time: 4 years Arm 1: Sample size 333 Arm 2: Sample size 313
Meldrum et al., 2012[140] Study name: Infant FishOil Supplementation Study (IFOS) Study dates: Recruitment from June 2005 through October 2008 Study design: Trial randomized parallel Location: Australia	Study Population: Pregnant women with allergies Pregnant enrolled 420 Infants enrolled 420 Infants completers 287 Mother age: NR (NR) NR Infant age: Birth (NA) NA Race of Mother: NR	Inclusion Criteria: allergic pregnant women were recruited as their infants are at a higher risk of developing allergic disease. Maternal atopy was defined by at least one positive skin prick test to at least one of a defined panel of allergens. Exclusion Criteria: maternal smoking, a pre-existing medical	Start time: Infants birth Duration: Infants 6 months Arm 1: placebo Description: olive oil capsule Manufacturer: Ocean Nutrition, Canada Active ingredients: 66·6 % n-9 oleic acid Viability: he composition was regularly tested by an independent laboratory during the trial Dose: one 650 mg capsule Blinding: image and scent matched Arm 2: fish oil capsule Manufacturer: Ocean Nutrition, Canada	Outcome: Bayley Scales of Infant and Toddler Development (BSID-III) Composite Scores Cognitive (Primary) Follow-up time: 18 months Arm 1: Sample size 149; mean 105.28; SD (19.9) Arm 2: Sample size 138; mean 107.65; SD (11.6) Outcome: Bayley Scales of Infant and Toddler Development (BSID-III) Standard Scores Cognitive (Primary) Follow-up time: 18 months Arm 1: Sample size 149; mean 11.43; SD (2.3) Arm 2: Sample size 138; mean 11.55; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Funding source / conflict: Government, None, Manufacturer supplied product Original, same study, or follow-up studies: D'Vaz, 2012[142]	Baseline biomarker information: Cord blood data Fish oil group LA, linoleic acid 3.71 ALA, a-linolenic acid 0·496 EPA 0·334 DHA 7·36 DPA 0·700 AA, arachidonic acid 15·76 Olive oil group LA, linoleic acid 3.81 ALA, a-linolenic acid 0·513 EPA 0·308 DHA 7·44 DPA 0·673 AA, arachidonic acid 15·54 Baseline Omega-3 intake: From maternal food questionnaire, while pregnant Fish oil group LA, linoleic acid 10·59 ALA, a-linolenic acid 0·87 EPA 0·07 DHA 0·09 AA, arachidonic acid 0·87 Olive oil group LA, linoleic acid 9·90 ALA, a-linolenic acid 0·89 EPA 0.06 DHA 0·08 AA, arachidonic acid 0·84	condition or high-risk pregnancy, more than three fish meals consumed per week or fish oil intake during pregnancy in excess of 1000 mg/d, preterm delivery, and infants with significant congenital abnormalities or medical conditions.	Viability: he composition was regularly tested by an independent laboratory during the trial. Dose: one 650 mg capsule DHA: 280 mg EPA: 110 mg	(2.2) Outcome: Macarthur-Bates Communicative Development Inventory raw score: early gestures (Primary) Follow-up time: 12 months Arm 1: Sample size 66; mean 9.56; SD (3.14) Arm 2: Sample size 62; mean 10.29; SD (3.5) Follow-up time: 18 months Arm 1: Sample size 84; mean 13.62; SD (7.7) Arm 2: Sample size 77; mean 14.09; SD (2.3) Outcome: Macarthur-Bates Communicative Development Inventory raw score: later gestures (Primary) Follow-up time: 12 months Arm 1: Sample size 66; mean 11.26; SD (7.5) Arm 2: Sample size 62; mean 15.16; SD (8.3) Follow-up time: 18 months Arm 1: Sample size 84; mean 28.08; SD (7.7) Arm 2: Sample size 77; mean 30.81; SD (7.6) Outcome: Macarthur-Bates Communicative Development Inventory raw score: phrases understood (Primary) Follow-up time: 12 months Arm 1: Sample size 66; mean 13.6; SD (5.8) Arm 2: Sample size 62; mean 13.34; SD (6.7) Follow-up time: 18 months Arm 1: Sample size 84; mean 23.5; SD (5.1) Arm 2: Sample size 77; mean 24.06; SD (4.7) Outcome: Macarthur-Bates Communicative Development Inventory raw score: total gestures (Primary) Follow-up time: 12 months

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 1: Sample size 66; mean 20.76; SD (10.1) Arm 2: Sample size 62; mean 25.47; SD (10.9) Follow-up time: 18 months Arm 1: Sample size 84; mean 41.48; SD (9.3) Arm 2: Sample size 77; mean 44.75; SD (9) Outcome: Macarthur-Bates Communicative Development Inventory raw score: words spoken (Primary) Follow-up time: 12 months Arm 1: Sample size 66; mean 5.52; SD (8.7) Arm 2: Sample size 62; mean 6.11; SD (7.5) Follow-up time: 18 months Arm 1: Sample size 84; mean 58.5; SD (63.5) Arm 2: Sample size 77; mean 49.16; SD (55.8) Outcome: Macarthur-Bates Communicative Development Inventory raw score: words understood (Primary) Follow-up time: 12 months Arm 1: Sample size 66; mean 61.42; SD (52.2) Arm 2: Sample size 62; mean 68.3; SD (47.6) Follow-up time: 18 months Arm 1: Sample size 84; mean 190.43; SD (94.5) Arm 2: Sample size 77; mean 199.09; SD (83.7)
Meldrum et al., 2015[51] Study name: Dunstan Study dates: 10/2012-12/2013 for 12-year followup Study design: Trial	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 98 Pregnant completers 82 Infants enrolled 82 Infants completers 50	Inclusion Criteria: Pregnant women with allergies Exclusion Criteria: Women were ineligible for the study if they smoked, had medical problems, a complicated	Start time: Pregnant 20 weeks gestation Duration: Pregnant to birth Arm 1: Placebo Description: Olive oil capsules Manufacturer: Pan Laboratories Dose: 4 1g capsules per day Blinding: Randomization and allocation of capsules	Outcome: Wechsler Intelligence Scale for Children IV (Secondary) Follow-up time: 12 years Arm 1: Sample size 25; mean 107.6; SD (9.9) Arm 2: Sample size 25; mean 108.6; SD (12.2)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
randomized parallel Location: Australia Funding source / conflict: Multiple foundations and Societies, None Study follow-up: 12 years Original, same study, or follow-up studies: Dunstan, 2003[50]; Dunstan, 2008[44];	Pregnant age: Fish oil 30.9 Control 32.6 (Fish oil: 3.7 Control: 3.6) Infant age: NR (NR) Race of Mother: NR (100)	pregnancy, seafood allergy, or if their normal dietary intake exceeded two meals of fish per week. Children were excluded from the study if they were born before 36 weeks' gestation or with major disease (to avoid the confounding effects on immune response) or if cord blood was not collected	was carried out in a blinded manner, and capsules in the two groups were image matched Arm 2: Fish oil Manufacturer: Ocean Nutrition Active ingredients: 3–4 mg/g oil a-tocopherol (vitamin E) Dose: 4 1g capsules per day DHA: 2.2g EPA: 1.1g	
Mulder et al., 2014[75] Study name: NR Study dates: 2004 to 2008 Study design: Trial randomized parallel Location: Canada Funding source / conflict: Government Study follow-up: 18 months	Study Population: Healthy pregnant women Pregnant enrolled 271 Pregnant completers 200 Pregnant age: 33 years (4 years) NR Race of Mother: White European (73%) Other race/ethnicity (27%) Baseline biomarker information: maternal RBC Phusphatidylethanolamine DHA: placebo group 6.25 (1.60) g/ 100g DHA group 6.36 (1.62) g/ 100g Baseline Omega-3 intake: median (2.5 to 97.5th percentile range) intake: placebo group 80.0 (0.00-334) mg/day, DHA group 90.0 (6.00-472) mg/d	Inclusion Criteria: at least 16 wk gestation, not taking any lipid or fatty acid supplement, and were expected to deliver one infant at full-term gestation, with no maternal or fetal complications Exclusion Criteria: NR	Start time: Pregnant 16 weeks gestation Duration: Pregnant Until birth Arm 1: placebo Description: corn and soybean oil supplement Manufacturer: Martek Biosciences Blinding: supplements were identical in appearance, contained an orange flavor mask Arm 2: DHA supplement Description: algal oil DHA supplement Manufacturer: Martek Biosciences DHA: 400 mg	Outcome: Number in highest quartile of Bayley Scales of Infant Development III: cognitive (Unspecified) Follow-up time: 18 months Arm 1: 18/80 (23.1%) Arm 2: 15/74 (20.0%) Outcome: Number in highest quartile of Bayley Scales of Infant Development III: expressive language (Unspecified) Follow-up time: 18 months Arm 1: 19/80 (24.1%) Arm 2: 28/74 (37.5%) Outcome: Number in highest quartile of Bayley Scales of Infant Development III: receptive language (Unspecified) Follow-up time: 18 months Arm 1: 16/80 (20.5%) Arm 2: 27/74 (36.5%) Outcome: Number in highest quartile of Infant MacArthur Communicative Development Inventory: words produced (Unspecified) Follow-up time: 14 months Arm 1: 13/81 (16.0%) Arm 2: 26/78 (33.3%) Follow-up time: 18 months Arm 1: 12/61 (19.1%) Arm 2: 27/73 (37.3%) Outcome: Number in highest quartile of

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Infant MacArthur Communicative Development Inventory: words understood (Unspecified) Follow-up time: 14 months Arm 1: 12/81 (14.8%) Arm 2: 28/78 (35.9%) Follow-up time: 18 months Arm 1: 11/61 (18.8%) Arm 2: 27/73 (37.3%) Outcome: Number in highest quartile of Toddler MacArthur Communicative Development Inventory: words produced (Unspecified) Follow-up time: 18 months Arm 1: 10/61 (17.1%) Arm 2: 26/73 (35.0%)
Ramakrishnan et al., 2015[61] Study name: POSGRAD Study dates: 2005-2009 Study design: Trial randomized parallel Location: Mexico Funding source / conflict: Government, None, March of Dimes Study follow-up: 18 months Original, same study, or follow-up studies: Ramakrishnan, 2010[32]; Stein, 2012[33]; Imhoff-Kunsch, 2011[58]; Escamilla-Nunez, 2014[59]; Gonzalez-Casanova, 2015[60]; Ramakrishnan,	Study Population: Healthy pregnant women Pregnant enrolled 1094 Pregnant completers 968 Infants enrolled 973 Infants completers 730 Pregnant age: Placebo: 26.3 Intervention: 26.5 (Placebo: 4.6 Intervention: 4.9) Infant age: Placebo: 20.5 weeks gestation Intervention: 20.6 weeks gestation (Placebo: 2.1 weeks Intervention: 2.0 weeks) Race of Mother: NR (NR) Baseline Omega-3 intake: From original study ref 3364 mg/day for all: LA: 17,846 in	Inclusion Criteria: Women who were in gestation week 18–22, age 18–35 years, planned to deliver at the IMSS General Hospital and to remain in the area for the next 2 years, and planned predominant breastfeeding for at least 3 months Exclusion Criteria: High risk pregnancy, had any lipid metabolism/absorption conditions, regularly took DHA or fish oil supplements, or used certain chronic medications (such as antiepileptic drugs)	Start time: Pregnant 18-22 weeks gestation Duration: Pregnant 18-22 weeks gestation until delivery Arm 1: Control Description: Corn and soy oils with no added antioxidants Dose: 2 capsules/day Blinding: Similar in appearance and taste to the DHA capsules Arm 2: Intervention Description: Algal-sourced DHA capsule Manufacturer: Martek Biosciences Dose: 2 capsules/day DHA: 200 mg * 2 = 400 mg/d	Outcome: Bayley Mental Development Index (Primary) Follow-up time: 18 months Arm 1: Sample size 365; mean 95.2; SD (9.3) Arm 2: Sample size 365; mean 94.3; SD (10.7)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
2015[61]	controls, 17,645 in DHA AA: 137 in controls, 140 in DHA ALA: 1,488 in controls, 1,477 in DHA EPA: 18 in controls, 18 in DHA DHA: 54 in controls, 56 in DHA			
Smithers et al., 2010[117] Study name: DINO Study dates: April 2001 through September 2003 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies, Manufacturer supplied product, Some authors serve on scientific advisory boards for corporations, Some authors have received research funding from infant formula manufacturers Study follow-up: 3-5 years Original, same study, or follow-up studies: Smithers, 2008[104]; Makrides, 2009[116]; Manley, 2011[118]; Collins, 2011[105]; Atwell, 2013[119]; Collins, 2015[120]	Study Population: Preterm infants Lactating enrolled 545 Infants enrolled 657 Infants completers 614 Lactating enrolled 545 Lactating age: 30 years (5.5 years) NR Infant age: 4 days after birth (29 weeks gestation) 2 to 6 days after birth Race of Mother: White European (90%)	Inclusion Criteria: infants born at < 33 wk of gestation Exclusion Criteria: Infants born with major congenital or chromosomal abnormalities or born to lactating women for whom tuna oil was contraindicated (women with bleeding disorders or taking anticoagulants)	Start time: Lactating 4 days after birth Infants 4 days after birth Duration: Lactating until infants reached their "expected" date of delivery. Infants until infants reached their "expected" date of delivery Arm 1: Placebo Description: Soy oil capsules or standard preterm formula if not breastfeeding Manufacturer: Clover Corporation Dose: six 500-mg soy oil capsules Blinding: all capsules were similar in size, shape, and color DHA: Formula: 0.35% AA: Formula: 0.6% Total N-3: Capsules: did not change FA content of breastmilk Arm 2: DHA Description: DHA-rich tuna oil capsules or high-DHA formula Manufacturer: Clover Corporation Dose: six 500 mg capsules per day DHA: Capsules: Achieved breast milk concentration of 1.0%. Formula: 1.0% AA: Capsules: Did not change AA in breast-milk. Formula 0.6% Other dose 1: DHA-rich tuna oil capsules to achieve a breast milk DHA concentration that was approximately 1% of total fatty acids without altering the naturally occurring concentration of arachidonic acid (AA) in breast milk	Outcome: MacArthur Communicative Development Inventory (MCDI) vocabulary production score (Secondary) Follow-up time: 26 months CA Arm 1: Sample size 67; mean 316.0; SD (192) Arm 2: Sample size 60; mean 308.0; SD (179)
Tofail et al., 2006[77]	Study Population:	Inclusion Criteria: seems	Start time: Pregnant 25 weeks gestation	Outcome: Bayley Scale of Infant

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study name: NR Study dates: Enrollment January to March 2000 Study design: Trial randomized parallel Location: Bangladesh Funding source / conflict: Government Study follow-up: 10 months	Healthy infants Healthy pregnant women Pregnant enrolled 400 Pregnant completers 151 Pregnant age: 22.7 years (4.35 years) NR Race of Mother: Asian (100%)	as if all pregnant women at 25 weeks gestation were enrolled, no inclusion criteria specified Exclusion Criteria: NR	Duration: Pregnant until birth Arm 1: placebo Description: soy oil capsule Dose: 4 one gram capsules per day Blinding: capsules were identical in appearance Other dose 1: LNA 0.27 g Other dose 2: linoleic acid 2.25 g Arm 2: DHA supplement Description: fish oil capsules Dose: 4 one gram capsules per day DHA: 1.2 g EPA: 1.8 g	Development (Mental developmental index) (Unspecified) Follow-up time: 10 months Arm 1: Sample size 124; mean 101.5; SD (7.8) Arm 2: Sample size 125; mean 102.5; SD (8)
Werkman et al., 1996[154] Study name: NR Study dates: 1987-1990 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product Study follow-up: 12 months	Study Population: Preterm infants Infants enrolled 67 Infants completers 64 Mother age: 23 y (6 y) Infant age: Born at 29 wks gestation (2 wks) Race of Mother: NR (100)	Inclusion Criteria: Preterm infants weighing between 748 and 1398 g at birth. They were eligible for this study when they had tolerated enteral intakes > 462 kJ/kg body weight/day for 5-7 days Exclusion Criteria: Need for mechanical ventilation at that time, intraventricular hemorrhage > grade 2, retinopathy of prematurity > stage 2, surgery for necrotizing enterocolitis, a weight less than the fifth percentile for gestational age, and a history of maternal substance abuse	Start time: Infants 25 days Duration: Infants 25 days - 9 months Arm 1: Placebo term and pre-term infant formulas Active ingredients: n-6: 19.1-33.2% of total FA Dose: Formula remained the infants' major source of nutrients and energy through at least 9 mo past expected term, but other foods were gradually added to the diet beginning at -4 mon past term Blinding: NR Total N-3: Preterm: 3% of total FA; term: 4.8% of total FA Arm 2: DHA-supplemented term and pre-term infant formulas Description: Marine oil replaced fat blend in commercial formulas Brand name: Similac Manufacturer: Ross Products Division Active ingredients: 18.7-32.6% of total FA Dose: Formula remained the infants' major source of nutrients and energy through at least 9 mo past expected term, but other foods were gradually added to the diet beginning at -4 mon past term ALA: Preterm: 3.1% of total FA; Term: 4.9% of total FA	Outcome: Fagan Test of Intelligence: average time/look (seconds) (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 1.18; SD (0.05) Arm 2: Sample size 33; mean 1.11; SD (0.05) Follow-up time: 6.5 months Arm 1: Sample size 34; mean 1.75; SD (0.06) Arm 2: Sample size 33; mean 1.62; SD (0.06) Follow-up time: 9 months Arm 1: Sample size 34; mean 1.3; SD (0.06) Arm 2: Sample size 33; mean 1.13; SD (0.05) Outcome: Fagan Test of Intelligence: looks to familiar (number) (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 18.8; SD (0.8) Arm 2: Sample size 33; mean 21.7; SD (0.8) Follow-up time: 6.5 months Arm 1: Sample size 34; mean 18.8; SD (1) Arm 2: Sample size 33; mean 22.1; SD (1)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			DHA: 0.2% of total FA EPA: 0.3% of total FA Other dose 1: Preterm: 3.6% of total FA; term: 5.4% of total FA	Follow-up time: 9 months Arm 1: Sample size 34; mean 18.2; SD (0.9) Arm 2: Sample size 33; mean 21.4; SD (0.9) Outcome: Fagan Test of Intelligence: looks to novel (number) (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 23.6; SD (0.8) Arm 2: Sample size 33; mean 26.0; SD (0.8) Follow-up time: 6.5 months Arm 1: Sample size 34; mean 22.2; SD (1) Arm 2: Sample size 33; mean 26.0; SD (1) Follow-up time: 9 months Arm 1: Sample size 34; mean 22.1; SD (0.9) Arm 2: Sample size 33; mean 25.2; SD (0.8) Outcome: Fagan Test of Intelligence: novel time (% of total) (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 64.6; SD (1.2) Arm 2: Sample size 33; mean 60.5; SD (1.3) Follow-up time: 6.5 months Arm 1: Sample size 34; mean 60.4; SD (1.4) Arm 2: Sample size 33; mean 59.8; SD (1.3) Follow-up time: 9 months Arm 1: Sample size 34; mean 62.2; SD (1.2) Arm 2: Sample size 33; mean 62.2; SD (1.2) Outcome: Fagan Test of Intelligence: time to familiar (seconds) (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 16.3; SD (0.8) Arm 2: Sample size 33; mean 19.3; SD (0.9)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Follow-up time: 6.5 months Arm 1: Sample size 34; mean 26.6; SD (1.1) Arm 2: Sample size 33; mean 26.6; SD (1.1) Follow-up time: 9 months Arm 1: Sample size 34; mean 18.2; SD (1) Arm 2: Sample size 33; mean 18.3; SD (0.9) Outcome: Fagan Test of Intelligence: time to novel (seconds) (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 32.6; SD (1.2) Arm 2: Sample size 33; mean 31.9; SD (1.2) Follow-up time: 6.5 months Arm 1: Sample size 34; mean 45.3; SD (1.5) Arm 2: Sample size 33; mean 45.9; SD (1.5) Follow-up time: 9 months Arm 1: Sample size 34; mean 32.9; SD (1.3) Arm 2: Sample size 33; mean 32.6; SD (1.3) Outcome: Fagan Test of Intelligence: time/familiar look (seconds) (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 0.85; SD (0.05) Arm 2: Sample size 33; mean 0.91; SD (0.05) Follow-up time: 6.5 months Arm 1: Sample size 34; mean 1.42; SD (0.06) Arm 2: Sample size 33; mean 1.31; SD (0.06) Follow-up time: 9 months Arm 1: Sample size 34; mean 1.04; SD (0.06) Arm 2: Sample size 33; mean 0.91; SD (0.05) Outcome: Fagan Test of Intelligence:

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				time/novel look (seconds) (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 1.43; SD (0.07) Arm 2: Sample size 33; mean 1.27; SD (0.07) Follow-up time: 6.5 months Arm 1: Sample size 34; mean 2.03; SD (0.09) Arm 2: Sample size 33; mean 1.88; SD (0.08) Follow-up time: 9 months Arm 1: Sample size 34; mean 1.51; SD (0.08) Arm 2: Sample size 33; mean 1.33; SD (0.07) Outcome: Fagan Test of Intelligence: total looks (number) (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 42.4; SD (1.3) Arm 2: Sample size 33; mean 47.7; SD (1.4) Follow-up time: 6.5 months Arm 1: Sample size 34; mean 41.0; SD (1.7) Arm 2: Sample size 33; mean 48.2; SD (1.7) Follow-up time: 9 months Arm 1: Sample size 34; mean 40.3; SD (1.5) Arm 2: Sample size 33; mean 47.0; SD (1.5) Outcome: Fagan Test of Intelligence: total time (seconds) (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 48.9; SD (1.4) Arm 2: Sample size 33; mean 51.2; SD (1.4) Follow-up time: 6.5 months Arm 1: Sample size 34; mean 72.0; SD (1.8) Arm 2: Sample size 33; mean 72.6; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(1.7) Follow-up time: 9 months Arm 1: Sample size 34; mean 51.1; SD (1.6) Arm 2: Sample size 33; mean 50.9; SD (1.5)
Willatts et al., 2013[170] Study name: NR Study dates: 1992 Study design: Trial randomized parallel Location: Italy, UK, Belgium Funding source / conflict: Industry Study follow-up: 6 years	Study Population: Healthy infants Infants enrolled 237 Infants completers 147 Infant age: birth Race of Mother: NR (100)	Inclusion Criteria: Healthy term singletons, 37-42 weeks gestation, 2500-4000g birth weight Exclusion Criteria: NR	Start time: Infants Birth to 1 week Duration: Infants 4 months Arm 1: Non-LC-PUFA Description: Control formula lacking LCPUFA Manufacturer: Milupa GmbH Viability: g/100 g fat Dose: NR Blinding: NR ALA: 0.7 DHA: 0 AA: <0.10 Arm 2: LC-PUFA formula Manufacturer: Milupa GmbH Dose: NR ALA: 0.62 g/100g fat DHA: 0.21 g/100g fat AA: 0.35 g/100g fat	Outcome: Wechsler Preschool and Primary Scale of Intelligence: Full-Scale IQ (Secondary) Follow-up time: 6 year Arm 1: Sample size 76; mean 100.9; SD (16.2) Arm 2: Sample size 71; mean 98.0; SD (14.8) Outcome: Wechsler Preschool and Primary Scale of Intelligence: Performance IQ (Secondary) Follow-up time: 6 year Arm 1: Sample size 76; mean 101.3; SD (15.5) Arm 2: Sample size 71; mean 99.6; SD (13.6) Outcome: Wechsler Preschool and Primary Scale of Intelligence: Verbal IQ (Secondary) Follow-up time: 6 year Arm 1: Sample size 76; mean 100.2; SD (16.4) Arm 2: Sample size 71; mean 97.3; SD (17.5)
de Jong et al., 2012[65] Study name: Groningen LCPUFA study Study dates: Enrollment from February 1997 through October 1999, follow-up 9 years later Study design: Trial randomized parallel	Study Population: Healthy infants Infants enrolled 314 Infants completers 214 Mother age: 31 years (5 years) NR Infant age: birth (NA) NA Race of Mother: White	Inclusion Criteria: healthy infants Exclusion Criteria: infants who had a congenital disorder that interfered with adequate functioning in daily life, infants from multiple births, infants whose mothers did not have mastery of the Dutch language or suffered from significant	Start time: Infants birth Duration: Infants 2 months Arm 1: Control formula Description: Standard formula with no supplemental LCPUFA Brand name: Nutrilon premium Manufacturer: Nutricia, Zoetermeer, Netherlands Active ingredients: linoleic acid (11mol%); ALA 1.27 mol% Blinding: NR Maternal conditions	No usable data. Outcome: (Secondary)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Location: Netherlands Funding source / conflict: Industry, Government, Some authors have received research funding from infant formula manufacturers Study follow-up: 9 years Original, same study, or follow-up studies: Bouwstra, 2003[62]; Bouwstra, 2005[63]; de Jong, 2010[64]; van Goor, 2010[36]; van Goor, 2011[66]	European (100%)	illness or disability, adopted and foster infants, and formula-fed infants who had received human milk for >5 d.	Current smoker 23% during pregnancy Other maternal conditions 1arm_1_maternal_conditions_other1 Other maternal conditions 10 maternal hypertension 17% Arm 2: Omega 3 supplemented formula Description: LCPUFA formula Manufacturer: Nutricia, Zoetermeer, Netherlands Active ingredients: linoleic acid (11mol%); ALA 1.30 mol% Maternal conditions DHA: 0.30% by weight AA: 0.45% by weight Current smoker 32% during pregnancy Other maternal conditions 1arm_2_maternal_conditions_other1 Other maternal conditions 10 maternal hypertension 12% Arm 3: breastfeeding comparison group Maternal conditions Current smoker 10% during pregnancy Other maternal conditions 1arm_3_maternal_conditions_other1 Other maternal conditions 10 maternal hypertension 9%	

Table 18. Observational studies for cognitive development

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Bakker, et al., 2003[163] Outcome domain: Cognitive Study name: Maastricht Essential Fatty Acid Birth (MEFAB) Cohort Study dates: Recruitment December 1990 to January 1994 Study design: Observational prospective Location: Netherlands Funding source / conflict: Government Follow-up: 7 years Original, same study, or follow-up studies: Bakker, 2009[134] and two articles in original report: Ghys, 2002 and Al, 1995	Study Population: Healthy infants Infants enrolled 750 Infants withdrawals 444 Infants completers 306 Pregnant age: 29.8 (4.1) Infant age: birth Race of Mother: White European (100)	Inclusion Criteria: 750 Caucasian children, 7 y old, born between December 1990 and January 1994 in the course of an earlier study on maternal and neonatal LCPUFA status and pregnancy outcome Exclusion Criteria: Not reported	Adjustments: Social class, maternal intelligence, parenting skills, maternal smoking and drinking habits during pregnancy, breastfeeding duration, and the child's sex, birth order and birth weight
Bernard, et al., 2013[89] Outcome domain: Cognitive Study name: EDEN Study dates: Recruitment 2003 to 2005 Study design: Observational prospective Location: NR Funding source / conflict: Industry, Government Follow-up: 2 and 3 years Original, same study, or follow-up studies: Drouillet, 2009[80]	Study Population: Healthy pregnant women Pregnant enrolled 2,002 Pregnant completers 1,882 Infants enrolled 1.882 Infants completers 1,510 Pregnant age: 29.2 years (at conception) (4.8 years) NR Infant age: < 24 weeks gestation (NR) NR Race of Mother: NR (100)	Inclusion Criteria: < 24 weeks amenorrhea Exclusion Criteria: multiple pregnancies, known diabetes before pregnancy, illiteracy, and intention to move outside the region in the next 3 years	Adjustments: Center, child gender & age, gestational age, maternal age, obesity, energy intake, tobacco & alcohol consumption, parental education & income, first born, main daytime caregiver, and frequency of maternal stimulations
Guxens, et al., 2011[144] Outcome domain: Cognitive	Study Population: Healthy infants Breast-feeding women Pregnant enrolled 657 Pregnant completers 622	Inclusion Criteria: age older than 16 years, intent to deliver at the reference hospital, singleton pregnancy	Adjustments: Child's age, maternal and paternal: education, social class, attachment to child, mental

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Study name: INMA Study dates: Recruitment: July 2004 to July 2006 Followup: 14 months Study design: Observational prospective Location: Spain Funding source / conflict: Government, Multiple foundations and Societies Follow-up: 14 months Original, same study, or follow-up studies: Julvez, 2014[143]	Lactating enrolled 622 Lactating completers 582 Infants enrolled 622 Infants completers 582 (319 with LCPUFA data) Lactating enrolled 622 Lactating completers 582 Lactating age: 31.6 years (4.2 years) Infant age: 2 to 5 days postpartum Race of Mother: NR (NR)	Exclusion Criteria: no problems of communication, no assisted conception	health; maternal age, maternal alcohol use during pregnancy, use of gas stove, child age of food introduction
Keim, et al., 2012[162] Outcome domain: Cognitive Study name: Pregnancy, Infection and Nutrition Study Study dates: Recruitment between January 2001 and June 2005 Followup: 1 year Study design: Observational prospective Location: US Funding source / conflict: Government Follow-up: 12 months	Study Population: Healthy infants Breast-feeding women Pregnant enrolled 1,169 Pregnant completers 689 Infants enrolled 408 Infants completers 358 Pregnant age: NR Infant age: 20 weeks gestation NA Race of Mother: White European (79.1%) Other race/ethnicity (21.0)	Inclusion Criteria: health women at less than 20 weeks of pregnancy Exclusion Criteria: pregnant with multiple fetuses, unable to communicate in English, under age 16 years, no access to a telephone, intention to go elsewhere for future care or delivery	Adjustments: Laboratory, infant sex, race, parity, maternal smoking, education, breastfeeding status and preterm status

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Steer, et al., 2013[164] Outcome domain: Cognitive Study name: Avon Longitudinal Study of Parents and Children (ALSPAC) Study dates: 1991-2000 Study design: Observational prospective Location: UK Funding source / conflict: Government Follow-up: 8 years	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 14,541 Infants completers 2,839 Mother age: 29.33 (4.48) Infant age: birth Race of Mother: White European (98.8) Black (0.6) Asian (0.6)	Inclusion Criteria: pregnant women with expected delivery date between 4/91 and 12/92 in Bristol UK Exclusion Criteria: Not reported	Adjustments: Maternal age, education, ethnicity, alcohol consumption and smoking; partner status, housing tenure, crowding index, parity, preterm gestation (37 wk), low birth weight (,2500 g), multiple births, sex, breastfeeding, and measures of adversity (in pregnancy and during the first 2 y after birth) and child stimulation (both from the home environment and maternal interaction with the child)
Valent, et al., 2013[132] Outcome domain: Cognitive Study dates: 2007-2011 Study design: Observational prospective Location: Italy Funding source / conflict: Government	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 900 Pregnant completers 767 Infants enrolled 767 Infants completers 632 Pregnant age: 33.3 (4.3) Infant age: Birth Race of Mother: NR (100)	Inclusion Criteria: Permanent residents of the study areas for at least 2 years, at least 18 years of age, and had no absence from the study area for more than 6 weeks during pregnancy, no history of drug abuse, no serious health problems or complications of pregnancy, and no twin gestation Exclusion Criteria: Preterm births (<37 weeks of gestational age), babies with congenital malformations or severe perinatal problems, and those with severe health problems that presented postnatally and potentially compromised their neurological development	Adjustments: Fish intake, fatty acids in maternal serum and proportion of PUFAs, sex, birth weight, maternal IQ, weight gain during pregnancy, marital status at delivery, SES index, number of children living in home, alcohol intake during pregnancy, breastfeeding history, child intake of fish until age 18 months, and daycare attendance at age 18 months

Autism Spectrum Disorders (ASD)

Description of Included Studies

Randomized Controlled Trials

The original report did not include ASD as an outcome of interest. Two RCTs reported autism outcomes at long-term follow-up (Table 19). One trial that randomized pregnant women to either high DHA supplement or placebo[57] reported that diagnoses of ASD among offspring at age four did not differ between groups (two cases in the DHA group and four cases in the control group). Another RCT that randomized pre-term infants to either high-DHA or standard DHA enteral feeds from two to four days after birth until term corrected age; parent reports of ASD diagnosis at seven years did not differ significantly between the groups.[120]

Observational Studies

One observational study investigated whether n-3 FA intake before and during pregnancy was associated with risk of ASD in offspring (Table 20).[171] Lyall et al (2013) conducted an analysis of data from the Nurses' Health Study II. They compared dietary intake between 317 mothers of children with ASD and 17,728 comparison mothers. Children were born from 1991 through 2007. Prepregnancy and pregnancy dietary information was reported via food frequency questionnaire (FFQ) and ASD diagnosis was self-reported by mothers. The authors found that women with the highest quartile of total PUFA intake were at lower risk of having a child with ASD than women in the lowest quartile (RR 0.67; 95% CI 0.49, 0.92). This model adjusted for maternal age, income level, race, BMI, total energy intake, pre-pregnancy smoking status, and child's year of birth. Using the same model and adjustments, the researchers also found that women whose intake of linoleic acid was in the highest quartile had a lower risk of having a child with ASD than those in the lowest quartile (RR 0.66 95% CI 0.48, 0.92). The authors advised that the results should be interpreted with caution, given the small number of cases.

Table 19. RCTs for autism spectrum disorders

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Collins et al., 2015[120] Study name: DINO Study dates: 2001-2013 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Industry, Government Study follow-up: 7 years Original, same study, or follow-up studies: Smithers, 2008[104]; Makrides, 2009[116]; Smithers, 2010[117]; Manley, 2011[118]; Collins, 2011[105]; Atwell, 2013[119]; Collins, 2015[120]	Study Population: Preterm infants Infants enrolled 657 Infants completers 604 Infant age: median 30 weeks gestational age 28-31 weeks Race of Mother: NR (100)	Inclusion Criteria: infants born at <33 weeks' gestation from five Australian tertiary hospitals between 2001 and 2005 Exclusion Criteria: a major congenital or chromosomal abnormality, multiple birth in which not all live-born infants were eligible, enrollment in other trials of fatty acid supplementation, or if fish oil was contraindicated in the lactating mother	Start time: Infants within 5 days of 1st enteral feeding Duration: Infants to expected due date Arm 1: standard DHA Description: DHA supplementation of infant formula or breastfeeding mothers to achieve DHA concentrations of term formula fed infants DHA: ___20 mg/kg/ day of DHA Arm 2: High DHA Description: DHA supplementation of infant formula or breastfeeding mothers to achieve DHA concentration of breastmilk DHA: ___50 mg/kg/ day of DHA	Outcome: number with autism spectrum disorder Follow-up time: 7 years Arm 1: 9/298 (3.0%) Arm 2: 10/285 (3.5%)
Makrides et al., 2014[57] Study name: DOMInO Study dates: October 31, 2005 to September 25, 2012 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Manufacturer supplied product, Some authors	Study Population: Healthy pregnant women Infants enrolled 726 Infants completers 646 Race of Mother: NR (100)	Inclusion Criteria: Women with singleton pregnancies at less than 21 weeks' gestation Exclusion Criteria: Already taking a prenatal supplement with DHA, fetus had a known major abnormality, had a bleeding disorder in which tuna oil was contraindicated, were taking anticoagulant therapy, had a documented history of drug or alcohol abuse,	Start time: Pregnant <21 weeks gestation Duration: Pregnant <21 weeks gestation until birth Arm 1: Placebo Description: rapeseed, sunflower, and palm oil capsules Manufacturer: Enfamol Dose: 3 500mg capsules/day Blinding: similar in size, shape, and color Arm 2: DHA supplement Description: DHA-rich fish oil capsules Manufacturer: Enfamol Dose: 3 500mg capsules/day DHA: 800 mg/d EPA: 100 mg/day	Outcome: diagnosis of autism Follow-up time: 4 years Arm 1: 4/333 (1.2%) Arm 2: 2/313 (0.64%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
have received research funding from infant formula manufacturers Original, same study, or follow-up studies: Makrides, 2010 [35] Smithers, 2011[53]; Palmer, 2012[54]; Zhou, 2012[55]; Palmer, 2013[56]		were participating in another fatty acid trial, were unable to give written informed consent, or if English was not the main language spoken at home		

Table 20. Observational studies for autism spectrum disorders

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Lyall, et al., 2013[171] Outcome domain: Autism Study name: Nurses' Health Study Study dates: Births 1991 to 2007 Study design: NR Location: US Funding source / conflict: Government	Study Population: Healthy pregnant women Pregnant enrolled 18,045 Pregnant completers 5,884 Pregnant age: Q1 34.7y Q4 33.7 y NR Infant age: birth Race of Mother: White European (Q1: 96%; Q4: 98%) Other race/ethnicity (Q1 4%; Q4 2%)	Inclusion Criteria: female nurses who were 25–42 years of age in 1989, with index births between 1991 (the year of first collection of dietary information) and 2007; women reported a child with ASD either in 2005 or 2009 not both, if 1) the reason for nonreporting on the other questionnaire was on participation in that questionnaire year; 2) the nurse confirmed the diagnosis in a previous substudy; or 3) for women reporting on the 2009 questionnaire only, the child was born after 2000 (in which case, the child might have been too young for report of diagnosis by the 2005 questionnaire mailing) Exclusion Criteria: Women reporting competing diagnoses (fragile X syndrome, Ret syndrome, tuberous sclerosis, Down syndrome, trisomy 18; in a previous sub-study were not included. Women without food frequency questionnaire data or without autism diagnosis info on child	Adjustments: Adjusted for total energy intake, maternal age, child's year of birth, income level, race, body mass index, and prepregnancy smoking status. Removal of adjustment for smoking did not affect results. Additional adjustment for child birth order, maternal physical activity level, spouse's education level, or multivitamin use, or for trans-fat in PUFA model, did not materially alter estimates

Attention Deficit Hyperactivity Disorder (ADHD)

Description of Included Studies

Randomized Controlled Trials

The original report did not include ADHD as an outcome of interest. We identified three RCTs that reported on ADHD or attention outcomes (see Table 21). The first, Isaacs et al., 2011[99], randomized pre-term infants in the UK to either control formula or LCPUFA supplemented formula containing DHA, EPA, and AA. At ten year follow-up there were no significant differences between groups on the any of the scales of the Test of Everyday Attention for Children. Another identified study was a seven year follow-up of the DINO trial conducted in Australia.[120] Pre-term infants were randomized to either standard (20 mg/kg/ day of DHA) or high-dose DHA (50 mg/kg/ day) formula. There were no significant differences between groups on the any of the scales of the Test of Everyday Attention for Children or the Conners ADHD score. Finally, there was no difference in the rate of "hyperactivity disorder" at four years among offspring of mothers receiving DHA supplementation or placebo during pregnancy in the DOMINO study, an Australian RCT.[57]

Observational Studies

No observational studies on ADHD or attention were identified.

Table 21. RCTs for attention deficit hyperactivity disorder

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Collins et al., 2015[120] Study name: DINO Study dates: 2001-2013 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Industry, Government Study follow-up: 7 years Original, same study, or follow-up studies: Smithers, 2008[104]; Makrides, 2009[116]; Smithers, 2010[117]; Manley, 2011[118]; Collins, 2011[105]; Atwell, 2013[119]; Collins, 2015[120]	Study Population: Preterm infants Infants enrolled 657 Infants completers 604 Infant age: median 30 weeks gestational age 28-31 weeks Race of Mother: NR (100)	Inclusion Criteria: infants born at <33 weeks' gestation from five Australian tertiary hospitals between 2001 and 2005 Exclusion Criteria: a major congenital or chromosomal abnormality, multiple birth in which not all live-born infants were eligible, enrollment in other trials of fatty acid supplementation, or if fish oil was contraindicated in the lactating mother	Start time: Infants within 5 days of 1st enteral feeding Duration: Infants to expected due date Arm 1: standard DHA Description: DHA supplementation of infant formula or breastfeeding mothers to achieve DHA concentrations of term formula fed infants DHA: ___20 mg/kg/ day of DHA Arm 2: High DHA Description: DHA supplementation of infant formula or breastfeeding mothers to achieve DHA concentration of breastmilk DHA: ___50 mg/kg/ day of DHA	Outcome: ADHD Conners 3 AI-parent: ADHD t score (total score) (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 64.4; SD (18.7) Arm 2: Sample size 291; mean 65.6; SD (18.5) Outcome: number with ADHD (parent reported) (Secondary) Follow-up time: 7 years Arm 1: 7/298 (2.3%) Arm 2: 9/285 (3.16%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Isaacs et al., 2011[99] Study name: Unnamed Trial A Study dates: Recruitment of infants from 1995 through 1997 with 10-year followup Study design: Trial randomized parallel Location: UK Funding source / conflict: Industry, Government, Some authors have received research funding from infant formula manufacturers Study follow-up: 10 years Original, same study, or follow-up studies: Fewtrell, 2002[158] is the original study; Llorente, 2003[98] reports post-partum depression	Study Population: Preterm infants Infants enrolled 238 Infants completers 107 Infant age: birth (at < 35 weeks gestation) NA Race of Mother: NR (NR)	Inclusion Criteria: birth weight of < 2000 g, and gestational age of < 35 weeks Exclusion Criteria: congenital malformations	Start time: Infants at hospital discharge Duration: Infants 9 months Arm 1: control Description: control formula Active ingredients: protein, minerals, vitamins A, E, K, D DHA: 0 EPA: 0 AA: 0 Other dose 1: C18:2, n-6, linoleic acid 11.5 g / 100g fat Other dose 2: C18:3, n-3, alpha_x0004_-linolenic acid 1.6 g / 100g fat Arm 2: Omega 3 supplemented formula Description: LCPUFA-Supplemented Formula Active ingredients: protein, minerals, vitamins A, E, K, D Infant conditions DHA: 0.5 g / 100g fat EPA: 0.1 g/ 100g fat AA: 0.04 g / 100g fat Other dose 1: C18:2, n-6, linoleic acid 12.3 g / 100g fat Other dose 2: C18:3, n-6, gamma-linoleic acid 0.9 g / 100g fat Other dose 3: C18:3, n-3, _x0004_alpha-linolenic acid 1.5 g / 100g fat Pre-term birth 100% Low birth weight 100%	Outcome: Test of Everyday Attention for Children: Attention scaled score (Secondary) Follow-up time: 10 years Arm 1: Sample size 57; mean 8.3; SD (2.6) Arm 2: Sample size 50; mean 8.2; SD (2.5) Outcome: Test of Everyday Attention for Children: Creature counting scale score (Secondary) Follow-up time: 10 years Arm 1: Sample size 57; mean 9.6; SD (2.1) Arm 2: Sample size 50; mean 10.0; SD (2.7) Outcome: Test of Everyday Attention for Children: Dual-task decrement scaled score (Secondary) Follow-up time: 10 years Arm 1: Sample size 57; mean 7.3; SD (2.8) Arm 2: Sample size 50; mean 7.6; SD (2.5) Outcome: Test of Everyday Attention for Children: Opposite Worlds different scaled score (Secondary) Follow-up time: 10 years Arm 1: Sample size 57; mean 8.4; SD (2.8) Arm 2: Sample size 50; mean 8.9; SD (3.5) Outcome: Test of Everyday Attention for Children: Score! Scale scored (Secondary) Follow-up time: 10 years Arm 1: Sample size 57; mean 7.8; SD (3.4) Arm 2: Sample size 50; mean 7.7; SD (3.4)
Makrides et al., 2014[57] Study name: DOMInO Study dates: October 31, 2005 to September 25, 2012 Study design: Trial randomized parallel	Study Population: Healthy pregnant women Infants enrolled 726 Infants completers 646 Race of Mother: NR (100)	Inclusion Criteria: Women with singleton pregnancies at less than 21 weeks' gestation Exclusion Criteria: Already taking a prenatal supplement with DHA, fetus had a known major abnormality, had a bleeding disorder in	Start time: Pregnant <21 weeks gestation Duration: Pregnant <21 weeks gestation until birth Arm 1: Placebo Description: rapeseed, sunflower, and palm oil capsules Manufacturer: Enfamol Dose: 3 500mg capsules/day Blinding: similar in size, shape, and color	Outcome: hyperactivity disorder Follow-up time: 4 years Arm 1: 0/333 (0.0%) Arm 2: 0/313 (0.0%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Location: Australia Funding source / conflict: Government, Manufacturer supplied product, Some authors have received research funding from infant formula manufacturers Original, same study, or follow-up studies: Makrides, 2010 [35] Smithers, 2011[53]; Palmer, 2012[54]; Zhou, 2012[55]; Palmer, 2013[56]		which tuna oil was contraindicated, were taking anticoagulant therapy, had a documented history of drug or alcohol abuse, were participating in another fatty acid trial, were unable to give written informed consent, or if English was not the main language spoken at home	Arm 2: DHA supplement Description: DHA-rich fish oil capsules Manufacturer: Enfamol Dose: 3 500mg capsules/day DHA: 800 mg/d EPA: 100 mg/day	

Atopic Dermatitis and Eczema

Key Points

- Of four interventions and two follow-up studies that examined the effects of prenatal n-3 FA on the risk for developing eczema (DHA + EPA, varying doses), one of the studies found a significant association between n-3 FA supplementation and decreasing risk of eczema, whereas the other studies found no effects. A single trial that investigated ALA supplementation found no significant association with eczema risk.
- Three postnatal n-3 interventions and three follow-up studies found no effect of supplementation of infant formula with n-3 FA (DHA or DHA+EPA, varying doses) and eczema prevalence up to8 years of age.
- One biomarker study found associations between higher infant plasma DHA, erythrocyte EPA, and EPA/AA ratio and lower risk of eczema as well as increased symptoms of eczema with higher levels of AA and total n-6 PUFA.
- Six of seven prospective observational studies found no associations between n-3 FA exposure (measured through maternal dietary intake or breast milk composition) and eczema. One of four prospective observational studies of n-3 FA biomarkers (in cord blood or maternal blood sample) found decreased risk of eczema and increasing AA levels, with null findings for the remaining three studies.

This outcome is an additional outcome of interest that was not included in the original review. A total of 13 eligible studies (8 original RCTs and 5 follow-up studies) and 11 observational studies were identified for this report. The study population included healthy pregnant women and infants with history of allergy as well as preterm infants.

Description of Included Studies

Randomized Controlled Trials

Prenatal Maternal Interventions/Exposures

We identified seven studies (five RCTs and two follow-up studies) that evaluated n-3 FA interventions given to the mothers during the prenatal period (see Table 22). [50, 54, 56, 79, 88, 172, 173] Among these studies, five studies assessed interventions with duration from pregnancy until birth.[50, 54, 56, 88, 174] Three studies with maternal supplementation started during pregnancy and continued into breastfeeding, [79, 172, 173] with one of those trials also adding infant supplementation following breastfeeding.[79] All of these trials except for one [79] recruited pregnant women whose infants were at risk of atopy (i.e., one or more first-degree relatives of the infant affected by atopy, asthma, or allergy).

DHA Plus EPA Versus Placebo

Four RCTs and two follow-up studies compared EPA plus DHA versus placebo.[50, 54, 56, 88, 172, 173]

Dunstan (2003) randomized 98 pregnant, atopic Australian women to fish oil (3.7g n-3 PUFA, 56.0% DHA, 27.7% EPA) or placebo (olive oil [4g]) daily from 20 weeks gestation until delivery.[50] A total of 83 mothers and their children completed the 12-month follow-up. The authors report that infants in the fish oil group had higher odds of eczema, although this increase in risk is not statistically significant (OR1.88, 95% CI 0.77, 4.65; p=0.167). In addition, of the infants with eczema, those in the fish oil group were less likely to have severe disease, defined as a modified SCORAD index>25, than those in the placebo group (OR=0.09; 95% CI 0.01, 0.94; p=0.045).[50]

In the Salmon in Pregnancy Study (SiPS), 123 pregnant women in the UK were randomized to the salmon group (300g salmon / week) or control group (no changes in diet) from 20 weeks gestation until delivery.[88] Clinical outcomes were available for 86 infants at 6 months. No differences in the incidence or severity (using the SCORAD index) of atopic dermatitis were observed between the salmon and control groups.[88]

In a subset of the Docosahexaenoic Acid (DHA) to Optimise Mother Infant Outcome (DOMInO) trial, 706 pregnant Australian women whose child was at high risk for genetic allergy were randomized to an n-3 LCPUFA group (800 g/d DHA + 100 g/d EPA) or placebo group (vegetable oil) from 21 weeks gestation until delivery.[54, 56] In a 1-year follow-up study, the n-3 LCPUFA group showed an unadjusted decrease in the risk for eczema with sensitization, however, once adjusted for study center, parity, maternal history, and sex, this difference was only marginal (RR 0.64; 95% CI 0.40, 1.03; p=0.06).[54] In a longer follow-up, medical assessments were completed for 638 children (90.4%) at 3 years of age: No differences were seen between treatment groups for eczema with sensitization during the first 3 years of life (RR=0.75; 95% CI 0.53, 1.05) or at age 3 (RR=0.86, 95% CI 0.58, 1.27) in analyses adjusted and unadjusted for study center, parity, maternal history, and sex.[56]

One RCT randomized 145 pregnant women in Sweden to daily n-3 FA (1.6g EPA + 1.1g DHA) or placebo (soy oil) supplementation from the 25th gestational week through the exclusive breastfeeding period (average 3-4 months). Period prevalence for the first 12 months of life was lower in infants of n-3 FA supplemented mothers in adjusted analyses for IgE-associated eczema, defined as clinical diagnosis of eczema and positive SPT/IgE to egg, milk, and/or wheat (OR 0.22, 95% CI 0.06-0.81).[173] In another follow-up study with 143 infants, no differences were observed in cumulative eczema through 24 months or current eczema at 24 months between the treatment groups. A significant difference in IgE-associated eczema was seen, favoring the EPA+DHA intervention (9% vs 24%, p=0.04); however this difference became marginal in an adjusted multiple regression model (OR 0.33; 95% CI 0.1, 1.1, p=0.06).[172]

ALA Versus Placebo

We identified a single trial that examined ALA supplementation during pregnancy, breastfeeding, and infancy. [79] Linnamaa (2010) randomized 313 pregnant Finnish women (<16 weeks gestation) to blackcurrant seed oil (14% ALA by weight of 3g/d) or olive oil (placebo). The first dose was administered between the 8th and 16th week of pregnancy and continued during breastfeeding. Once the exclusive breastfeeding period was over, infants received 1 mL/day of supplemental oil until age 2 years. Of the 313 mother-infant pairs, 241 were analyzed at 3 months, 210 at 12 months, and 177 at 24 months. No differences were seen in prevalence of atopic dermatitis at 3 months or 24 months. However, at 12 months, fewer cases of atopic dermatitis were noted (33.0% vs 47.3%, p=0.035) and severity of symptoms was lower (p=0.035) in the ALA group compared to the placebo.

Postnatal Maternal or Infant Interventions/Exposures

Three RCTs and three follow-up studies evaluated maternal n-3 FA interventions during the postnatal period.[118, 142, 166-169] One of the RCTs evaluated preterm infants [118] while the remaining two assessed term infants who were at genetic risk for allergy. All RCTs evaluated DHA or DHA+EPA.

DHA, DHA Plus EPA Versus Placebo

One RCT began the n-3 FA intervention during the postnatal period.[118] The DINO trial randomized 657 preterm Australian infants (<33 weeks gestation) to receive a high-DHA diet (~1% DHA and 0.6% AA) or standard DHA diet (~0.35% DHA and 0.6% AA) through breast milk or formula until their expected delivery date. Eczema data were available for 232 infants at 12 months and 292 infants at 18 months. No differences were seen in the risk for eczema (adjusted or unadjusted for gestational age at delivery and gender).[118]

In the Infant Fish Oil Supplementation Study (IFOS), 420 infants at high risk for atopy were randomized to daily fish oil capsules (280 mg DHA + 110 mg EPA) or placebo capsules (olive oil) from birth to 6 months. At 12 months, no significant overall difference in eczema was seen between the fish oil and placebo groups; however when infants were stratified by adherence, among those in the highest adherence quartile, the fish oil group had a lower prevalence of eczema (p=0.041).[142]

In the Childhood Asthma Prevention Study (CAPS), 616 pregnant women (<36 weeks gestation) whose child was at high risk for developing asthma were randomized into four groups, including two groups with a dietary component (500 mg tuna fish oil supplement + canola-based oils and spreads or placebo supplement + polyunsaturated oils and margarines) from 6 months. In an 18-month follow-up with 543 infants (88% of the total sample size), no significant difference in prevalence of eczema or dermatitis was seen by parental report or nurse examination between the diet intervention and control groups.[166] In a 3-year follow-up with 526 infants, no difference was observed between the diet and control groups for prevalence of eczema.[167] In a 5-year follow-up with 516 children (84%), the diet intervention and control groups did not differ significantly in risk for current eczema (RR=0.85; 95% CI 0.61, 1.17).[168] In an 8-year follow-up with 450 children (73%), no significant differences were seen between the diet intervention and control groups for eczema (ARR= 21.1, 95% CI 27.8, 5.6). [169]

Biomarker Studies

Biomarker associations were also captured in the previously mentioned IFOS trial.[142] The study found that infants with higher erythrocyte EPA composition (P = .033) and higher EPA/AA ratio (P = .022) as well as higher plasma DHA levels (P = .047) at 6 months of age were significantly less likely to develop eczema by 12 months. Also, higher levels of AA (P = .004) and total n-6 PUFA (P = .005) levels at 6 months were associated with increased symptoms of eczema at 6 months of age.[142]

Observational Studies

Eleven observational studies were identified that evaluated the association between some measure of n-3 FA exposure and risk of atopic dermatitis/eczema (see Table 23).[175-185]

All studies enrolled populations of healthy infants except one[180] that enrolled infants with human leucocyte antigen (HLA)-conferred susceptibility to type I diabetes. All the studies were prospective cohort studies. The range of exposures included maternal dietary intake of n-3 FA, [180-183] breast milk n-3 FA, [175, 178, 184] and maternal biomarkers.[176, 177, 179,185] Publications dated from 2004 to 2015.

Maternal n-3 FA Intake and Risk for Atopic Dermatitis/Eczema

Four studies evaluated the association between maternal dietary n-3 FA intake and risk of atopic dermatitis.[180-183]

In a 2009 study of 763 healthy mother-infant pairs from the Osaka Maternal and Child Health Study in Japan, no significant association was detected between maternal intake of n-3 fatty acids during pregnancy and risk of eczema in the offspring.[182] Maternal dietary intake was assessed with a validated diet history questionnaire during pregnancy, whereas eczema was assessed by maternal report based on the International Study of Asthma and Allergies in Childhood for offspring at 16-24 months postpartum.

A 2010 study of 771 healthy Japanese infants aged 3-4 months found no relationship between maternal intake of n-3 FAs during pregnancy (calculated based on a validated diet history questionnaire) and risk of atopic eczema.[181]

A 2012 study assessed the association between maternal n-3 FA intake in a cohort of 2,441 newborn infants born between 1997 and 2004 in Finland and atopic dermatitis after 5 years of follow-up. Enrolled infants had a history of human leucocyte antigen (HLA)-conferred susceptibility to type I diabetes. No significant difference was observed in total maternal n-3 FA intake or n-3/n-6 FA ratio (assessed using a validated FFQ) between offspring who developed atopic eczema and those who did not.[180]

Also, in a 2013 study of 1,354 healthy mother-infant pairs from the Kyushu Okinawa Maternal and Child Health Study (KOMCHS) in Japan, no significant association was detected between maternal intake of n-3 fatty acids during pregnancy and risk of eczema in the offspring.[183] Maternal dietary intake was assessed with a dietary history questionnaire during pregnancy, whereas infantile eczema was assessed by parental report based on the International Study of Asthma and Allergies in Childhood for offspring at 23-29 months postpartum.

Breastmilk n-3 FAs and Risk for Atopic Dermatitis/Eczema

Three studies assessed the association of breast milk fatty acids with risk for atopic eczema.[175, 178, 184]

A 2006 study of 265 mother-infant pairs in the Netherlands found no relationship between breast milk n-3 fatty acid concentration (measured at 3 months postpartum) and risk of atopic eczema in children at 1 year and 4 years of age. Similar results were found in children of mothers both with and without allergy.[175]

However, in a 2011 study of 310 mother-infant pairs in the Netherlands, higher concentrations of breast milk n-3 fatty acid (EPA+DHA+DPA) were significantly associated with lower risk of developing atopic dermatitis (using the UK Working Party criteria [p for trend=0.024]) and parent-reported eczema (p for trend=0.040) at 2 years of age, adjusted for recruitment group, maternal age, maternal education, infant's gender, number of older siblings and their atopic history, parental atopic history, maternal smoking during pregnancy and/or smoking in presence of the infant, place of birth, season of breast milk collection and other potential confounders.[178]

A 2012 study of 580 infants in Spain found no significant association between colostrum n-3 LC-PUFA and risk of atopic eczema during the first 14 months of life.[184] Only random samples of colostrum were collected for analysis (n=352), with n-3 LC-PUFA values imputed for the rest of the sample; however no differences were observed in analyses with the colostrum subsample only.

Blood n-3 FA Biomarkers and Risk for Atopy/Eczema

Four studies examined the association between n-3 FA biomarkers and risk of atopic dermatitis.[176, 177, 179, 185]

A 2004 study of 1238 mother-infant pairs conducted in the UK found a positive association between the ratio of AA: EPA in cord blood and risk of eczema at 18 to 30 months (adjusted odds ratio [OR] per doubling, 1.14; 95% CI, 1.00-1.31; P = .044). However, the association was no longer significant after adjusting for multiple comparisons. No significant associations were observed for late pregnancy maternal plasma phospholipid n-3 fatty acid exposures (n=2945).[176]

In a 2011 study of 1,275 children from the KOALA Birth Cohort Study who were followed for 6-7 years, lower risk of eczema was associated with a higher ratio of maternal plasma phospholipid n-6 to n-3 LCPUFAs, measured at 34–36 weeks of pregnancy (p for trend = 0.012). In addition, a decreased risk of eczema in the first 7 months of life was observed with increasing AA levels (p for trend = 0.013).[179]

A 2014 study of 436 infants from the Munich LISA plus birth cohort study in Germany found no significant association between n-3 LC-PUFA or n-6/n-3 ratio in cord blood serum and eczema at 2, 6, and 10 years follow-up.[177]

In a 2010 study of 1162 children from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort study who were followed for 18 months, no significant associations were found between maternal plasma phospholipid DHA, EPA, ALA, total n-3 LC-PUFA or n-6/n-3 ratio measured at 26-28 weeks and risk for developing eczema.[185]

Observational study subgroup analyses

None of the studies reported subgroup analyses.

Table 22. RCTs for atopic dermatitis

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
D'Vaz et al., 2012[142] Study name: IFOS Study dates: 2005-2009 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies, None, Manufacturer supplied product Original, same study, or follow-up studies: Meldrum, 2012[140]	Study Population: Pregnant women with allergies Infants enrolled 420 Infants completers 323 Pregnant age: Placebo: 33.2 Fish Oil: 32.5 (Placebo: 4.2 Fish Oil: 4.8) Infant age: Term (39.3 weeks gestation) Race of Mother: NR (100)	Inclusion Criteria: Maternal: Pregnant History of doctor diagnosed asthma or allergic rhinitis Skin prick positive to at least one allergen Exclusion Criteria: Maternal: Smoking Auto-immune disease Pre-existing medical conditions other than asthma High-risk pregnancy Seafood allergy Fish eaten more than three times per week Fish oil supplementation already taken (in excess of 1000 mg per day) Exclusion from data analysis criteria due to protocol deviations: Pre-term delivery (gestation <36 weeks) Infant with congenital abnormalities or significant disease not related to intervention	Start time: Infants Birth Duration: Infants 6 months Arm 1: Placebo Description: Olive oil Manufacturer: Ocean Nutrition, Ltd Dose: 650 mg olive oil Blinding: Randomization was completed by external staff via computer software using an unpredictable allocation sequence, stratified according to maternal and paternal atopic history and parity. Mothers and study personnel were unaware of the group allocation. Maternal conditions Maternal allergies 100 Arm 2: Fish oil group Manufacturer: Ocean Nutrition Ltd. Purity Data: fatty acid composition remained unchanged over the study period Dose: 1 capsule contents, to be administered orally, prior to feeding in the morning Maternal conditions DHA: 280 mg EPA: 110 mg Maternal allergies 100	Outcome: eczema (Primary) Follow-up time: 12 months Arm 1: 68/167 (40.72%) Arm 2: 61/156 (39.1%)
Dunstan et al., 2003[50] Study name: Dunstan Study dates: 1999-2001 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 98 Pregnant withdrawals 15 Pregnant completers 83 Pregnant age: NR (NR) NR Race of Mother: NR (100)	Inclusion Criteria: All women had a history of physician-diagnosed allergic rhinitis and/or asthma and 1 or more positive skin prick tests to common allergens (house dust mite; grass pollens; molds; and cat, dog, and cockroach extracts) Exclusion Criteria:	Start time: Pregnant 20 weeks of gestation Duration: Pregnant till delivery Arm 1: Placebo group Description: 46 women allocated and received placebo-olive oil Manufacturer: Pan Laboratories, Moorebank, NSW, Australia Active ingredients: 66.6% n-9 oleic acid Dose: 4 (1-g) capsules of olive oil per day Blinding: Randomization and allocation of capsules occurred at a different center separate from the	Outcome: atopic dermatitis (Secondary) Follow-up time: 1 year Arm 1: 13/43 (30.23%) Arm 2: 18/40 (45.0%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study follow-up: 1 year Original, same study, or follow-up studies: Dunstan, 2008[44]; Meldrum, 2015[51]		Women were ineligible for the study if they smoked; if they had other medical problems, complicated pregnancies, or seafood allergy; or if their normal dietary intake exceeded 2 meals of fish per week.	recruitment of participants. Capsules were administered to the participants by someone separate from those doing the allocation. The capsules in the 2 groups were image-matched. Total N-3: <1% n-3 PUFAs Arm 2: Fish oil group Description: 52 women were randomized to receive fish oil Manufacturer: Ocean Nutrition, Halifax, Nova Scotia, Canada Dose: 4 (1g) fish oil capsules per day _x001E__x0007__x0005__x0015__x0013__x0007__x001E__x0013__x000F_ DHA: 56.0% EPA: 27.7% Total N-3: 3.7 g	
Furuhjelm et al., 2009[173] Study name: NR Study dates: 2003-2006 Study design: Trial randomized parallel Location: Sweden Funding source / conflict: Industry, Multiple foundations and Societies Study follow-up: 1 year Original, same study, or follow-up studies: Furuhjelm, 2011[172]	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 145 Pregnant withdrawals 28 Pregnant completers 117 Infants enrolled 145 Infants withdrawals 28 Infants completers 117 Mother age: Intervention: 31.1 years (at delivery) Placebo: 31.7 years (at delivery) (Intervention: 4.1 years (at delivery) Placebo: 3.9 years (at delivery)) NR Race of Mother: NR (100) Baseline biomarker information: Treatment - mean(sd) mol % EPA-	Inclusion Criteria: a family history of past of current allergic symptoms in at least one parent or older child. Exclusion Criteria: Mothers with an allergy to soy or fish or undergoing treatment with anticoagulants or commercial w-3 fatty acid supplements	Start time: Pregnant 25 weeks of gestation Duration: Pregnant 15 weeks (i.e., until delivery) Arm 1: Placebo Description: 75 women received soy oil as placebo Manufacturer: Pharma Nord Active ingredients: w-6 PUFA LA (58%, 2.5 g / day), a small amount (6%, 0.28 g / day) of the w-3 PUFA LNA and 36 mg a-tocopherol Viability: alpha-tocopherol was given as an antioxidant, a necessary ingredient according to the standard procedure of the manufacturer to assure the durability of the oil. Dose: nine soy oil capsules a day N-6 N-3: 9 Arm 2: w3 group Description: 70 women are randomized into this group Brand name: Bio Marin capsules Manufacturer: Pharma Nord, Vejle, Denmark Active ingredients: 23 mg alpha-tocopherol Viability: alpha-tocopherol was given as an antioxidant, a necessary ingredient according to the standard procedure of the manufacturer to assure	Outcome: IgE associated eczema (Primary) Follow-up time: 12 months Arm 1: 15/63 (23.81%) Arm 2: 4/52 (7.69%) Follow-up time: 6 months Arm 1: 13/65 (20.0%) Arm 2: 4/52 (7.69%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	1.3 (0.8) DHA- 5.5 (1.1) AA- 9.2 (1.7) AA/EPA- 9.1 (4.3) Placebo - mean(sd) mol % EPA- 1.2 (0.6) DHA- 5.4 (1.2) AA- 8.6 (1.5) AA/EPA- 8.6 (4.0) Baseline Omega-3 intake: DHA - 0.2g/day EPA- 0.1g/day		the durability of the oil. Dose: nine 500-mg capsules, once daily DHA: 1.1g EPA: 1.6g N-6 N-3: <0.1	
Furuhjelm et al., 2011[172] Study name: NR Study dates: 2003-2007 Study design: Trial randomized parallel Location: Sweden Funding source / conflict: Industry, Multiple foundations and Societies Study follow-up: 2 years Original, same study, or follow-up studies: Furuhjelm, 2009[173]	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 145 Pregnant withdrawals 28 Pregnant completers 117 Infants enrolled 145 Infants withdrawals 28 Infants completers 117 Pregnant age: NR (NR) NR Race of Mother: NR (100)	Inclusion Criteria: family history of current or previous allergic symptoms, i.e. bronchial asthma, eczema, allergic food reactions, itching and running eyes and nose at exposure to pollen, pets or other known allergens. Exclusion Criteria: Allergy to soya or fish, treatment with anticoagulants or omega-3 fatty acid supplements.	Start time: Pregnant 25 weeks of gestation Duration: Pregnant 15 weeks (i.e., until delivery) Arm 1: Placebo Description: soya bean oil Manufacturer: Pharma Nord, Vejle, Denmark Active ingredients: 58% linoleic acid (LA), 2.5 g/day Viability: the antioxidant a-tocopherol (placebo: 36 mg/day) to assure the stability of the oil Dose: nine capsules a day Blinding: The mothers, as well as the staff handling clinical and laboratory follow-up, were blinded to group allocation, and the mothers were identified by their study number only. ALA: 6%, 0.28 g/day Arm 2: w-3 group Description: w-3 fatty acids Viability: the antioxidant a-tocopherol (w-3 group: 28 mg/day) to assure the stability of the oil Dose: nine capsules a day DHA: 25% DHA, 1.1 g/day EPA: 35% EPA, 1.6 g/day	Outcome: any eczema (Primary) Follow-up time: 2 years Arm 1: 21/65 (32.31%) Arm 2: 11/54 (20.37%)
Linnamaa et al., 2010[79] Study name: NR Study dates: 2004-2008 Study design: Trial randomized parallel	Study Population: Healthy infants Healthy pregnant women Infants enrolled 314 Infants withdrawals 137 Infants completers 177	Inclusion Criteria: All pregnant mothers <16 weeks of gestation Exclusion Criteria: Sick children and those born prematurely who required more intensive care	Start time: Pregnant 8th to 16th weeks of pregnancy and then continued Infants when exclusive breastfeeding ended Duration: Pregnant until the end of the exclusive breastfeeding period Infants until 2 years of age Arm 1: Controls	Outcome: atopic dermatitis (Primary) Follow-up time: 12 months Arm 1: 52/110 (47.27%) Arm 2: 33/100 (33.0%) Follow-up time: 24 months Arm 1: 10/92 (11.11%) Arm 2: 9/85 (11.11%) Follow-up time: 3 months

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Location: Finland Funding source / conflict: Government, Multiple foundations and Societies	Mother age: NR (NR) NR Race of Mother: NR (NR)	(n=8)	Description: Olive oil Manufacturer: Santagata Luigi s.r.l., Genova, Italia Dose: 3 g/day for mothers, 1 mL/day for infants Blinding: NR "double-blind" ALA: 0 DHA: 0 EPA: 0 EPA-DHA: 0 AA: 0 Total N-3: 0 Other dose 1: LA (18:2n-6): 9 weight% of total Arm 2: Intervention Description: Blackcurrant seed oil Manufacturer: Aromtech Ltd, Tornio, Finland Dose: 3 g/day for mothers, 1 mL/day for infants ALA: 14 weight% of total DHA: 0 EPA: 0 EPA-DHA: 0 AA: 0 Total N-3: 17 weight% of total Other dose 1: SDA: 3 weight% of total	Arm 1: 14/129 (11.11%) Arm 2: 12/112 (11.11%)
Manley et al., 2011[118] Study name: DINO Study dates: 2001-2007 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies, Manufacturer supplied product, Some authors serve on scientific advisory boards for corporations	Study Population: Preterm infants Breast-feeding women Infants enrolled 657 Infants completers 614 Lactating age: Intervention: 29.9 (5.8) Placebo: 30.2 (5.4) Infant age: 4 days (median) Race of Mother: NR (100%)	Inclusion Criteria: Infants born before 33 weeks' gestation, within 5 days of the infant commencing any enteral feedings. Exclusion Criteria: major congenital or chromosomal abnormalities, from a multiple birth in which not all live-born infants were eligible, enrolled in other trials of fatty acid supplementation, or mother with contraindication to fish oil	Start time: Infants Within 5 days (or less) of starting enteral feeding Duration: Infants NR Arm 1: Standard DHA diet Description: Soy bean oil Manufacturer: Clover Corporation Dose: 6 capsules per day Maternal conditions Infant conditions Current smoker 25% during pregnancy Other maternal conditions 1arm_1_maternal_conditions_other1 Other maternal conditions 10 Birth by C-section: 69% Pre-term birth 100% Low birth weight 18.6% Arm 2: High DHA	Outcome: eczema (Secondary) Follow-up time: 12 months Arm 1: 40/249 (16.06%) Arm 2: 29/232 (12.5%) Follow-up time: 12 or 18 months Arm 1: 67/248 (27.02%) Arm 2: 61/236 (25.85%) Follow-up time: 18 months Arm 1: 51/311 (16.4%) Arm 2: 48/292 (16.44%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study follow-up: 18 months Original, same study, or follow-up studies: Smithers, 2008[104]; Makrides, 2009[116]; Smithers, 2010[117]; Collins, 2011[105]; Atwell, 2013[119]; Collins, 2015[120]			Description: Tuna fish oil Manufacturer: Clover Corporation Dose: 6 500-mg DHA-rich tuna oil capsules per day Maternal conditions Infant conditions DHA: DHA to achieve a breast milk concentration that was 1% of total fatty acids Other dose 1: If supplementary formula was required, infants were given a high- DHA preterm formula (approximately 1.0%DHAand 0.6% AA). Current smoker 25% during pregnancy Other maternal conditions 1arm_2_maternal_conditions_other1 Other maternal conditions 10 Birth by C-section: 68.3% Pre-term birth 100% Low birth weight 18.9%	
Marks et al., 2006[168] Study name: CAPS Study dates: 1997-2004 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies Study follow-up: 5 years Original, same study, or follow-up studies: Mihrshahi, 2003[166]; Mihrshahi, 2004[167]; Brew, 2015[165]; Toelle, 2010[169]	Study Population: Pregnant women with allergies Pregnant enrolled 616 Pregnant withdrawals 100 Pregnant completers 516 Infants completers 516 Race of Mother: NR	Inclusion Criteria: pregnant women whose unborn children were at increased risk of developing asthma because 1 or more parents or siblings had asthma or wheezing Exclusion Criteria: with a pet cat at home, strict vegetarians, women with a nonsingleton pregnancy, and infants born earlier than 36 weeks of gestation. Infants had birth weights less than 2.5 kg, significant congenital malformations, or other significant neonatal disease.	Start time: Infants from the time the child started bottle-feeding, or to solid foods from age 6 months Duration: NR Arm 1: Diet control Description: polyunsaturated oils and spreads, containing 40% w6 FA, and Sunola oil capsules Manufacturer: Crisco-Meadow Lea Foods Inc, Sydney, Australia Blinding: The approach to blinding participants and research staff is described in this article’s Online Repository at www.jacionline.org. Arm 2: Active Description: canola-based oils and spreads, which are low in n-6 fatty acids, and tuna oil capsules, which contain n-3 fatty acids.	Outcome: current eczema (Secondary) Follow-up time: 5 years Arm 1: 59/249 (23.69%) Arm 2: 54/267 (20.22%)
Mihrshahi et al., 2003[166] Study name: CAPS	Study Population: Pregnant women with allergies	Inclusion Criteria: At least one parent or sibling with symptoms of asthma as	Start time: Infants initiation of bottle feeding or 6 months of age	Outcome: eczema or dermatitis (Primary) Follow-up time: 18 months Arm 1: 77/275 (28.1%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study dates: 1997-2002 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies, Manufacturer supplied product Study follow-up: 18 months Original, same study, or follow-up studies: Mihrshahi, 2004[167]; Mihrshahi, 2006[168]; Brew, 2015[165] Toelle, 2010[169]	Pregnant enrolled 616 (all 4 arms) Pregnant withdrawals 62 Pregnant completers 554 Pregnant age: 28.5 (5.3) Race of Mother: NR (96.9%) Other race/ethnicity (Aboriginal 3.1%)	assessed by screening questionnaire, Reasonable fluency in English, Telephone at home, Reside within 30 km from center of recruitment Exclusion Criteria: Pet cat at home, Families on strict vegetarian diet, Multiple births, Babies born earlier than 36 weeks gestation, with congenital malformations or other serious disease, or requiring major surgery or hospitalization for greater than 1 week	Duration: Infants NR Arm 1: Diet Control/HDM control or intervention Brand name: Sunola oil Manufacturer: Clover Corporation Arm 2: Dietary intervention/HDM control or intervention Description: 500mg n-3 rich tuna fish oil supplement Manufacturer: Clover Corporation DHA: 76-128 mg EPA: 18-30 mg Other dose 1: based on age and fluid intake	Arm 2: 85/279 (30.5%)
Noakes et al., 2012[88] Study name: SiPS Study dates: Not reported Study design: Trial randomized parallel Location: UK Funding source / conflict: Government, None Original, same study, or follow-up studies: Miles, 2011[78]	Study Population: Healthy pregnant women Pregnant enrolled 123 Pregnant withdrawals 37 Pregnant completers 86 Pregnant age: Mean(SEM)(n):Control group -28.4 (0.6)(61); Salmon group- 29.5(0.5) (62) (NR) 18-40 years Race of Mother: NR (100)	Inclusion Criteria: age 18–40 y; >19 wk gestation; healthy uncomplicated singleton pregnancy; infant at risk of atopy (one or more first-degree relatives of the infant affected by atopy, asthma or allergy by self-report); consumption of < 2 portions oily fish per month, excluding tinned tuna; and no use of fish-oil supplements currently or in the previous 3 months. Exclusion Criteria: age <18 or >40 y; <19 wk gestation; no first-degree	Start time: Pregnant 20 weeks of gestation Duration: Pregnant until birth Arm 1: Control group Description: Women in the control group (n = 61) were asked to continue their habitual diet Blinding: Researchers responsible for assessing outcome measures (both laboratory and clinical) remained blinded to the groups Arm 2: Salmon group Description: Women in the salmon group (n = 62) were asked to incorporate 2 portions of farmed salmon (150 g/portion) into their diet per week Active ingredients: 30.5 g protein, 16.4 g fat,4.1 mg alpha-tocopherol, 1.6 mg gamma-tocopherol, 6 micro-g vitamin A, 14 micro-g vitamin D3, and 43 micro-g Selenium Dose: two 150-g portions per week DHA: 1.16 g per portion	Outcome: atopic dermatitis (Primary) Follow-up time: 6 months Arm 1: 12/48 (25.0%) Arm 2: 7/38 (18.42%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		relatives of the infant affected by atopy, asthma, or allergy; consumption of >2 portions oily fish per month, excluding tinned tuna; use of fish-oil supplements within the previous 3 mo; participation in another research study; known diabetes; presence of any autoimmune disease; learning disability; terminal illness; and mental health problems.	EPA: 0.57g per portion EPA-DHA: 1.73 per portion Total N-3: 3.56g per portion Other dose 1: Docosapentaenoic acid-0.35g	
Palmer et al., 2012[54] Study name: DOMInO Study dates: 2006-2009 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Industry, Government, Manufacturer supplied product Original, same study, or follow-up studies: Makrides, 2010[35]; Smithers, 2011[53]; Zhou, 2012[55]; Palmer, 2013[56]; Makrides, 2014 [57]	Study Population: Pregnant women with allergies Pregnant enrolled 706 Pregnant withdrawals 25 Pregnant completers 681 Infants enrolled 706 Infants withdrawals 25 Infants completers 681 Pregnant age: Treatment: 29.6 Placebo: 29.5 (Treatment: 5.7 Placebo: 5.6) NR Race of Mother: NR (100)	Inclusion Criteria: Included if the unborn baby had a mother, father, or sibling with a history of any medically diagnosed allergic disease (asthma, allergic rhinitis, eczema) and they were enrolled from the Women's and Children's Hospital or Flinders Medical Centre in Adelaide. Exclusion Criteria: NR	Start time: Pregnant 21 weeks of gestation Infants 21 weeks of gestation Duration: Pregnant until delivery Infants till delivery Arm 1: Placebo Description: 338 women assigned to control supplements-vegetable oil capsules Dose: three 500 mg vegetable oil capsules daily Blinding: All capsules were similar in size, shape, and color. Neither the women nor the research staff were aware of the treatment allocated. Arm 2: n-3 LCPUFA group Description: 368 women assigned to fish oil concentrate Brand name: Incromega 500 TG Manufacturer: Croda Chemicals, East Yorkshire, UK Dose: e three 500 mg capsules daily DHA: 800mg EPA: 100mg	Outcome: eczema with sensitization (Primary) Follow-up time: 1 year Arm 1: 39/338 (11.54%) Arm 2: 26/368 (7.07%)
Palmer et al., 2013[56] Study name: DOMInO	Study Population: Children with family history of allergy	Inclusion Criteria: Women whose infants had a parent or sibling with a history of any	Start time: Pregnant <21 weeks gestation Duration: Pregnant to term	Outcome: eczema (Primary) Follow-up time: 3 years Arm 1: 64/338 (18.93%) Arm 2: 15/368 (4.08%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study dates: 2006-2011 (allergy follow-up to Domino study) Study design: Trial randomized parallel Location: Australia Funding source / conflict: Industry, Government, Some authors serve on scientific advisory boards for corporations Study follow-up: 3 years Original, same study, or follow-up studies: Makrides, 2010[35]; Smithers, 2011[53]; Palmer, 2012[54]; Zhou, 2012[55]	Pregnant enrolled 706 Pregnant completers 638 Infants enrolled 706 Infants completers 638 Pregnant age: DHA: 28.9 Control: 28.9 (DHA: 5.7) Control: 5.6) Infant age: Birth Race of Mother: NR (100)	medically diagnosed allergic disease (asthma, allergic rhinitis, eczema) Exclusion Criteria: Already taking a prenatal supplement with DHA Fetus had a known major abnormality, Bleeding disorder in which tuna oil was contraindicated, Taking anticoagulant therapy A documented history of drug or alcohol abuse, Participating in another fatty acid trial, Unable to give written informed consent, or English was not the main language spoken at home	Arm 1: Control Description: vegetable oil Dose: 3 500-mg vegetable oil capsules per day Blinding: This was a double-blinded study; all capsules were similar in size, shape and color Arm 2: Fish oil Brand name: Incromega 500 TG, Manufacturer: Croda Chemicals, East Yorkshire, England Dose: 3 500-mg capsules per day DHA: 800 mg per day EPA: 100 mg per day	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Peat et al., 2004[167] Study name: CAPS Study dates: 2000-2003 Study design: Trial randomized factorial design Location: Australia Funding source / conflict: Industry, Government Study follow-up: 3 years Original, same study, or follow-up studies: Mihrshahi, 2003[166]; Mihrshahi, 2006[168]; Brew, 2015[165] Toelle, 2010[169]	Study Population: Pregnant women whose unborn children were at high risk of developing asthma Pregnant enrolled 616 Pregnant withdrawals 90 Pregnant completers 526 Pregnant age: Placebo: 29.1 Diet: 28.6 (Placebo: 5.0 Diet: 5.3) NR Race of Mother: NR (100)	Inclusion Criteria: at least 1 parent or sibling with current asthma or frequent wheeze as assessed by screening questionnaire, fluency in English, a telephone at home, and residence within 30 km of the recruitment center. Exclusion Criteria: a pet cat at home, a vegetarian diet, multiple births, and less than 36 weeks gestation.	Start time: Infants 6 months of age Duration: Infants NR Arm 1: Placebo group Description: The control group received placebo supplement capsules of Sunola oil containing 83% monounsaturated oils (Clover Corp) and were provided with widely used soybean-based polyunsaturated oils and margarines high in omega-6 fatty acids for use in all food preparation Manufacturer: Clover Corp; Goodman Fielder Blinding: The research team responsible for recruitment was blind to the methods of randomization until recruitment was complete. The research nurses and research assistants who undertook the outcome assessments, laboratory analyses, and statistical analyses were blind to the group allocation of the participants. Arm 2: Active intervention group Description: tuna fish oil capsules Manufacturer: Clover Corp; Goodman Fielder Dose: 500 mg tuna fish oil capsules daily Total N-3: 184 mg	Outcome: any eczema (Secondary) Follow-up time: 3 years Arm 1: 81/259 (31.3%) Arm 2: 74/267 (27.7%)
Toelle et al., 2010[169] Study name: CAPS Study dates: 1997-2008 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Manufacturer supplied product Study follow-up: 8 years	Study Population: Healthy infants Pregnant enrolled 616 Pregnant completers Infants enrolled 616 Infants completers 450 Pregnant age: 28.5 years (5.3 years) Race of Mother: NR (NR)	Inclusion Criteria: Pregnant women whose unborn children were at high risk of developing asthma because of a family history (at least one parent or sibling with symptoms of asthma as assessed by screening questionnaire), reasonable fluency in English, telephone at home, reside within 30 km from center of recruitment Exclusion Criteria: Pet cat at home, families on	Start time: Infants birth Duration: Infants 5 years Arm 1: Control Description: Low-n3 capsules and cooking oils Brand name: Sunola Active ingredients: Capsules: 7% n-6 FA, 82% monounsaturated FA, 9% saturated FA, and 1.7% minor FA; cooking oils: 40% n-6 FA, 20% n-9 FA Dose: Designed to maintain the current n-3 to n-6 ingested FA ratio in the general population (1:15 to 1:20) Blinding: Similar appearance Total N-3: Capsules: 0.3%; cooking oil: 1.2% Arm 2: Omega 3 supplementation Description: High n-3 FA capsules and cooking oils	Outcome: eczema (Secondary) Follow-up time: 8 yrs Arm 1: 31/220 (14.2%) Arm 2: 35/230 (15.3%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Original, same study, or follow-up studies: Mihrshahi, 2003[166]; Mihrshahi, 2004[167]; Mihrshahi, 2006[168]; Brew, 2015[165]		strict vegetarian diet, multiple births, babies born earlier than 36 weeks gestation, birth weight below 2.5 kg, babies requiring surgery, babies requiring hospitalization for more than 1 week, babies with significant neonatal disease, babies with congenital malformations	Active ingredients: Capsules: 6% n-6 polyunsaturated FA, 24% monounsaturated FA, 28% saturated FA, and 5% minor FA; cooking oil: 6% n-6 FA, 40% n-9 FA Blinding: Similar appearance N-6 N-3: 5:1 Total N-3: Capsules: 37%; cooking oil: 6%	

Table 23. Observational studies for atopic dermatitis

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Miyake, et al., 2009[182] Outcome domain: Atopic Study name: Osaka maternal and child health study Study dates: 2002-2003 Study design: Observational prospective Location: Japan Funding source / conflict: Government, None	Study Population: Healthy infants Pregnant enrolled 1,002 Pregnant completers 763 Infants enrolled 1,002 Infants completers 763 Pregnant age: 30.0 (4.0) Race of Mother: NR (100)	Inclusion Criteria: pregnant women living in Neyagawa City, Osaka Prefecture or the surrounding cities Exclusion Criteria: Not reported	Adjustments: Maternal age, gestation at baseline, residential municipality, family income, maternal and paternal education, maternal and paternal history of asthma, atopic eczema and allergic rhinitis, maternal intake of vitamins D and E during pregnancy, changes in maternal diet in the previous 1 month, season when data at baseline were collected, maternal smoking during pregnancy, baby's older siblings, baby's sex, baby's birth weight, household smoking in the same room as the infant, breastfeeding duration and time of delivery before the third survey
Miyake, et al., 2013[183] Outcome domain: Atopic Study name: Kyushu Okinawa Maternal and Child Health Study Study dates: 2007-2010 Study design: Observational prospective Location: Japan Funding source / conflict: Industry, Government, Multiple foundations and Societies Follow-up: 23-29 months	Study Population: Healthy infants Pregnant enrolled 1757 Pregnant completers 1354 Infants enrolled 1757 Infants completers 1354 Pregnant age: 31.5 (4.1) Race of Mother: NR (100)	Inclusion Criteria: Women living in one of 7 prefectures on Kyushu Island who became pregnant from 2007-2008 Exclusion Criteria: Failure to complete the study surveys	Adjustments: Maternal age, gestation at baseline, residential municipality, family income, maternal and paternal education, maternal and paternal history of asthma, atopic eczema and allergic rhinitis, maternal intake of vitamins D and E during pregnancy, changes in maternal diet in the previous 1 month, season when data at baseline were collected, maternal smoking during pregnancy, baby's older siblings, baby's sex, baby's birth weight, household smoking in the same room as the infant, breastfeeding duration and time of delivery before the third survey
Newson, et al., 2004[176]	Study Population: Healthy infants	Inclusion Criteria: Pregnant women with expected date of delivery between April 1, 1991, and	Adjustments: Child's sex, gestational age at birth, and

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Outcome domain: Atopic Study name: Avon Longitudinal Study of Parents and Children (ALSPAC) Study dates: Recruitment: April 1, 1991 to December 31, 1992 Followup: 42 months Study design: Observational prospective Location: UK Funding source / conflict: Government, Multiple foundations and Societies Follow-up: 42 months Original, same study, or follow-up studies: Golding et al., 2001 (ALSPAC)	Pregnant enrolled 4136 Infants enrolled 4202 Infants completers 1762 Infant age: Prenatal Race of Mother: NR (100%)	December 31, 1992, and place of residence within the 3 Bristol-based health districts of the former county of Avon, United Kingdom Exclusion Criteria: NR for enrollment. Exclusion for analysis: multiple pregnancies or in small missing value categories for various confounders.	birth weight, and for the mother's age, education level, housing tenure, parity, ethnicity, and smoking in pregnancy (for variable categories see Table EI in the Journal's Online Repository at http://www.mosby.com/jaci), as well as maternal atopic disease (asthma, eczema, rhinoconjunctivitis), child's head circumference at birth (< 33 cm, 33-34.99 cm, 35-36.99 cm, 37+ cm, unknown), child's crown to heel length at birth (< 48 cm, 48-50.99 cm, 51-53.99 cm, 54+ cm, unknown), mother's body mass index (from prepregnancy self-reported weight and height; < 18.5 kg/m2 , 18.5-24.99 kg/m2 , 25-29.99 kg/m2 , 30+ kg/m2 , unknown), breast-feeding
Notenboom, et al., 2011[179] Outcome domain: Atopic Study name: KOALA Birth Cohort Study Study dates: Recruitment from October 2000 onwards and Followup: 6-7 years Study design: Observational prospective Location: Netherlands Funding source / conflict: Industry, Government, Multiple foundations and Societies Follow-up: 3 - 84 months	Study Population: Healthy infants Healthy pregnant women Infants enrolled 1275 Infants completers 1253 (samples for 815) Mother age: 32.6 (3.8) Race of Mother: White European (Dutch 96.3%)	Inclusion Criteria: Conventional participants: participation in ongoing study of pelvic girdle pain Alternative participants: frequented locations associated with organic diet and similar lifestyles Subsample: participants recruited from January 2002 onwards who consented to biosampling. Exclusion Criteria: Current multiple pregnancy n=9 Prematurity n=15 Perinatal infant death n=2 Down syndrome n=4 No response after birth n=51	Adjustments: Adjusted for recruitment group, maternal age, maternal ethnicity, maternal education level, maternal smoking during pregnancy, parental history of atopy, term of gestation, season of birth, gender, birth weight, mode of delivery, exposure to environmental tobacco, presence of older siblings and sibling atopy, breastfeeding, child day care, and pets at home
Nwaru, et al., 2012[180] Outcome domain: Atopic Study name: Finnish Type 1 Diabetes Prediction	Study Population: NR Pregnant enrolled NR Pregnant completers 3523	Inclusion Criteria: Newborn infants with human leucocyte antigen (HLA)- conferred susceptibility to type 1 diabetes recruited from three university hospitals in Finland	Adjustments: Sex of child, hospital of birth, duration of gestation, maternal age at delivery, maternal basic education, maternal smoking

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
and Prevention Nutrition Study Study dates: Infants recruited between 20 October 1997 and 29 February 2004; Followup to 5 years of age Study design: Observational prospective Location: Finland Funding source / conflict: Government, Multiple foundations and Societies Follow-up: 5 years	Infants enrolled 3253 Infants completers 2441 Infant age: birth Race of Mother: White European (100%)	Exclusion Criteria: Infants with severe systemic disease or anomalies, or both parents non-Caucasian	during pregnancy, mode of delivery, number of siblings at the time of the child's birth, parental asthma, parental allergic rhinitis, pets at home by 1 year of age. A second adjusted model was computed for the FA in which potentially confounding nutrients, vitamin C, Zn, Se, vitamin D and vitamin E were included as additional covariates
Pike, et al., 2012[186] Outcome domain: Atopic Study name: Southampton Women's Survey Study dates: 2006-2010 Study design: Observational prospective Location: UK Funding source / conflict: Government, Some authors serve on scientific advisory boards for corporations Follow-up: Birth to 6 years	Study Population: Healthy infants Pregnant enrolled Infants enrolled 1485 Infants completers 865 Pregnant age: 30.4 (3.8) Race of Mother: NR (100)	Inclusion Criteria: mothers and children in the Southampton Women's Survey Exclusion Criteria: Infants born = 35 weeks' gestation were excluded to avoid abnormal lung development associated with prematurity	Adjustments: Child's age, maternal asthma, and paternal rhinitis for airway inflammation outcome
Saito, et al., 2010[181] Outcome domain: Atopic Study name: Osaka maternal and child health study Study dates: Recruitment: November 2001 to March 2003 Followup: 3-4 months Study design: Observational prospective Location: Japan Funding source / conflict: Government	Study Population: Healthy infants Healthy pregnant women Pregnant completers 771 Infants completers 771 Pregnant age: 29.9 (4.0) Race of Mother: NR (100%)	Inclusion Criteria: Pregnant women living in Neyagawa City (one of the 43 municipalities in Osaka Prefecture) and a few municipalities other than Neyagawa Exclusion Criteria: Survey completed outside 3-5 month postpartum window	Adjustments: Maternal age, gestation at baseline, family income, maternal and paternal education, maternal and paternal history of asthma, atopic eczema and allergic rhinitis, mite allergen level from maternal bedclothes, vacuuming living room, mold in kitchen, changes in maternal diet in the previous 1 month, season when data at baseline were collected, baby's older siblings, baby's sex, baby's

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Follow-up: 3-4 months			birth weight, breastfeeding and bathing or showering infant.
Standl, et al., 2014[177] Outcome domain: Atopic Study name: LISAplus Study dates: Recruitment 1997-1999 Study design: Observational prospective Location: Germany Funding source / conflict: Government Follow-up: 10 years	Study Population: Healthy infants Infants enrolled 436 Infants completers 243 Mother age: 32.7 (3.9) NR Infant age: Birth (NR) NR Race of Mother: NR (100)	Inclusion Criteria: NR Exclusion Criteria: Neonates displaying at least one of the following criteria: preterm birth (maturity <37 gestational weeks), low birth weight (<2,500 g), congenital malformation, symptomatic neonatal infection, antibiotic medication, hospitalization or intensive medical care during neonatal period. In addition, newborns from mothers with immune-related diseases (autoimmune disorders, diabetes, hepatitis B), on long-term medication or who abuse drugs and/or alcohol, and newborns from parents with a nationality other than German or who were not born in Germany, were excluded.	Adjustments: Parental education, sex, time of follow-up (2 yr, 6 yr or 10 yr for eczema; 6 yr and 10 yr for asthma, hay fever/allergic rhinitis and aeroallergen sensitization), age, maternal age at birth, parental atopy, total sum of fatty acids
Thijs, et al., 2011[178] Outcome domain: Atopic Study name: KOALA Birth Cohort Study Study dates: 2003 Study design: Observational prospective Location: Netherlands Funding source / conflict: Government, None Follow-up: 2 years	Study Population: Healthy pregnant women Pregnant enrolled 312 Pregnant completers 304 Infants enrolled 312 Infants completers 304 Pregnant age: 33.3 (3.9) NR Race of Mother: NR (100)	Inclusion Criteria: availability of complete baseline data from the 34 weeks pregnancy questionnaire and availability of a breast milk sample. Exclusion Criteria: NR	Adjustments: Recruitment group, maternal age, maternal education, infant's gender, number of older siblings and their atopic history, parental atopic history, maternal smoking during pregnancy and/or smoking in presence of the infant, place of birth, season of breast milk collection, duration and exclusivity of breastfeeding, maternal n-3 fatty acids supplement use, maternal probiotic supplement use, maternal probiotic dairy use, maternal antibiotic use during lactation, infant's antibiotic use, vaccination schedule, dampness of the home, pet animals in the home.

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Wijga, et al., 2006[175] Outcome domain: Atopic Study name: The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study Study dates: 1995-2000 Study design: Observational prospective Location: Netherlands Funding source / conflict: Industry, Government Follow-up: 4 years	Study Population: NR Pregnant enrolled 276 Pregnant withdrawals 11 Pregnant completers 265 Infants enrolled 276 Infants withdrawals 11 Infants completers 265 Pregnant age: 31.0 (3.9) NR Race of Mother: NR (100)	Inclusion Criteria: Mothers reporting at least 1 of the following: (a history of) asthma, current hay fever, current allergy for pets, or current allergy for house dust or house dust mite were defined as allergic, and mothers reporting that they had none of these were defined as nonallergic. Exclusion Criteria: NR	Adjustments: Sex, number of older siblings, maternal age, maternal smoking during pregnancy, and maternal body mass index before pregnancy
Yu, et al., 2015[185] Outcome domain: Atopic Study dates: Participants recruited between June 2009 and September 2010 Study design: Observational prospective Location: NR Funding source / conflict: Industry, Government	Study Population: Healthy infants Healthy pregnant women Infants enrolled 1162 Infants completers 960 Pregnant age: NR (NR) NR Race of Mother: NR (100%)	Inclusion Criteria: Participants were mother–child pairs in the Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort. Exclusion Criteria: NR	Adjustments: In the models, we adjusted for maternal characteristics including maternal age, ethnicity, gravidity, education level and energy intake. The same was done for infant characteristics including sex, birth weight, gestational age, duration of breast-feeding, family history of allergic diseases (which includes allergic rhinitis, eczema and asthma in first-degree relatives of the children (i.e. father, mother and/or sibling), exposure to environmental tobacco smoking, child day care attendance and having a cat or dog at home up to 18 months of age.

Risk for Allergies

Key Points

- Among the three prenatal n-3 interventions and two follow-up studies, three found associations between maternal n-3 FA supplementation (DHA + EPA, varying doses) and lower risk of allergies (denoted by sensitization to egg allergen and positive skin prick test). However, in all but one study, these relationships were no longer observed or became marginal after adjusting for potential confounders or after long-term follow-up. Meta-analysis of three RCTs (n=949) with 12-month food allergy outcomes yielded an insignificant summary effect. A single trial with ALA supplementation also found no relationship.
- In three postnatal n-3 interventions and two follow-up studies, there was no consistent association between infant n-3 FA supplementation (DHA or DHA+EPA, varying doses) and allergy outcomes.
- One biomarker study found associations between higher levels of DHA and lower incidence of IgE-associated disease as well as lower AA/EPA ratio with higher incidence of IgE-associated disease, although these findings were not consistent over time.
- There was no robust association between n-3 FA exposure (measured through maternal dietary intake or breast milk composition) and allergy outcomes among three prospective observational studies. The associations found in these studies lost significance after adjusting for multiple comparisons or after longer term follow-up. All four studies of n-3 FA biomarkers (in cord blood or maternal blood sample) and risk of allergy found no significant association.

The risk for allergies is an additional outcome of interest that was not included in the original review. A total of 11 eligible RCTs (composed of 7 original RCTs and four follow-up assessments) and 7 observational studies were included.

Description of Included Studies

Randomized Controlled Trials

Prenatal interventions/exposures

Four RCTs[50, 54, 79, 173]and two follow-up assessments [56, 172] evaluated prenatal maternal n-3 FA interventions (see Table 24). Two interventions were exclusively during the prenatal period with the mother stopping supplementation at birth.[50, 54, 56] The two remaining trials with maternal supplementation started during pregnancy and continued into breastfeeding, [79, 172, 173] with one of those trials also adding infant supplementation following breastfeeding.[79] All of these trials except for one[79] recruited pregnant women whose infants were at high risk for atopy (e.g., parent diagnosis of allergy, or sibling has diagnosed or suspected allergy). All studies tested DHA and DHA+EPA n-3 FAs except for a single RCT that evaluated ALA.[79]

DHA, DHA Plus EPA Versus placebo

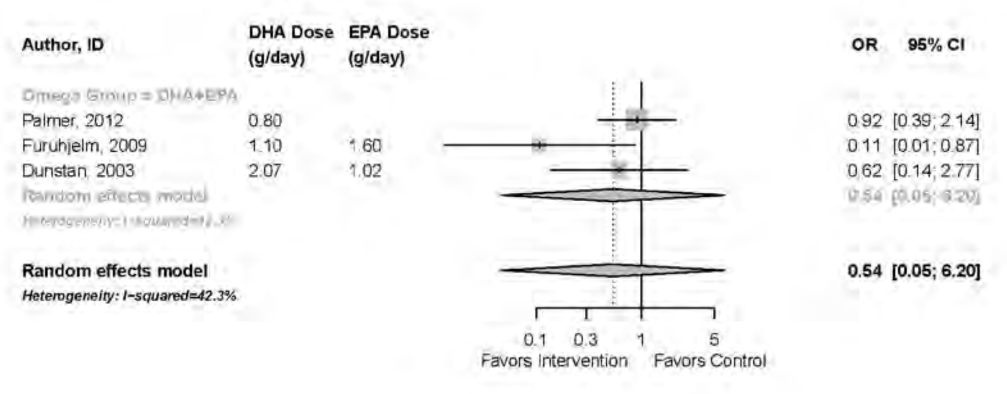
One RCT randomized 145 pregnant women in Sweden to daily n-3 FA (1.6g EPA + 1.1g DHA) or placebo (soy oil) supplementation from the 25th gestational week through the exclusive breastfeeding period (average 3-4 months). Period prevalence for the first 12 months of life was lower in adjusted analyses for all skin prick tests (OR 0.36; 95% CI 0.14, 0.95), egg skin prick test (OR 0.31, 95% CI 0.11-0.89), and food allergy (OR 0.09, 95% CI 0.01-0.74).[173] In a later follow-up study at 24 months with 143 infants, marginal differences were observed in crude incidence and prevalence rates for food reactions between the treatment groups. In adjusted multiple regression models, risk of any positive skin prick test through 24 months was marginally but not statistically lower for the n-3 FA group (OR 0.43, 95% CI 0.17, 1.1; p=0.06).[172]

Dunstan et al. (2003) randomized 98 pregnant, atopic Australian women to fish oil (3.7g n-3 PUFA, 56.0% DHA, 27.7% EPA) or olive oil (4g) daily from 20 weeks gestation until delivery.[50] A total of 83 mothers and their children completed the 12-month follow-up. The authors report that infants in the fish oil group were less likely to be sensitized to egg allergen (OR 0.34, 95% CI 0.11, 1.02; p=0.055). There were no significant differences in other clinical outcomes, including food allergy and anaphylaxis, between the fish oil and control groups.[50]

In a subset of the Docosahexaenoic Acid (DHA) to Optimise Mother Infant Outcome (DOMInO) trial, 706 pregnant Australian women whose child was at high risk for genetic allergy were randomized to n-3 LCPUFA group (800 mg DHA + 100 mg EPA) or placebo group (vegetable oil) from 21 weeks gestation until delivery.[54, 56] In a 1-year follow-up, no differences were seen between treatment groups for allergic disease with sensitization, allergic disease without sensitization, food allergy with sensitization, sensitization with/without allergic disease, or allergic disease without sensitization in analyses adjusted and unadjusted for study center, parity, maternal history, and sex, although some relationships reached marginal significance.[54] The one exception was that the n-3 LCPUFA group were at lower risk for egg sensitization compared to the placebo group (RR0.75; 95% CI 0.41, 0.93; p=0.02). In a longer follow-up, no differences were observed between treatment groups for allergic disease with sensitization, allergic disease without sensitization, food allergy with sensitization, allergic rhinitis with sensitization, sensitization during the first 3 years of life or at age 3 in analyses adjusted and unadjusted for study center, parity, maternal history, and sex.[56]

Meta-analysis of the three RCTs with a 12-month follow-up [50, 54, 173] yielded an insignificant summary effect size for DHA+EPA supplementation and risk of food allergy (OR 0.54 95% CI 0.05, 6.2, I^2=42.3%) (Figure 26).

Figure 26. Food allergy – Intervention given to pregnant women, 12-month follow-up



ALA Versus Placebo

One trial examined ALA supplementation during pregnancy, breastfeeding, and infancy. [79] Specifically, Linnamaa (2010) randomized 313 pregnant Finnish women (<16 weeks gestation) to blackcurrant seed oil (14% ALA by weight of 3g/d) or olive oil (placebo). The first dose was administered between the 8th and 16th week of pregnancy and continued during breastfeeding. Once the exclusive breastfeeding period was over, infants received 1 mL/day of supplemental oil until age 2 years. Total IgE antibodies were available for 136 infants at 3 and 12 months and 64 infants at 24 months; results from skin prick tests with egg were available for 238, 202, and 166 infants at 3, 12, and 25 months, respectively. No significant differences were observed between the intervention and placebo groups at any time point.

Postnatal Interventions/Exposures

Three RCTs [118, 142, 168] and two follow-up studies [166], [169] evaluated n-3 FA interventions during the postnatal period. One of the RCTs evaluated preterm infants [118] while the remaining two RCTs assessed term infants who were at genetic risk for allergy.[142, 168] All RCTs evaluated DHA or DHA+EPA n-3 FAs.

DHA or DHA Plus EPA Versus Placebo

One RCT, which enrolled mothers of preterm infants, began the n-3 FA intervention during the postnatal breastfeeding period.[118] The DINO trial randomized 657 preterm Australian infants (<33 weeks gestation) to receive a high-DHA diet (~1% DHA and 0.6% AA) or standard DHA diet (~0.35% DHA and 0.6% AA) through breast milk or formula until their expected delivery date. Data from parent questionnaires on hay fever were available for 481 infants at 12 months and 603 infants at 18 months. In adjusted analyses, infants in the high-DHA diet group had lower risk of reported hay fever at 12 or 18 months (RR 0.41; 95% CI 0.18-0.91; p=0.03), but not at either time points separately (12 mo RR 0.41, 95% CI 0.15, 1.16; p=0.09; and 18 mo RR 0.75, 95% CI 0.28, 2.01; p=0.57). Data on special diet for food allergy were available for 480 infants at 12 months and 603 infants at 18 months. No differences were seen in food allergy at either time point (adjusted or unadjusted for gestational age at delivery and gender).[118]

In the Infant Fish Oil Supplementation Study (IFOS), 420 infants at high risk for atopy were randomized to daily fish oil capsules (0.280 g DHA + 0.110 g EPA) or placebo capsules (olive oil) from birth to 6 months. No significant overall difference was observed in the prevalence of any allergic disease, overall sensitization, specific sensitization, or food allergy at 12 months between the fish oil and placebo groups in both adjusted and unadjusted analyses.[142]

One RCT and two follow-up studies on infant n-3 supplementation were conducted as part of the Childhood Asthma Prevention Study (CAPS).[166, 168],[169]. In CAPS, 616 pregnant women (<36 weeks gestation) with a child at high risk for developing asthma were randomized into four groups, including two with a dietary component (500 g/d tuna fish oil supplement + canola-based oils and spreads or placebo supplement + polyunsaturated oils and margarines). The intervention began at 6 months or the beginning of formula feeding if that occurred earlier than 6 months. In an 18-month follow-up with 543 infants (88% of the total sample size), geometric mean IgE concentrations did not differ between the diet intervention and control groups.[166] In a 5-year follow-up with 516 children (84%), no significant differences were seen between the diet intervention and control groups for rhinitis (RR 1.42; 95% CI 0.97, 2.09), any atopy (RR 0.93, 95% CI 0.76, 1.13), inhalant atopy (RR 0.96, 95% CI 0.78, 1.18), house dust mite atopy (RR 1.04, 95% CI 0.81, 1.33), or IgE (ratio of means, 0.86, 95% CI 0.64, 1.16).[168] In an 8-year follow-up with 450 children (73%), no significant differences were seen between the diet intervention and control groups for atopy (ARR=-0.2, 95% CI -9.9, 9.6), house dust mite allergy (ARR=-5.4, 95% CI -14.8, 3.9), or serum IgE > 1000 IU (ARR=1.5, 95% CI -4.9, 7.8). [169]

Biomarker Studies

One trial examined the association between biomarkers and allergy outcomes.[172] Results suggest that higher maternal (p for trend=0.001) plasma phospholipid DHA is significantly associated with lower incidence of IgE-associated disease at 12 months of age. Higher infant (p for trend=0.003) plasma phospholipid DHA was significantly associated with lower incidence of IgE-associated disease at 12 months of age. Infant plasma phospholipid DHA was not significantly associated with IgE-associated disease at 3 or 24 months of age. In addition, lower maternal plasma phospholipid AA/EPA ratio was associated with higher incidence of IgE-associated disease (p for trend=0.008). Lower quartiles of AA/EPA ratios in infant phospholipids at birth and at 3 months of age were associated with lower incidence of IgE-associated disease (p = NS for both, but p for trend = 0.01 and 0.03 respectively), but no significant relationship with infant phospholipids was seen at 12 or at 24 months. At 12 and 24 months of age, AA/EPA ratios in infant phospholipids were also not significantly associated with IgE-associated disease.[172]

Observational Studies

Seven observational studies evaluated the association between some measure of n-3 FA exposure and risk of allergies (see Table 25).[175, 177-180, 186], [185]

All studies enrolled populations of healthy infants except for one [180] which enrolled infants with human leucocyte antigen (HLA)-conferred susceptibility-hence high or moderate genetic risk - to type I diabetes. All the studies were prospective cohort studies. The exposures include dietary intake of n-3 FA,[180] breast milk FA,[175, 178] and maternal biomarkers.[177, 179, 185, 186] Studies were published between 2004 and 2014.

Maternal n-3 FA Intake

A single study evaluated the association between maternal dietary n-3 FA intake and risk of allergies.[180]

A 2012 study examined the association between maternal n-3 FA intake in a cohort of 2441 newborn infants born between 1997 and 2004 in Finland and risk of allergies after 5 years of follow-up. Enrolled infants had a history of human leucocyte antigen (HLA)-conferred susceptibility to type I diabetes. Maternal intake of n-3 FA was assessed using a validated FFQ. High maternal intakes of ALA (HR 0·73; 95 % CI 0·54, 0·98) were associated with a decreased risk of allergic rhinitis. Also, higher ratios of n-6: n-3 FA (HR 1·37; 95 % CI 1·07, 1·77) during pregnancy were associated with an increased risk of allergic rhinitis in the offspring by 5 years of age, adjusted for potential confounding variables. The results however lost their significance after adjustment for multiple comparisons.[180]

n-3 FA Breastmilk Intake

Two studies examined the association between breastmilk n-3 fatty acids and the risk for allergies in infants.[175, 178]

A 2006 study of 265 mother-infant pairs in Netherland found no relationship between breast milk n-3 fatty acid concentration (measured at 3 months postpartum) and sensitization (defined as specific IgE higher than 0.35 IU/mL to any of measured allergens) in children with maternal history of allergy at 4 years of age. However in children with no maternal history at 4 years of age, ALA and ALA/LA ratio were positively associated with sensitization ($p<0.05$).[175]

In a 2011 study of 310 mother-infant pairs in the Netherlands, higher concentrations of breast milk n-3 fatty acid (EPA+DHA+DPA) were significantly associated with lower risk of allergic sensitization at 1year of age (p for trend=0.029), adjusted for recruitment group, maternal age, maternal education, infant's gender, number of older siblings and their atopic history, parental atopic history, maternal smoking during pregnancy and/or smoking in presence of the infant, place of birth, season of breast milk collection, and other potential confounders). However, no significant associations were found at 2 years of age.[178]

n-3 FA Biomarkers

Four studies examined the association between n-3 FA biomarkers and the risk of allergies.[177, 179, 186]

In a 2011 study of 1275 children from the KOALA Birth Cohort Study who were followed for 6-7 years, no associations were found between maternal plasma phospholipid n-3 fatty acids measured at 34–36 weeks of pregnancy and allergic sensitization, allergic rhinoconjunctivitis, or high total IgE.[179]

In a 2012 study of 1485 healthy mother-infant pairs from the Southampton Women's Survey in the UK who were followed for 6 years, no associations were found between maternal plasma phospholipid n-3 fatty acids measured at 34 weeks of gestation and risk of atopy (positive skin prick test defined as positive wheal >=3mm to a common allergen panel).[186]

A 2014 study of 436 infants from the Munich LISA plus birth cohort study in Germany found no significant association between n-3 LC-PUFA or n-6/n-3 ratio in cord blood serum and hay fever or allergic rhinitis and aeroallergen sensitization at 6 and 10 years' follow-up.[177]

In a 2010 study of 1162 children from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort study who were followed for 18 months, no significant associations were found between maternal plasma phospholipid DHA, EPA, ALA, total n-3 LC-PUFA or n-6/n-3 ratio measured at 26-28 weeks of pregnancy and allergic sensitization or rhinitis.[185]

Observational study subgroup analyses

A 2006 study of 265 mother-infant pairs in Netherland stratified its analysis by presence or absence of allergy in mothers. The study found no relationship between breast milk n-3 fatty acid concentration (measured at 3 months postpartum) and sensitization (defined as specific IgE higher than 0.35 IU/mL to any of measured allergens) in children with maternal history of allergy at 4 years of age. However in children of mothers with no allergy, alpha-linolenic acid (18:3n-3) and ALA/LA ratio was positively associated with sensitization at 4 years of age ($p<0.05$).[175]

Table 24. RCTs for allergies

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
D'Vaz et al., 2012[142] Study name: IFOS Study dates: 2005-2009 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies, None, Manufacturer supplied product Original, same study, or follow-up studies: Meldrum, 2012[140]	Study Population: Pregnant women with allergies Infants enrolled 420 Infants completers 323 Pregnant age: Placebo: 33.2 Fish Oil: 32.5 (Placebo: 4.2 Fish Oil: 4.8) Infant age: Term (39.3 weeks gestation) Race of Mother: NR (100)	Inclusion Criteria: Maternal: Pregnant History of doctor diagnosed asthma or allergic rhinitis Skin prick positive to at least one allergen Exclusion Criteria: Maternal: Smoking Auto-immune disease Pre-existing medical conditions other than asthma High-risk pregnancy Seafood allergy Fish eaten more than three times per week Fish oil supplementation already taken (in excess of 1000 mg per day) Exclusion from data analysis criteria due to protocol deviations: Pre-term delivery (gestation <36 weeks) Infant with congenital abnormalities or significant disease not related to intervention	Start time: Infants Birth Duration: Infants 6 months Arm 1: Placebo Description: Olive oil Manufacturer: Ocean Nutrition, Ltd Dose: 650 mg olive oil Blinding: Randomization was completed by external staff via computer software using an unpredictable allocation sequence, stratified according to maternal and paternal atopic history and parity. Mothers and study personnel were unaware of the group allocation. Maternal conditions Maternal allergies 100 Arm 2: Fish oil group Manufacturer: Ocean Nutrition Ltd. Purity Data: fatty acid composition remained unchanged over the study period Dose: 1 capsule contents, to be administered orally, prior to feeding in the morning Maternal conditions DHA: 280 mg EPA: 110 mg Maternal allergies 100	Outcome: allergic disease (any of IgE mediated food allergy, eczema or asthma) (Primary) Follow-up time: 12 months Arm 1: 66/167 (39.52%) Arm 2: 59/156 (37.82%) Outcome: food allergy (Primary) Follow-up time: 12 months Arm 1: 25/167 (14.97%) Arm 2: 19/156 (12.18%)
Dunstan et al., 2003[50] Study name: Dunstan Study dates: 1999-2001 Study design: Trial randomized parallel Location: Australia Funding source / conflict:	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 98 Pregnant withdrawals 15 Pregnant completers 83 Pregnant age: NR (NR) NR Race of Mother: NR	Inclusion Criteria: All women had a history of physician-diagnosed allergic rhinitis and/or asthma and 1 or more positive skin prick tests to common allergens (house dust mite; grass pollens; molds; and cat, dog, and cockroach extracts)	Start time: Pregnant 20 weeks of gestation Duration: Pregnant till delivery Arm 1: Placebo group Description: 46 women allocated and received placebo-olive oil Manufacturer: Pan Laboratories, Moorebank, NSW, Australia Active ingredients: 66.6% n-9 oleic acid Dose: 4 (1-g) capsules of olive oil per day Blinding: Randomization and allocation of capsules	Outcome: food allergy (Secondary) Follow-up time: 1 year Arm 1: 5/43 (11.63%) Arm 2: 3/40 (7.5%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Government Study follow-up: 1 year Original, same study, or follow-up studies: Dunstan, 2008[44]; Meldrum, 2015[51]	(100)	Exclusion Criteria: Women were ineligible for the study if they smoked; if they had other medical problems, complicated pregnancies, or seafood allergy; or if their normal dietary intake exceeded 2 meals of fish per week.	occurred at a different center separate from the recruitment of participants. Capsules were administered to the participants by someone separate from those doing the allocation. The capsules in the 2 groups were image-matched. Total N-3: <1% n-3 PUFAs Arm 2: Fish oil group Description: 52 women were randomized to receive fish oil Manufacturer: Ocean Nutrition, Halifax, Nova Scotia, Canada Dose: 4 (1g) fish oil capsules per day _x001E__x0007__x0005__x0015__x0013__x0007__x001E__x0013__x000F_ DHA: 56.0% EPA: 27.7% Total N-3: 3.7 g	
Furuhjelm et al., 2009[173] Study name: NR Study dates: 2003-2006 Study design: Trial randomized parallel Location: Sweden Funding source / conflict: Industry, Multiple foundations and Societies Study follow-up: 1 year Original, same study, or follow-up studies: Furuhjelm, 2011[172]	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 145 Pregnant withdrawals 28 Pregnant completers 117 Infants enrolled 145 Infants withdrawals 28 Infants completers 117 Mother age: Intervention: 31.1 years (at delivery) Placebo: 31.7 years (at delivery) (Intervention: 4.1 years (at delivery) Placebo: 3.9 years (at delivery)) NR Race of Mother: NR (100) Baseline biomarker information: Treatment -	Inclusion Criteria: a family history of past of current allergic symptoms in at least one parent or older child. Exclusion Criteria: Mothers with an allergy to soy or fish or undergoing treatment with anticoagulants or commercial w-3 fatty acid supplements	Start time: Pregnant 25 weeks of gestation Duration: Pregnant 15 weeks (i.e., until delivery) Arm 1: Placebo Description: 75 women received soy oil as placebo Manufacturer: Pharma Nord Active ingredients: w-6 PUFA LA (58%, 2.5 g / day), a small amount (6%, 0.28 g / day) of the w-3 PUFA LNA and 36 mg a-tocopherol Viability: alpha-tocopherol was given as an antioxidant, a necessary ingredient according to the standard procedure of the manufacturer to assure the durability of the oil. Dose: nine soy oil capsules a day N-6 N-3: 9 Arm 2: w3 group Description: 70 women are randomized into this group Brand name: Bio Marin capsules Manufacturer: Pharma Nord, Vejle, Denmark Active ingredients: 23 mg alpha-tocopherol Viability: alpha-tocopherol was given as an antioxidant, a necessary ingredient according to the	Outcome: Food Allergy (Primary) Follow-up time: 12 months Arm 1: 10/65 (15.38%) Arm 2: 1/52 (1.92%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	mean(sd) mol % EPA- 1.3 (0.8) DHA- 5.5 (1.1) AA- 9.2 (1.7) AA/EPA- 9.1 (4.3) Placebo - mean(sd) mol % EPA- 1.2 (0.6) DHA- 5.4 (1.2) AA- 8.6 (1.5) AA/EPA- 8.6 (4.0) Baseline Omega-3 intake: DHA - 0.2g/day EPA- 0.1g/day		standard procedure of the manufacturer to assure the durability of the oil. Dose: nine 500-mg capsules, once daily DHA: 1.1g EPA: 1.6g N-6 N-3: <0.1	
Furuhjelm et al., 2011[172] Study name: NR Study dates: 2003-2007 Study design: Trial randomized parallel Location: Sweden Funding source / conflict: Industry, Multiple foundations and Societies Study follow-up: 2 years Original, same study, or follow-up studies: Furuhjelm, 2009[173]	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 145 Pregnant withdrawals 28 Pregnant completers 117 Infants enrolled 145 Infants withdrawals 28 Infants completers 117 Pregnant age: NR (NR) NR Race of Mother: NR (100)	Inclusion Criteria: family history of current or previous allergic symptoms, i.e. bronchial asthma, eczema, allergic food reactions, itching and running eyes and nose at exposure to pollen, pets or other known allergens. Exclusion Criteria: Allergy to soya or fish, treatment with anticoagulants or omega-3 fatty acid supplements.	Start time: Pregnant 25 weeks of gestation Duration: Pregnant 15 weeks (i.e., until delivery) Arm 1: Placebo Description: soya bean oil Manufacturer: Pharma Nord, Vejle, Denmark Active ingredients: 58% linoleic acid (LA), 2.5 g/day Viability: the antioxidant a-tocopherol (placebo: 36 mg/day) to assure the stability of the oil Dose: nine capsules a day Blinding: The mothers, as well as the staff handling clinical and laboratory follow-up, were blinded to group allocation, and the mothers were identified by their study number only. ALA: 6%, 0.28 g/day Arm 2: w-3 group Description: w-3 fatty acids Viability: the antioxidant a-tocopherol (w-3 group: 28 mg/day) to assure the stability of the oil Dose: nine capsules a day DHA: 25% DHA, 1.1 g/day EPA: 35% EPA, 1.6 g/day	Outcome: any food reactions (Primary) Follow-up time: 2 years Arm 1: 16/65 (24.62%) Arm 2: 6/54 (11.11%)
Linnamaa et al., 2010[79] Study name: NR Study dates: 2004-2008 Study design: Trial	Study Population: Healthy infants Healthy pregnant women Infants enrolled 314 Infants withdrawals 137 Infants completers 177	Inclusion Criteria: All pregnant mothers <16 weeks of gestation Exclusion Criteria: Sick children and those born prematurely who required	Start time: Pregnant 8th to 16th weeks of pregnancy and then continued Infants when exclusive breastfeeding ended Duration: Pregnant until the end of the exclusive breastfeeding period Infants until 2 years of age	Outcome: positive egg skin test (Secondary) Follow-up time: 12 months Arm 1: 18/104 (17.31%) Arm 2: 14/98 (14.29%) Follow-up time: 24 months Arm 1: 7/87 (8.05%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
randomized parallel Location: Finland Funding source / conflict: Government, Multiple foundations and Societies	 Mother age: NR (NR) NR Race of Mother: NR (NR)	more intensive care (n=8)	Arm 1: Controls Description: Olive oil Manufacturer: Santagata Luigi s.r.l., Genova, Italia Dose: 3 g/day for mothers, 1 mL/day for infants Blinding: NR "double-blind" ALA: 0 DHA: 0 EPA: 0 EPA-DHA: 0 AA: 0 Total N-3: 0 Other dose 1: LA (18:2n-6): 9 weight% of total Arm 2: Intervention Description: Blackcurrant seed oil Manufacturer: Aromtech Ltd, Tornio, Finland Dose: 3 g/day for mothers, 1 mL/day for infants ALA: 14 weight% of total DHA: 0 EPA: 0 EPA-DHA: 0 AA: 0 Total N-3: 17 weight% of total Other dose 1: SDA: 3 weight% of total	Arm 2: 4/79 (5.06%) Follow-up time: 3 months Arm 1: 1/126 (0.79%) Arm 2: 1/112 (0.89%)
Manley et al., 2011[118] Study name: DINO Study dates: 2001-2007 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies, Manufacturer supplied product, Some authors serve on scientific advisory boards for corporations	Study Population: Preterm infants Breast-feeding women Infants enrolled 657 Infants completers 614 Lactating age: Intervention: 29.9 (5.8) Placebo: 30.2 (5.4) Infant age: 4 days (median) Race of Mother: NR (100%)	Inclusion Criteria: Infants born before 33 weeks' gestation, within 5 days of the infant commencing any enteral feedings. Exclusion Criteria: major congenital or chromosomal abnormalities, from a multiple birth in which not all live-born infants were eligible, enrolled in other trials of fatty acid supplementation, or mother with contraindication to fish oil	Start time: Infants Within 5 days (or less) of starting enteral feeding Duration: Infants NR Arm 1: Standard DHA diet Description: Soy bean oil Manufacturer: Clover Corporation Dose: 6 capsules per day Maternal conditions Infant conditions Current smoker 25% during pregnancy Other maternal conditions 1arm_1_maternal_conditions_other1 Other maternal conditions 10 Birth by C-section: 69% Pre-term birth 100% Low birth weight 18.6%	Outcome: hay fever (Secondary) Follow-up time: 12 months Arm 1: 13/249 (5.22%) Arm 2: 5/232 (2.16%) Follow-up time: 12 or 18 months Arm 1: 21/244 (8.61%) Arm 2: 8/231 (3.46%) Follow-up time: 18 months Arm 1: 10/311 (3.22%) Arm 2: 7/292 (2.4%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study follow-up: 18 months Original, same study, or follow-up studies: Smithers, 2008[104]; Makrides, 2009[116]; Smithers, 2010[117]; Collins, 2011[105]; Atwell, 2013[119]; Collins, 2015[120]			Arm 2: High DHA Description: Tuna fish oil Manufacturer: Clover Corporation Dose: 6 500-mg DHA-rich tuna oil capsules per day Maternal conditions Infant conditions DHA: DHA to achieve a breast milk concentration that was 1% of total fatty acids Other dose 1: If supplementary formula was required, infants were given a high- DHA preterm formula (approximately 1.0%DHAand 0.6% AA). Current smoker 25% during pregnancy Other maternal conditions 1arm_2_maternal_conditions_other1 Other maternal conditions 10 Birth by C-section: 68.3% Pre-term birth 100% Low birth weight 18.9%	
Marks et al., 2006[168] Study name: CAPS Study dates: 1997-2004 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies Study follow-up: 5 years Original, same study, or follow-up studies: Mihrshahi, 2003[166]; Mihrshahi, 2004[167]; Brew, 2015[165]; Toelle, 2010[169]	Study Population: Pregnant women with allergies Pregnant enrolled 616 Pregnant withdrawals 100 Pregnant completers 516 Infants completers 516 Race of Mother: NR	Inclusion Criteria: pregnant women whose unborn children were at increased risk of developing asthma because 1 or more parents or siblings had asthma or wheezing Exclusion Criteria: with a pet cat at home, strict vegetarians, women with a nonsingleton pregnancy, and infants born earlier than 36 weeks of gestation. Infants had birth weights less than 2.5 kg, significant congenital malformations, or other significant neonatal disease.	Start time: Infants from the time the child started bottle-feeding, or to solid foods from age 6 months Duration: NR Arm 1: Diet control Description: polyunsaturated oils and spreads, containing 40% w6 FA, and Sunola oil capsules Manufacturer: Crisco-Meadow Lea Foods Inc, Sydney, Australia Blinding: The approach to blinding participants and research staff is described in this article's Online Repository at www.jacionline.org. Arm 2: Active Description: canola-based oils and spreads, which are low in n-6 fatty acids, and tuna oil capsules, which contain n-3 fatty acids.	Outcome: any atopy (from skin prick test) (Secondary) Follow-up time: 5 years Arm 1: 108/249 (43.37%) Arm 2: 109/267 (40.82%) Outcome: rhinitis (Secondary) Follow-up time: 5 years Arm 1: 102/249 (40.96%) Arm 2: 111/267 (41.57%)
Mihrshahi et al., 2003[166]	Study Population: Pregnant women with	Inclusion Criteria: At least one parent or sibling with	Start time: Infants initiation of bottle feeding or 6 months of age	Outcome: any atopy Follow-up time: 18 months

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study name: CAPS Study dates: 1997-2002 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies, Manufacturer supplied product Study follow-up: 18 months Original, same study, or follow-up studies: Mihrshahi, 2004[167]; Mihrshahi, 2006[168]; Brew, 2015[165] Toelle, 2010[169]	allergies Pregnant enrolled 616 (all 4 arms) Pregnant withdrawals 62 Pregnant completers 554 Pregnant age: 28.5 (5.3) Race of Mother: NR (96.9%) Other race/ethnicity (Aboriginal 3.1%)	symptoms of asthma as assessed by screening questionnaire, Reasonable fluency in English, Telephone at home, Reside within 30 km from center of recruitment Exclusion Criteria: Pet cat at home, Families on strict vegetarian diet, Multiple births, Babies born earlier than 36 weeks gestation, with congenital malformations or other serious disease, or requiring major surgery or hospitalization for greater than 1 week	Duration: Infants NR Arm 1: Diet Control/HDM control or intervention Brand name: Sunola oil Manufacturer: Clover Corporation Arm 2: Dietary intervention/HDM control or intervention Description: 500mg n-3 rich tuna fish oil supplement Manufacturer: Clover Corporation DHA: 76-128 mg EPA: 18-30 mg Other dose 1: based on age and fluid intake	Arm 1: 58/275 (21.1%) Arm 2: 51/279 (18.2%)
Palmer et al., 2012[54] Study name: DOMInO Study dates: 2006-2009 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Industry, Government, Manufacturer supplied product Original, same study, or follow-up studies: Makrides, 2010[35]; Smithers, 2011[53]; Zhou,	Study Population: Pregnant women with allergies Pregnant enrolled 706 Pregnant withdrawals 25 Pregnant completers 681 Infants enrolled 706 Infants withdrawals 25 Infants completers 681 Pregnant age: Treatment: 29.6 Placebo: 29.5 (Treatment: 5.7 Placebo: 5.6) NR Race of Mother: NR (100)	Inclusion Criteria: Included if the unborn baby had a mother, father, or sibling with a history of any medically diagnosed allergic disease (asthma, allergic rhinitis, eczema) and they were enrolled from the Women's and Children's Hospital or Flinders Medical Centre in Adelaide. Exclusion Criteria: NR	Start time: Pregnant 21 weeks of gestation Infants 21 weeks of gestation Duration: Pregnant until delivery Infants till delivery Arm 1: Placebo Description: 338 women assigned to control supplements-vegetable oil capsules Dose: three 500 mg vegetable oil capsules daily Blinding: All capsules were similar in size, shape, and color. Neither the women nor the research staff were aware of the treatment allocated. Arm 2: n-3 LCPUFA group Description: 368 women assigned to fish oil concentrate Brand name: Incromega 500 TG Manufacturer: Croda Chemicals, East Yorkshire, UK Dose: e three 500 mg capsules daily DHA: 800mg	Outcome: food allergy with sensitization (Primary) Follow-up time: 1 year Arm 1: 11/338 (3.25%) Arm 2: 11/368 (2.99%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
2012[55]; Palmer, 2013[56]; Makrides, 2014 [57]			EPA: 100mg	
Palmer et al., 2013[56] Study name: DOMInO Study dates: 2006-2011 (allergy follow-up to Domino study) Study design: Trial randomized parallel Location: Australia Funding source / conflict: Industry, Government, Some authors serve on scientific advisory boards for corporations Study follow-up: 3 years Original, same study, or follow-up studies: Makrides, 2010[35]; Smithers, 2011[53]; Palmer, 2012[54]; Zhou, 2012[55]	Study Population: Children with family history of allergy Pregnant enrolled 706 Pregnant completers 638 Infants enrolled 706 Infants completers 638 Pregnant age: DHA: 28.9 Control: 28.9 (DHA: 5.7) Control: 5.6) Infant age: Birth Race of Mother: NR (100)	Inclusion Criteria: Women whose infants had a parent or sibling with a history of any medically diagnosed allergic disease (asthma, allergic rhinitis, eczema) Exclusion Criteria: Already taking a prenatal supplement with DHA Fetus had a known major abnormality, Bleeding disorder in which tuna oil was contraindicated, Taking anticoagulant therapy A documented history of drug or alcohol abuse, Participating in another fatty acid trial, Unable to give written informed consent, or English was not the main language spoken at home	Start time: Pregnant <21 weeks gestation Duration: Pregnant to term Arm 1: Control Description: vegetable oil Dose: 3 500-mg vegetable oil capsules per day Blinding: This was a double-blinded study; all capsules were similar in size, shape and color Arm 2: Fish oil Brand name: Incromega 500 TG, Manufacturer: Croda Chemicals, East Yorkshire, England Dose: 3 500-mg capsules per day DHA: 800 mg per day EPA: 100 mg per day	Outcome: allergic rhinitis (Primary) Follow-up time: 3 years Arm 1: 20/338 (5.92%) Arm 2: 18/368 (4.89%) Outcome: food allergy (Primary) Follow-up time: 3 years Arm 1: 14/338 (4.14%) Arm 2: 18/368 (4.89%)
Toelle et al., 2010[169] Study name: CAPS Study dates: 1997-2008 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Manufacturer supplied product	Study Population: Healthy infants Pregnant enrolled 616 Pregnant completers Infants enrolled 616 Infants completers 450 Pregnant age: 28.5 years (5.3 years) Race of Mother: NR (NR)	Inclusion Criteria: Pregnant women whose unborn children were at high risk of developing asthma because of a family history (at least one parent or sibling with symptoms of asthma as assessed by screening questionnaire), reasonable fluency in English, telephone at home, reside within 30 km from center of recruitment	Start time: Infants birth Duration: Infants 5 years Arm 1: Control Description: Low-n3 capsules and cooking oils Brand name: Sunola Active ingredients: Capsules: 7% n-6 FA, 82% monounsaturated FA, 9% saturated FA, and 1.7% minor FA; cooking oils: 40% n-6 FA, 20% n-9 FA Dose: Designed to maintain the current n-3 to n-6 ingested FA ratio in the general population (1:15 to 1:20) Blinding: Similar appearance Total N-3: Capsules: 0.3%; cooking oil: 1.2%	Outcome: atopy (Primary) Follow-up time: 8 yrs Arm 1: 99/220 (45.0%) Arm 2: 104/230 (45.1%) Outcome: rhinitis (Secondary) Follow-up time: 8 yrs Arm 1: 65/220 (29.6%) Arm 2: 70/230 (30.4%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study follow-up: 8 years Original, same study, or follow-up studies: Mihrshahi, 2003[166]; Mihrshahi, 2004[167]; Mihrshahi, 2006[168]; Brew, 2015[165]		Exclusion Criteria: Pet cat at home, families on strict vegetarian diet, multiple births, babies born earlier than 36 weeks gestation, birth weight below 2.5 kg, babies requiring surgery, babies requiring hospitalization for more than 1 week, babies with significant neonatal disease, babies with congenital malformations	Arm 2: Omega 3 supplementation Description: High n-3 FA capsules and cooking oils Active ingredients: Capsules: 6% n-6 polyunsaturated FA, 24% monounsaturated FA, 28% saturated FA, and 5% minor FA; cooking oil: 6% n-6 FA, 40% n-9 FA Blinding: Similar appearance N-6 N-3: 5:1 Total N-3: Capsules: 37%; cooking oil: 6%	

Table 25. Observational studies for allergies

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Notenboom, et al., 2011[179] Outcome domain: Allergies Study name: KOALA Birth Cohort Study Study dates: Recruitment from October 2000 onwards and Followup: 6-7 years Study design: Observational prospective Location: Netherlands Funding source / conflict: Industry, Government, Multiple foundations and Societies Follow-up: 3 - 84 months	Study Population: Healthy infants Healthy pregnant women Infants enrolled 1275 Infants completers 1253 (samples for 815) Mother age: 32.6 (3.8) Race of Mother: White European (Dutch 96.3%)	Inclusion Criteria: Conventional participants: participation in ongoing study of pelvic girdle pain Alternative participants: frequented locations associated with organic diet and similar lifestyles Subsample: participants recruited from January 2002 onwards who consented to biosampling. Exclusion Criteria: Current multiple pregnancy n=9 Prematurity n=15 Perinatal infant death n=2 Down syndrome n=4 No response after birth n=51	Adjustments: Adjusted for recruitment group, maternal age, maternal ethnicity, maternal education level, maternal smoking during pregnancy, parental history of atopy, term of gestation, season of birth, gender, birth weight, mode of delivery, exposure to environmental tobacco, presence of older siblings and sibling atopy, breastfeeding, child day care, and pets at home
Nwaru, et al., 2012[180] Outcome domain: Allergies Study name: Finnish Type 1 Diabetes Prediction and Prevention Nutrition Study Study dates: Infants recruited between 20 October 1997 and 29 February 2004; Followup to 5 years of age Study design: Observational prospective Location: Finland Funding source / conflict: Government, Multiple foundations and Societies Follow-up: 5 years	Study Population: NR Pregnant enrolled NR Pregnant completers 3523 Infants enrolled 3253 Infants completers 2441 Infant age: birth Race of Mother: White European (100%)	Inclusion Criteria: Newborn infants with human leucocyte antigen (HLA)- conferred susceptibility to type 1 diabetes recruited from three university hospitals in Finland Exclusion Criteria: Infants with severe systemic disease or anomalies, or both parents non-Caucasian	Adjustments: Sex of child, hospital of birth, duration of gestation, maternal age at delivery, maternal basic education, maternal smoking during pregnancy, mode of delivery, number of siblings at the time of the child's birth, parental asthma, parental allergic rhinitis, pets at home by 1 year of age. A second adjusted model was computed for the FA in which potentially confounding nutrients, vitamin C, Zn, Se, vitamin D and vitamin E were included as additional covariates
Pike, et al., 2012[186] Outcome domain: Allergies Study name: Southampton Women's Survey Study dates: 2006-2010	Study Population: Healthy infants Pregnant enrolled Infants enrolled 1485 Infants completers 865 Pregnant age: 30.4 (3.8)	Inclusion Criteria: mothers and children in the Southampton Women's Survey Exclusion Criteria: Infants born = 35 weeks' gestation were excluded to avoid abnormal lung development associated with prematurity	Adjustments: Child's age, maternal asthma, and paternal rhinitis for airway inflammation outcome

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Study design: Observational prospective Location: UK Funding source / conflict: Government, Some authors serve on scientific advisory boards for corporations Follow-up: Birth to 6 years	Race of Mother: NR (100)		
Standl, et al., 2014[177] Outcome domain: Allergies Study name: LISAplus Study dates: Recruitment 1997-1999 Study design: Observational prospective Location: Germany Funding source / conflict: Government Follow-up: 10 years	Study Population: Healthy infants Infants enrolled 436 Infants completers 243 Mother age: 32.7 (3.9) NR Infant age: Birth (NR) NR Race of Mother: NR (100)	Inclusion Criteria: NR Exclusion Criteria: Neonates displaying at least one of the following criteria: preterm birth (maturity <37 gestational weeks), low birth weight (<2,500 g), congenital malformation, symptomatic neonatal infection, antibiotic medication, hospitalization or intensive medical care during neonatal period. In addition, newborns from mothers with immune-related diseases (autoimmune disorders, diabetes, hepatitis B), on long-term medication or who abuse drugs and/or alcohol, and newborns from parents with a nationality other than German or who were not born in Germany, were excluded.	Adjustments: Parental education, sex, time of follow-up (2 yr, 6 yr or 10 yr for eczema; 6 yr and 10 yr for asthma, hay fever/allergic rhinitis and aeroallergen sensitization), age, maternal age at birth, parental atopy, total sum of fatty acids
Thijs, et al., 2011[178] Outcome domain: Allergies Study name: KOALA Birth Cohort Study Study dates: 2003 Study design: Observational prospective Location: Netherlands Funding source / conflict: Government, None Follow-up: 2 years	Study Population: Healthy pregnant women Pregnant enrolled 312 Pregnant completers 304 Infants enrolled 312 Infants completers 304 Pregnant age: 33.3 (3.9) NR Race of Mother: NR (100)	Inclusion Criteria: availability of complete baseline data from the 34 weeks pregnancy questionnaire and availability of a breast milk sample. Exclusion Criteria: NR	Adjustments: Recruitment group, maternal age, maternal education, infant's gender, number of older siblings and their atopic history, parental atopic history, maternal smoking during pregnancy and/or smoking in presence of the infant, place of birth, season of breast milk collection, duration and exclusivity of breastfeeding, maternal n-3 fatty acids supplement use, maternal probiotic supplement use, maternal probiotic dairy use, maternal antibiotic use during lactation, infant's antibiotic use, vaccination schedule, dampness of the home, pet animals in the home.

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Wijga, et al., 2006[175] Outcome domain: Allergies Study name: The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study Study dates: 1995-2000 Study design: Observational prospective Location: Netherlands Funding source / conflict: Industry, Government Follow-up: 4 years	Study Population: NR Pregnant enrolled 276 Pregnant withdrawals 11 Pregnant completers 265 Infants enrolled 276 Infants withdrawals 11 Infants completers 265 Pregnant age: 31.0 (3.9) NR Race of Mother: NR (100)	Inclusion Criteria: Mothers reporting at least 1 of the following: (a history of) asthma, current hay fever, current allergy for pets, or current allergy for house dust or house dust mite were defined as allergic, and mothers reporting that they had none of these were defined as nonallergic. Exclusion Criteria: NR	Adjustments: Sex, number of older siblings, maternal age, maternal smoking during pregnancy, and maternal body mass index before pregnancy
Yu, et al., 2015[185] Outcome domain: Allergies Study dates: Participants recruited between June 2009 and September 2010 Study design: Observational prospective Location: NR Funding source / conflict: Industry, Government	Study Population: Healthy infants Healthy pregnant women Infants enrolled 1162 Infants completers 960 Pregnant age: NR (NR) NR Race of Mother: NR (100%)	Inclusion Criteria: Participants were mother–child pairs in the Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort. Exclusion Criteria: NR	Adjustments: In the models, we adjusted for maternal characteristics including maternal age, ethnicity, gravidity, education level and energy intake. The same was done for infant characteristics including sex, birth weight, gestational age, duration of breast-feeding, family history of allergic diseases (which includes allergic rhinitis, eczema and asthma in first-degree relatives of the children (i.e. father, mother and/or sibling), exposure to environmental tobacco smoking, child day care attendance and having a cat or dog at home up to 18 months of age.

Respiratory Illness (Including Asthma)

Key Points

- In six prenatal n-3 interventions and two follow-up studies, maternal n-3 FA supplementation (DHA + EPA, varying doses) had no consistent significant effect on respiratory illness. Six studies found no significant effect on risk for respiratory outcomes; one study found a decreased risk for asthma in the treatment group after 16 years and another found lower risk of respiratory symptoms at 18 months, though not at earlier time points. In addition, meta-analysis of three of the RCTs (n=1315) with 12-month follow-up of wheeze outcomes yielded an insignificant summary effect.
- In three postnatal n-3 interventions and four follow-up studies, infant n-3 FA supplementation (DHA or DHA+EPA, varying doses) had no robust effect on respiratory outcomes. One study found a lower prevalence of wheeze at 18 months in the treatment group; however, this finding no longer remained at the 3- or 5-year follow-up. Another study found a higher prevalence of wheeze at 8 years of age in the treatment group. Pooled analysis of the three RCTs (n=1693) with 18-month follow-up asthma outcomes yielded a summary effect that was not significant.
- One biomarker study found higher levels of DHA and DHA + DPA + EPA at 6 months were associated with reduced risk of recurrent wheeze in the first 12 months.
- Four of five prospective observational studies found an inverse association between n-3 FA (measured through maternal dietary intake or breast milk composition) and risk of respiratory outcomes such as wheeze and asthma. The n-3 FA exposures in these studies included ALA, DHA, EPA, EPA+DHA, total n-3 PUFA, and n-3/n-6 LCPUFA. Four of five prospective observational studies of n-3 FA biomarkers (in cord blood or maternal blood sample) found no relationship between n-3 FA biomarkers and risk of respiratory illness, with only one study reporting higher maternal EPA, DHA, and total n-3 FAs being associated with reduced risk of non-atopic persistent/late wheeze.

Description of Included Studies

Asthma/wheeze is an additional outcome of interest that was not included in the original review. A total of 15 eligible studies (comprising of 9 RCTS and 6 follow-up studies) and 10 observational studies were included.

Randomized Controlled Trials

Prenatal maternal interventions/exposures

Eight studies (6 RCTs and 2 follow-up studies) evaluated prenatal maternal n-3 FA interventions (see Table 26). [50, 54, 56, 58, 59, 88, 172, 187] All interventions were exclusively during the prenatal period with the mother stopping supplementation at birth, except for one that continued into breastfeeding.[172] Most of the trials recruited pregnant women whose infants were at high risk for atopy (e.g., parent diagnosis of allergy, or sibling with diagnosed or suspected allergy), except for three that recruited healthy pregnant women.[58, 59, 187] All the studies compared DHA and DHA+EPA n-3 FAs with placebo.

DHA, DHA Plus EPA Versus Placebo

Olsen (2008), followed up with a population-based sample of 533 pregnant women in Denmark randomized to 2.7g marine n-3 PUFA, olive oil, or no oil daily from 30 weeks until term.[187] Medical records were available for 528 children for a 16-year follow-up. The fish oil group was less likely to have occurrences of asthma (HR 0.37; 95% CI 0.15, 0.92) and allergic asthma (HR 0.13; 95% CI 0.03, 0.60) compared to the olive oil group.

Dunstan (2003) randomized 98 pregnant, atopic Australian women to fish oil (3.7g n-3 PUFA, 56.0% DHA, 27.7% EPA) or olive oil (4g) daily from 20 weeks gestation until delivery.[50] A total of 83 mothers and their children completed the 12-month follow-up. No significant differences were seen in respiratory clinical outcomes, including recurrent wheeze, persistent cough, or diagnosed asthma, between the fish oil and control groups.[50]

In the Salmon in Pregnancy Study (SiPS), 123 pregnant women in the UK were randomized to the salmon group (300g salmon / week) or control group (no changes in diet) from 20 weeks gestation until delivery.[88] Clinical outcomes were available for 86 infants at 6 months. No differences were seen in the incidence of wheeze, bronchiolitis, or chest infections between the salmon and control groups.[88]

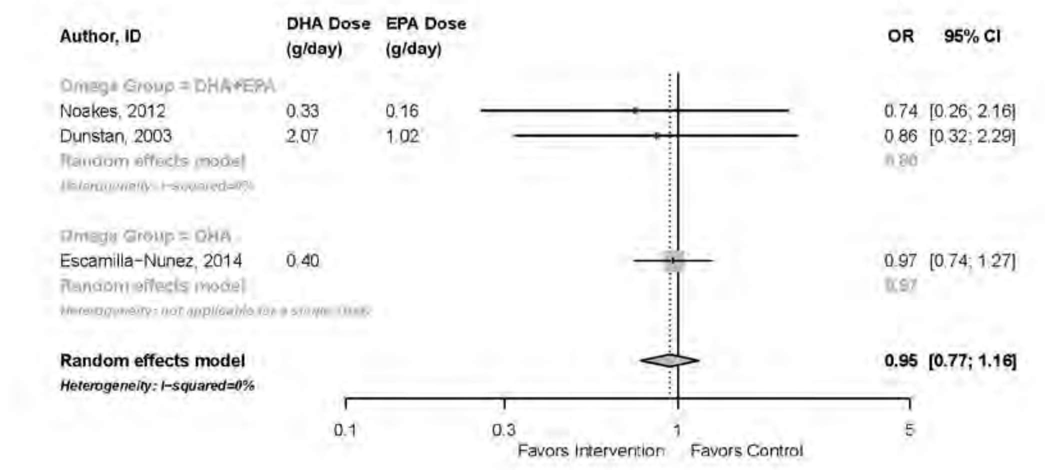
Another study randomized 1,094 pregnant women in Mexico to n-3 FA supplementation (400 mg DHA) or placebo (corn and soy oil) daily from mid-pregnancy (18-22 weeks gestation) until delivery.[59] A total of 973 women completed the treatment. In crude analyses of respiratory symptoms up to age 18 months, DHA supplementation was associated with lower risk of three respiratory symptoms : "phlegm with congestion and/or nasal discharge," fever with phlegm and congestion and/or nasal discharge," and "wheezing with fever" (IRR 0.74; 95% CI 0.63,0.87, IRR 0.52; 95% CI 0.38, 0.70, and IRR 0.43, 95% CI 0.21, 0.83, respectively). The authors reported significant interactions between the treatment group and the mother's atopic status on a number of respiratory symptoms, indicating a greater protective effect of DHA supplementation in children of atopic mothers. An earlier study of the same cohort examined morbidity data for 849, 834, and 834 infants at 1, 3 and 6 months, respectively.[58] The DHA group and placebo groups showed no differences at 1, 3, or 6 months for cough, wheezing, or difficulty breathing. The authors reported lower occurrence of cold (defined as any of the following: cough, phlegm, nasal congestion, nasal secretion) in the DHA group compared to the placebo group at 1 and 3 months (37.6% vs 44.6%; $P < .05$; and 37.8 vs 44.1; $P > .05$, respectively).

In a subset of the Docosahexaenoic Acid (DHA) to Optimise Mother Infant Outcome (DOMInO) trial, 706 pregnant Australian women whose child was at high familial risk for allergy were randomized to receive n-3 LCPUFA (800 mg DHA + 100 mg EPA) or placebo (vegetable oil) from 21 weeks gestation until delivery.[54, 56] A 1-year follow-up was completed with 706 infants, but outcomes for respiratory manifestations did not differ between treatment groups.[54] Asthma with sensitization was rare during the first 3 years of life (6% (SD 1.8) in the n-3 LCPUFA group and 5% (SD 1.6) in the placebo group) with no differences between treatment groups (Fisher's exact, p=1.00) .[56]

One RCT randomized 145 pregnant women in Sweden to daily n-3 FA (1.6g EPA + 1.1g DHA) or placebo (soy oil) supplementation from the 25th gestational week through the exclusive breastfeeding period (average 3-4 months). In a follow-up study with 143 infants, no differences were observed in cumulative asthma (with and without sensitization) through 24 months or current asthma (with and without sensitization) at 24 months between the treatment groups.[172]

Meta-analysis of three RCTs with a 12-month follow-up [50, 58, 88] showed no significant effect of DHA supplementation on risk of wheeze (OR 0.95 95% CI 0.77,1.13, I^2=0%)) (Figure 27).

Figure 27. Wheeze – Intervention given to pregnant women, 12-month follow-up



Postnatal maternal interventions/exposures

Three RCTs [118, 119, 142, 166] and four follow-up studies [167, 168],[169 119] evaluated n-3 FA interventions during the postnatal period. One of the RCTs evaluated preterm infants, and the remaining RCTs assessed term infants who were at genetic risk for allergy. All RCTs evaluated DHA or DHA+EPA.

DHA, DHA Plus AA, or DHA Plus EPA Versus Placebo

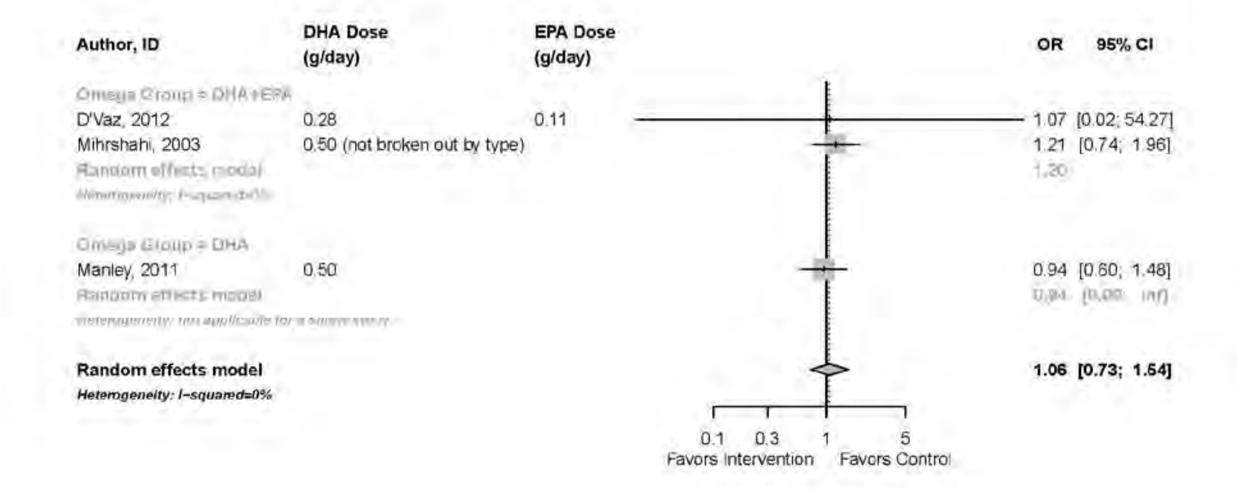
The DINO trial began the n-3 FA intervention during the postnatal breastfeeding period.[118, 119] This study randomized 657 preterm Australian infants (<33 weeks gestation) to receive a high-DHA diet (~1% DHA and 0.6% AA) or standard DHA diet (~0.35% DHA and 0.6% AA) through breast milk or formula until their expected delivery date. Data on asthma were available from a parent questionnaire for 481 infants at 12 months and 603 infants at 18 months. No differences were seen in asthma at either time point (adjusted or unadjusted for gestational age at delivery and gender).[118] Data on re-hospitalization were available for 648, 626, 615, and 611 at term, 4, 12, and 18 months' corrected age, respectively. No significant differences were observed between the high-DHA and standard DHA groups in prevalence of any hospitalization or the mean number of admissions for lower respiratory tract conditions such as wheezing and asthma, after 18 months.[119]

In the Infant Fish Oil Supplementation Study (IFOS), 420 infants at high risk for atopy were randomized to daily fish oil capsules (280 mg DHA + 110 mg EPA) or placebo capsules (olive oil) from birth to 6 months. No significant overall difference was observed in the prevalence of asthma at 12 months between the fish oil and placebo groups in unadjusted and adjusted analyses. Similarly, no differences were seen in wheeze or persistent coughing at 6 or 12 months.[142]

Four publications on infant n-3 supplementation came from the Childhood Asthma Prevention Study (CAPS).[166-168] In CAPS, 616 pregnant women (<36 weeks gestation) whose children were at high risk for developing asthma were randomized into 4 groups, including 2 with a dietary component (500 mg tuna fish oil supplement + canola-based oils and spreads or placebo supplement + polyunsaturated oils and margarines) from 6 months. In an 18-month follow-up with 543 infants (88% of the total sample size), the prevalence of wheeze was 9.8 percentage points lower and the prevalence of wheeze lasting longer than 1 week was 7.8 percentage points lower in the diet intervention group than in the control group (p=0.02 and p=0.04, respectively).[166] In a 3-year follow-up with 526 infants, no between-group differences were observed in the prevalence of asthma or wheeze, although mild cough was reduced by 7.1% and moderate cough by 4.1% in the diet group (p=0.03), with a larger reduction of 10.0% (95% CI 3.7, 16.4) in atopic cough when stratified by atopy.[167] In a 5-year follow-up with 516 children (84%), no significant differences were observed between the diet intervention and control groups for probable current asthma (RR=1.13; 95% CI 0.82, 1.57) or cough without cold (RR=1.42, 95% CI 0.97, 2.09).[168] In an 8-year follow-up with 450 children (73%), no significant differences were seen between the diet intervention and control groups for asthma (ARR=-4.8, 95% CI -12.5, 2.9). The prevalence of wheeze was higher in the diet intervention group compared with the diet control group (ARR=-8.6, 95% CI -16.8, -0.4).[169]

Meta-analysis of three RCTs with an 18-month follow-up [118, 142, 166] showed no significant effect for DHA supplementation on risk of asthma (OR [95% CI]= 1.06CI[0.73,1.54], I^2=0%) (Figure 28).

Figure 28. Asthma – Intervention given to infants, 18-month follow-up



Biomarker Studies

A single RCT examined associations between biomarkers and respiratory outcomes. Results suggest that elevated plasma levels of DHA (P = .027) and total n-3 PUFA (EPA + DPA + DHA) at 6 months were associated with a reduced risk of recurrent wheeze in the first 12 months of life (P = .028).[142]

Observational Studies

Ten observational studies evaluated the association between some measure of n-3 FA exposure and risk of respiratory illnesses (see Table 27).[175-177, 179, 182-184, 186, 188, 185]

All studies enrolled populations of healthy infants except for one[188] that enrolled infants who had high or moderate genetic risk of type I diabetes. All the studies were prospective cohort studies. The exposures included dietary intake of n-3 FA, [182, 183, 188] breast milk FA,[175, 184] and maternal biomarkers.[176, 177, 179, 185, 186] Included studies were published between 2004 and 2014.

n-3 FA Intake

We identified three studies that evaluated the association between dietary n-3 FA intake and risk of respiratory illness.[182, 183, 188]

Lumia (2011), in their analysis of 2679 infant-mother pairs from the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) Nutrition Study, examined the association between maternal dietary intake during the 8th month of pregnancy (assessed by a validated 181-item FFQ) and risk of asthma in offspring at 5 years of age. Enrolled infants had a high to moderate risk of type I diabetes. Low maternal intakes of ALA (lowest quartile vs. mid-half HR 1.70 [95% CI 1.14–2.53]) and total n-3-polyunsaturated fatty acids (PUFA) (HR 1.66 [95% CI 1.11–2.48]) during pregnancy were associated with an increased risk of asthma in the offspring, while a low intake of AA(HR 0.52 [95% CI 0.32–0.84)]) were associated with a decreased risk of asthma after adjusting for potential confounders. Adjusting for Vitamin D intake did not change the results.[188]

In a 2009 study of 763 healthy mother-infant pairs from the Osaka Maternal and Child Health Study in Japan, higher maternal intakes of ALA and DHA during pregnancy were independently associated with a reduced risk of wheeze in the offspring (adjusted ORs between extreme quartiles 0.52 [95% CI 0.28 to 0.97] and 0.37 [95% CI 0.15 to 0.91], respectively).[182] Maternal dietary intake was assessed with a validated diet history questionnaire during pregnancy, and wheeze was assessed by maternal report based on the International Study of Asthma and Allergies in Childhood for offspring at 16-24 months postpartum.

In a 2013 study of 1,354 healthy mother-infant pairs from the Kyushu Okinawa Maternal and Child Health Study (KOMCHS) in Japan, higher maternal intake of EPA (p for trend = 0.02) and EPA plus DHA (p for trend = 0.02) during pregnancy were associated with a reduced risk of wheeze in the offspring [183] Maternal dietary intake was assessed with a dietary history questionnaire during pregnancy while infantile wheeze was assessed by parental report based on the International Study of Asthma and Allergies in Childhood for offspring at 23-29 months postpartum.

n-3 FA Breastmilk Intake

Two studies examined the association between breastmilk n-3 fatty acids and the risk of respiratory illness.[175, 184]

A 2006 study of 265 mother-infant pairs in the Netherlands found an inverse association of breast milk DHA concentration (measured at 3 months postpartum) and n-3/ n-6 LCPFA ratio with risk of asthma in 4-year-old children of mothers with allergy($p<0.05$).[175]

A 2012 study of 580 infants in Spain found no significant association between colostrum n-3 LC-PUFA and risk of wheeze and lower respiratory tract infection during the first 14 months of life.[184] Colostrum was collected only for a random subsample (n=352) with n-3 LC-PUFA values imputed for the rest of the sample, however no differences were found in analyses with the colostrum subsample only.

n-3 FA Biomarkers

Five studies examined the association between n-3 FA biomarkers and children's risk of respiratory illness.[176, 177, 179, 185, 186]

A 2004 study of 1238 mother-infant pairs conducted in the UK found a positive association between the ratio of linoleic acid to ALA in cord blood and later-onset wheeze at 30-42 months of age (OR 1.30 95% CI 1.04-1.61; P = .019), after adjusting for potential confounders. However, the association was no longer significant after adjusting for multiple comparisons. No significant associations were observed for late pregnancy maternal plasma phospholipid fatty acid exposures (n=2945).[176]

In a 2011 study of 1275 children from the KOALA Birth Cohort Study who were followed for 6–7 years, no associations were found between maternal plasma phospholipid n-3 fatty acids measured at 34–36 weeks of pregnancy and risk of developing asthma or parentally reported wheeze.[179]

In a 2012 study of 1485 healthy mother-infant pairs from the Southampton Women's Survey in the UK who were followed for 6 years, the plasma phospholipid n-3 to n-6 FA ratio was not associated with childhood wheeze, airway inflammation, or childhood Forced Expiratory Volume (FEV_1, a measure of lung function). However, higher maternal EPA, DHA, and total n-3 FA were associated with reduced risk of non-atopic persistent/late wheeze (RR 0.57, 0.67 and 0.69, respectively; P = 0.01, 0.015, and 0.021, respectively). Also, maternal plasma phosphatidyl choline AA was positively associated with airway inflammation (P = 0.024).[186]

A 2014 study of 436 infants from the Munich LISAplus birth cohort study in Germany found no significant association between n-3 LC-PUFA or n-6/n-3 ratio in cord blood and risk of asthma at 6 and 10 year follow-up.[177]

In a 2010 study of 1162 children from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort study who were followed for 18 months, no significant associations were found between maternal plasma phospholipid DHA, EPA, ALA, total n-3 LC-PUFA or n-6/n-3 ratio measured at 26-28 weeks of pregnancy and wheezing.[185]

Observational study subgroup analyses

None of the studies reported subgroup analyses.

Table 26. RCTs for respiratory illness

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Atwell et al., 2013[119] Study name: DINO Study dates: 2001-2005 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies, Manufacturer supplied product, Some authors serve on scientific advisory boards for corporations Study follow-up: 18 months corrected age Original, same study, or follow-up studies: Smithers, 2008[104]; Makrides, 2009[116]; Smithers, 2010[117]; Manley, 2011[118]; Collins, 2011[105]; Collins, 2015[120]	Study Population: Preterm infants Infants enrolled 657 Infants completers 648 Infant age: birth Race of Mother: White European (90.5%) Other race/ethnicity (9.5%)	Inclusion Criteria: Infants were eligible if born before 33 weeks' gestation Exclusion Criteria: Infants in other trials of fatty acid supplementation, or with major congenital or chromosomal abnormalities, or maternal contraindication for tuna oil ingestion (allergy or coagulopathy) were excluded.	Start time: Infants birth Duration: Infants to 40 weeks' postmenstrual age (term) Arm 1: Standard DHA Description: Placebo/control group (soy oil) Dose: 6 soy oil capsules/ daily Blinding: capsules given to breastfeeding mothers or added to formula DHA: 0.35% in preterm formula Arm 2: High DHA Description: DHA maternal supplements or supplemented preterm formula Dose: 6 tuna oil capsules daily DHA: 900 mg in capsules or 1% infant formula	Outcome: one or more hospitalizations for lower respiratory conditions (Secondary) Follow-up time: 18 months Arm 1: 82/335 (24.48%) Arm 2: 72/322 (22.36%)
D'Vaz et al., 2012[142] Study name: IFOS Study dates: 2005-2009 Study design: Trial randomized parallel Location: Australia	Study Population: Pregnant women with allergies Infants enrolled 420 Infants completers 323 Pregnant age: Placebo: 33.2 Fish Oil: 32.5 (Placebo: 4.2 Fish Oil: 4.8)	Inclusion Criteria: Maternal: Pregnant History of doctor diagnosed asthma or allergic rhinitis Skin prick positive to at least one allergen Exclusion Criteria: Maternal: Smoking Auto-immune disease Pre-	Start time: Infants Birth Duration: Infants 6 months Arm 1: Placebo Description: Olive oil Manufacturer: Ocean Nutrition, Ltd Dose: 650 mg olive oil Blinding: Randomization was completed by external staff via computer software using an unpredictable allocation sequence, stratified according to maternal	Outcome: asthma (Primary) Follow-up time: 12 months Arm 1: 0/167 (0.0%) Arm 2: 0/156 (0.0%) Outcome: persistent cough (Primary) Follow-up time: 12 months Arm 1: 38/167 (22.75%) Arm 2: 42/156 (26.92%) Follow-up time: 6 months Arm 1: 27/167 (16.17%) Arm 2: 19/156 (12.18%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Funding source / conflict: Government, Multiple foundations and Societies, None, Manufacturer supplied product Original, same study, or follow-up studies: Meldrum, 2012[140]	Infant age: Term (39.3 weeks gestation) Race of Mother: NR (100)	existing medical conditions other than asthma High-risk pregnancy Seafood allergy Fish eaten more than three times per week Fish oil supplementation already taken (in excess of 1000 mg per day) Exclusion from data analysis criteria due to protocol deviations: Pre-term delivery (gestation <36 weeks) Infant with congenital abnormalities or significant disease not related to intervention	and paternal atopic history and parity. Mothers and study personnel were unaware of the group allocation. Maternal conditions Maternal allergies 100 Arm 2: Fish oil group Manufacturer: Ocean Nutrition Ltd. Purity Data: fatty acid composition remained unchanged over the study period Dose: 1 capsule contents, to be administered orally, prior to feeding in the morning Maternal conditions DHA: 280 mg EPA: 110 mg Maternal allergies 100	Outcome: recurrent wheeze (Primary) Follow-up time: 12 months Arm 1: 16/167 (9.58%) Arm 2: 21/156 (13.46%) Follow-up time: 6 months Arm 1: 27/167 (16.17%) Arm 2: 23/156 (14.74%)
Dunstan et al., 2003[50] Study name: Dunstan Study dates: 1999-2001 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government Study follow-up: 1 year Original, same study, or follow-up studies: Dunstan, 2008[44]; Meldrum, 2015[51]	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 98 Pregnant withdrawals 15 Pregnant completers 83 Pregnant age: NR (NR) NR Race of Mother: NR (100)	Inclusion Criteria: All women had a history of physician-diagnosed allergic rhinitis and/or asthma and 1 or more positive skin prick tests to common allergens (house dust mite; grass pollens; molds; and cat, dog, and cockroach extracts) Exclusion Criteria: Women were ineligible for the study if they smoked; if they had other medical problems, complicated pregnancies, or seafood allergy; or if their normal dietary intake exceeded 2 meals of fish per week.	Start time: Pregnant 20 weeks of gestation Duration: Pregnant till delivery Arm 1: Placebo group Description: 46 women allocated and received placebo-olive oil Manufacturer: Pan Laboratories, Moorebank, NSW, Australia Active ingredients: 66.6% n-9 oleic acid Dose: 4 (1-g) capsules of olive oil per day Blinding: Randomization and allocation of capsules occurred at a different center separate from the recruitment of participants. Capsules were administered to the participants by someone separate from those doing the allocation. The capsules in the 2 groups were image-matched. Total N-3: <1% n-3 PUFAs Arm 2: Fish oil group Description: 52 women were randomized to receive fish oil Manufacturer: Ocean Nutrition, Halifax, Nova Scotia, Canada Dose: 4 (1g) fish oil capsules per day	Outcome: asthma (Secondary) Follow-up time: 1 year Arm 1: 6/43 (13.95%) Arm 2: 2/40 (5.0%) Outcome: chronic cough (Secondary) Follow-up time: 1 year Arm 1: 11/43 (25.58%) Arm 2: 5/40 (12.5%) Outcome: recurrent wheeze (Secondary) Follow-up time: 1 year Arm 1: 12/43 (27.91%) Arm 2: 10/40 (25.0%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			_x001E__x0007__x0005__x0015__x0013__x0007_ _x001E__x0013__x000F_ DHA: 56.0% EPA: 27.7% Total N-3: 3.7 g	
Escamilla-Nunez et al., 2014[59] Study name: POSGRAD Study dates: 2005-2009 Study design: Trial randomized parallel Location: Mexico Funding source / conflict: Government Study follow-up: 18 months Original, same study, or follow-up studies: Ramakrishnan, 2010[32]; Stein, 2012[33]; Imhoff-Kunsch, 2011[58]; Gonzalez-Casanova, 2015[60]; Ramakrishnan, 2015[61]	Study Population: Pregnant women with allergies Pregnant enrolled 1,040 Pregnant completers 973 Pregnant age: 26.3 (4.8) 18-35 Race of Mother: Hispanic (100% Mexican) Baseline Omega-3 intake: DHA median (25th, 75th percentile), mg/d: 55(37, 99)	Inclusion Criteria: Maternal age 18 - 35 years, recruited between 18 and 22 weeks of gestation. Willingness to breastfeed exclusively or predominantly during at least the first 3 months of life of the newborn and with the intention to live in their area of residence for at least 2 years after delivery Exclusion Criteria: High-risk pregnancies (pregnancy complications, including premature placental abruption, preeclampsia, pregnancy-induced hypertension, severe bleeding episode in pregnancy or lipid absorption disorders; Regular consumption of fish oil or DHA supplements; Chronic use of certain medications (e.g., drugs for epilepsy)	Start time: Pregnant 18-22 weeks gestation Duration: Pregnant to term Arm 1: Placebo Description: olive oil capsule Dose: 2 capsules per day Arm 2: DHA Description: Algal DHA Manufacturer: Martek Biosciences Dose: 2 capsules of 200mg each DHA: 200 mg algal DHA/capsule	Outcome: breathing difficulty (number of episodes) Follow-up time: 18 months Arm 1: 48/440 Arm 2: 47/429 Outcome: cough (number of episodes) Follow-up time: 18 months Arm 1: 1151/440 Arm 2: 1178/429 Outcome: phlegm with congestion and/or nasal discharge, fever with phlegm and congestion and/or nasal discharge, or wheezing with fever (Primary) Follow-up time: 18 months Arm 1: 49/440 (11.11%) Arm 2: 48/429 (11.11%) Outcome: wheezing (number of episodes) Follow-up time: 18 months Arm 1: 262/440 Arm 2: 252/429
Furuhjelm et al., 2011[172] Study name: NR Study dates: 2003-2007 Study design: Trial	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 145 Pregnant withdrawals 28 Pregnant completers 117	Inclusion Criteria: family history of current or previous allergic symptoms, i.e. bronchial asthma, eczema, allergic food reactions, itching and running eyes and	Start time: Pregnant 25 weeks of gestation Duration: Pregnant 15 weeks (i.e., until delivery) Arm 1: Placebo Description: soya bean oil Manufacturer: Pharma Nord, Vejle, Denmark	Outcome: any asthma (Primary) Follow-up time: 2 years Arm 1: 8/65 (12.31%) Arm 2: 7/54 (12.96%) Outcome: any rhinoconjunctivitis (Primary) Follow-up time: 2 years Arm 1: 2/65 (3.08%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
randomized parallel Location: Sweden Funding source / conflict: Industry, Multiple foundations and Societies Study follow-up: 2 years Original, same study, or follow-up studies: Furuhjelm, 2009[173]	 Infants enrolled 145 Infants withdrawals 28 Infants completers 117 Pregnant age: NR (NR) NR Race of Mother: NR (100)	nose at exposure to pollen, pets or other known allergens. Exclusion Criteria: Allergy to soya or fish, treatment with anticoagulants or omega-3 fatty acid supplements.	Active ingredients: 58% linoleic acid (LA), 2.5 g/day Viability: the antioxidant a-tocopherol (placebo: 36 mg/day) to assure the stability of the oil Dose: nine capsules a day Blinding: The mothers, as well as the staff handling clinical and laboratory follow-up, were blinded to group allocation, and the mothers were identified by their study number only. ALA: 6%, 0.28 g/day Arm 2: w-3 group Description: w-3 fatty acids Viability: the antioxidant a-tocopherol (w-3 group: 28 mg/day) to assure the stability of the oil Dose: nine capsules a day DHA: 25% DHA, 1.1 g/day EPA: 35% EPA, 1.6 g/day	Arm 2: 2/54 (3.7%)
Imhoff-Kunsch et al., 2011[58] Study name: POSGRAD Study dates: February 2005 - February 2007 Study design: Trial randomized parallel Location: Mexico Funding source / conflict: Government, March of Dimes Original, same study, or follow-up studies: Ramakrishnan, 2010[32]; Stein, 2012[33]; Escamilla-Nunez, 2014[59]; Gonzalez-Casanova, 2015[60]; Ramakrishnan, 2015[61]	Study Population: Healthy pregnant women Pregnant enrolled 1094 Pregnant completers 851 Infants enrolled 851 Infants completers 834 Pregnant age: DHA: 26.3 Placebo:20.5 (DHA: 4.9 Placebo: 1.9) Race of Mother: NR (100%)	Inclusion Criteria: Women were considered for inclusion in the study if they were in gestation week 18 to 22, were aged 18 to 35 years, planned to deliver at the IMSS General Hospital in Cuernavaca, planned to predominantly breastfeed for at least 3 months, and planned to live in the area for 2 years after delivery Exclusion Criteria: Exclusion criteria included (1) high-risk pregnancy, (2) lipid metabolism/absorption disorders, (3) regular intake of fish oil or DHA supplements, or (4) chronic use of certain medications.	Start time: Pregnant 18 to 22 weeks gestation Duration: Pregnant until parturition Arm 1: Placebo Description: Placebo/control corn and soy oil capsule Dose: 2 capsules daily Blinding: The placebo capsules, which were similar in appearance and taste to the DHA capsules, contained a corn and soy oil blend with no added antioxidants. All participants and members of the study team were blinded to the treatment scheme throughout the intervention period of the study. Data were unblinded for the analytical study team after the last infant in the study was born and had reached the age of 6 months. Arm 2: DHA Description: DHA capsule Manufacturer: Martek Biosciences Corporation, Columbia, MD Dose: 2 capsules daily DHA: 200mg/ capsule	Outcome: cold (any of cough, phlegm, nasal congestion, nasal secretion) (Secondary) Follow-up time: 1 month (preceding 15 days) Arm 1: 190/427 (44.6%) Arm 2: 159/422 (37.6%) Follow-up time: 3 months Arm 1: 185/419 (44.1%) Arm 2: 157/415 (37.8%) Follow-up time: 6 months (preceding 15 days) Arm 1: 193/414 (46.6%) Arm 2: 194/420 (46.2%) Outcome: cough (Secondary) Follow-up time: 1 month (preceding 15 days) Arm 1: 47/427 (11.0%) Arm 2: 40/422 (9.5%) Follow-up time: 3 months Arm 1: 100/419 (23.9%) Arm 2: 80/415 (19.3%) Follow-up time: 6 months (preceding 15 days) Arm 1: 136/414 (32.9%) Arm 2: 139/420 (33.1%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Outcome: difficulty breathing (Secondary) Follow-up time: 1 month (preceding 15 days) Arm 1: 10/427 (2.3%) Arm 2: 10/422 (2.4%) Follow-up time: 3 months Arm 1: 10/419 (2.4%) Arm 2: 12/415 (2.9%) Follow-up time: 6 months (preceding 15 days) Arm 1: 7/414 (1.7%) Arm 2: 6/420 (1.4%) Outcome: nasal congestion (Secondary) Follow-up time: 1 month (preceding 15 days) Arm 1: 140/427 (32.8%) Arm 2: 119/422 (28.2%) Follow-up time: 3 months Arm 1: 119/419 (28.4%) Arm 2: 104/415 (25.1%) Follow-up time: 6 months (preceding 15 days) Arm 1: 116/414 (28.0%) Arm 2: 124/420 (29.6%) Outcome: nasal secretion (Secondary) Follow-up time: 1 month (preceding 15 days) Arm 1: 46/427 (10.8%) Arm 2: 30/422 (7.1%) Follow-up time: 3 months Arm 1: 72/419 (17.2%) Arm 2: 62/415 (14.9%) Follow-up time: 6 months (preceding 15 days) Arm 1: 122/414 (29.5%) Arm 2: 118/420 (28.2%) Outcome: phlegm (Secondary) Follow-up time: 1 month (preceding 15 days) Arm 1: 82/427 (19.2%) Arm 2: 71/422 (16.8%) Follow-up time: 3 months Arm 1: 78/419 (18.6%) Arm 2: 81/415 (19.5%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Follow-up time: 6 months (preceding 15 days) Arm 1: 100/414 (24.2%) Arm 2: 100/420 (23.9%) Outcome: wheezing (Secondary) Follow-up time: 1 month (preceding 15 days) Arm 1: 30/427 (7.0%) Arm 2: 35/422 (8.3%) Follow-up time: 3 months Arm 1: 34/419 (8.1%) Arm 2: 29/415 (7.0%) Follow-up time: 6 months (preceding 15 days) Arm 1: 45/414 (10.9%) Arm 2: 50/420 (11.9%)
Manley et al., 2011[118] Study name: DINO Study dates: 2001-2007 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies, Manufacturer supplied product, Some authors serve on scientific advisory boards for corporations Study follow-up: 18 months Original, same study, or follow-up studies: Smithers, 2008[104]; Makrides, 2009[116];	Study Population: Preterm infants Breast-feeding women Infants enrolled 657 Infants completers 614 Lactating age: Intervention: 29.9 (5.8) Placebo: 30.2 (5.4) Infant age: 4 days (median) Race of Mother: NR (100%)	Inclusion Criteria: Infants born before 33 weeks' gestation, within 5 days of the infant commencing any enteral feedings. Exclusion Criteria: major congenital or chromosomal abnormalities, from a multiple birth in which not all live-born infants were eligible, enrolled in other trials of fatty acid supplementation, or mother with contraindication to fish oil	Start time: Infants Within 5 days (or less) of starting enteral feeding Duration: Infants NR Arm 1: Standard DHA diet Description: Soy bean oil Manufacturer: Clover Corporation Dose: 6 capsules per day Maternal conditions Infant conditions Current smoker 25% during pregnancy Other maternal conditions 1arm_1_maternal_conditions_other1 Other maternal conditions 10 Birth by C-section: 69% Pre-term birth 100% Low birth weight 18.6% Arm 2: High DHA Description: Tuna fish oil Manufacturer: Clover Corporation Dose: 6 500-mg DHA-rich tuna oil capsules per day Maternal conditions Infant conditions DHA: DHA to achieve a breast milk concentration that was 1% of total fatty acids	Outcome: asthma (Secondary) Follow-up time: 12 months Arm 1: 25/249 (10.04%) Arm 2: 18/232 (7.76%) Follow-up time: 12 or 18 months Arm 1: 53/252 (21.03%) Arm 2: 47/237 (19.83%) Follow-up time: 18 months Arm 1: 46/311 (14.79%) Arm 2: 41/292 (14.04%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Smithers, 2010[117]; Collins, 2011[105]; Atwell, 2013[119]; Collins, 2015[120]			Other dose 1: If supplementary formula was required, infants were given a high- DHA preterm formula (approximately 1.0%DHAand 0.6% AA). Current smoker 25% during pregnancy Other maternal conditions 1arm_2_maternal_conditions_other1 Other maternal conditions 10 Birth by C-section: 68.3% Pre-term birth 100% Low birth weight 18.9%	
Marks et al., 2006[168] Study name: CAPS Study dates: 1997-2004 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies Study follow-up: 5 years Original, same study, or follow-up studies: Mihrshahi, 2003[166]; Mihrshahi, 2004[167]; Brew, 2015[165]; Toelle, 2010[169]	Study Population: Pregnant women with allergies Pregnant enrolled 616 Pregnant withdrawals 100 Pregnant completers 516 Infants completers 516 Race of Mother: NR	Inclusion Criteria: pregnant women whose unborn children were at increased risk of developing asthma because 1 or more parents or siblings had asthma or wheezing Exclusion Criteria: with a pet cat at home, strict vegetarians, women with a nonsingleton pregnancy, and infants born earlier than 36 weeks of gestation. Infants had birth weights less than 2.5 kg, significant congenital malformations, or other significant neonatal disease.	Start time: Infants from the time the child started bottle-feeding, or to solid foods from age 6 months Duration: NR Arm 1: Diet control Description: polyunsaturated oils and spreads, containing 40% w6 FA, and Sunola oil capsules Manufacturer: Crisco-Meadow Lea Foods Inc, Sydney, Australia Blinding: The approach to blinding participants and research staff is described in this article's Online Repository at www.jacionline.org. Arm 2: Active Description: canola-based oils and spreads, which are low in n-6 fatty acids, and tuna oil capsules, which contain n-3 fatty acids.	Outcome: cough without cold (Secondary) Follow-up time: 5 years Arm 1: 36/249 (14.46%) Arm 2: 55/267 (20.6%) Outcome: frequent wheeze (Secondary) Follow-up time: 5 years Arm 1: 4/249 (1.61%) Arm 2: 5/267 (1.87%) Outcome: probable current asthma (Primary) Follow-up time: 5 years Arm 1: 51/249 (20.48%) Arm 2: 62/267 (23.22%)
Mihrshahi et al., 2003[166] Study name: CAPS Study dates: 1997-2002 Study design: Trial randomized parallel Location: Australia	Study Population: Pregnant women with allergies Pregnant enrolled 616 (all 4 arms) Pregnant withdrawals 62 Pregnant completers 554 Pregnant age: 28.5 (5.3)	Inclusion Criteria: At least one parent or sibling with symptoms of asthma as assessed by screening questionnaire, Reasonable fluency in English, Telephone at home, Reside within 30 km from center of recruitment	Start time: Infants initiation of bottle feeding or 6 months of age Duration: Infants NR Arm 1: Diet Control/HDM control or intervention Brand name: Sunola oil Manufacturer: Clover Corporation Arm 2: Dietary intervention/HDM control or	Outcome: asthma (Primary) Follow-up time: 18 months Arm 1: 34/275 (12.5%) Arm 2: 41/279 (14.7%) Outcome: wheeze ever (Primary) Follow-up time: 18 months Arm 1: 145/275 (52.6%) Arm 2: 119/279 (42.8%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Funding source / conflict: Government, Multiple foundations and Societies, Manufacturer supplied product Study follow-up: 18 months Original, same study, or follow-up studies: Mihrshahi, 2004[167]; Mihrshahi, 2006[168]; Brew, 2015[165] Toelle, 2010[169]	Race of Mother: NR (96.9%) Other race/ethnicity (Aboriginal 3.1%)	Exclusion Criteria: Pet cat at home, Families on strict vegetarian diet, Multiple births, Babies born earlier than 36 weeks gestation, with congenital malformations or other serious disease, or requiring major surgery or hospitalization for greater than 1 week	intervention Description: 500mg n-3 rich tuna fish oil supplement Manufacturer: Clover Corporation DHA: 76-128 mg EPA: 18-30 mg Other dose 1: based on age and fluid intake	
Noakes et al., 2012[88] Study name: SiPS Study dates: Not reported Study design: Trial randomized parallel Location: UK Funding source / conflict: Government, None Original, same study, or follow-up studies: Miles, 2011[78]	Study Population: Healthy pregnant women Pregnant enrolled 123 Pregnant withdrawals 37 Pregnant completers 86 Pregnant age: Mean(SEM)(n):Control group -28.4 (0.6)(61); Salmon group- 29.5(0.5) (62) (NR) 18-40 years Race of Mother: NR (100)	Inclusion Criteria: age 18–40 y; >19 wk gestation; healthy uncomplicated singleton pregnancy; infant at risk of atopy (one or more first-degree relatives of the infant affected by atopy, asthma or allergy by self-report); consumption of < 2 portions oily fish per month, excluding tinned tuna; and no use of fish-oil supplements currently or in the previous 3 months. Exclusion Criteria: age <18 or >40 y; <19 wk gestation; no first-degree relatives of the infant affected by atopy, asthma, or allergy; consumption of >2 portions oily fish per month, excluding tinned tuna; use of fish-oil	Start time: Pregnant 20 weeks of gestation Duration: Pregnant until birth Arm 1: Control group Description: Women in the control group (n = 61) were asked to continue their habitual diet Blinding: Researchers responsible for assessing outcome measures (both laboratory and clinical) remained blinded to the groups Arm 2: Salmon group Description: Women in the salmon group (n = 62) were asked to incorporate 2 portions of farmed salmon (150 g/portion) into their diet per week Active ingredients: 30.5 g protein, 16.4 g fat,4.1 mg alpha-tocopherol, 1.6 mg gamma-tocopherol, 6 micro-g vitamin A, 14 micro-g vitamin D3, and 43 micro-g Selenium Dose: two 150-g portions per week DHA: 1.16 g per portion EPA: 0.57g per portion EPA-DHA: 1.73 per portion Total N-3: 3.56g per portion Other dose 1: Docosapentaenoic acid-0.35g	Outcome: chest infection (Secondary) Follow-up time: 6 months Arm 1: 1/46 (2.17%) Arm 2: 3/37 (8.11%) Outcome: pneumonia/bronchiolitis (Secondary) Follow-up time: 6 months Arm 1: 1/46 (2.17%) Arm 2: 1/37 (2.7%) Outcome: wheeze (Secondary) Follow-up time: 6 months Arm 1: 11/46 (23.91%) Arm 2: 7/37 (18.92%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		supplements within the previous 3 mo; participation in another research study; known diabetes; presence of any autoimmune disease; learning disability; terminal illness; and mental health problems.		
Olsen et al., 2008[187] Study name: NR Study dates: 1989-2006 Study design: Trial randomized parallel Location: Denmark Funding source / conflict: Multiple foundations and Societies Study follow-up: 16 years	Study Population: Healthy pregnant women Pregnant enrolled 533 Infants enrolled 531 Infants completers 522 Pregnant age: Fish oil: 29.4 Olive oil: 29.7 No oil: 29.1 (Fish oil: (4.4) Olive oil: (4.3) No oil: (4.1)) NR Race of Mother: NR (100)	Inclusion Criteria: Women seen in the main midwife clinic in Aarhus Denmark at week 30 gestation Exclusion Criteria: History of placental abruption in a previous pregnancy or a serious bleeding episode in the current pregnancy; multiple pregnancies; allergy to fish; regular use of fish oil or prostaglandin inhibitors	Start time: Pregnant 30 weeks gestation Duration: Pregnant to term Arm 1: Control Description: Olive oil Active ingredients: 72% oleic acid Dose: 4 one gram capsules Blinding: Gelatin capsules were colored, and the capsules and their boxes looked identical. ALA: 12% Arm 2: Fish oil Brand name: Pikasol Fish Oil Manufacturer: Lube Limited Active ingredients: 2mg tocopherol/ml Dose: 4 1-gm capsules EPA: 32% EPA-DHA: 23% Total N-3: 2.7g marine n-3PUFA/day Arm 3: No oil Description: no intervention at all	Outcome: asthma (all types) (Secondary) Follow-up time: 16 years Arm 1: 11/136 (8.09%) Arm 2: 8/263 (3.04%) Arm 3: 3/129 (2.33%) Outcome: asthma (allergic) (Secondary) Follow-up time: 16 years Arm 1: 8/136 (5.88%) Arm 2: 2/263 (0.76%) Arm 3: 0/129 (0.0%)
Palmer et al., 2012[54] Study name: DOMInO Study dates: 2006-2009 Study design: Trial randomized parallel Location: Australia	Study Population: Pregnant women with allergies Pregnant enrolled 706 Pregnant withdrawals 25 Pregnant completers 681 Infants enrolled 706 Infants withdrawals 25	Inclusion Criteria: Included if the unborn baby had a mother, father, or sibling with a history of any medically diagnosed allergic disease (asthma, allergic rhinitis, eczema) and they were enrolled from the Women's and	Start time: Pregnant 21 weeks of gestation Infants 21 weeks of gestation Duration: Pregnant until delivery Infants till delivery Arm 1: Placebo Description: 338 women assigned to control supplements-vegetable oil capsules Dose: three 500 mg vegetable oil capsules daily Blinding: All capsules were similar in size, shape,	Outcome: respiratory tract infection (Secondary) Follow-up time: 1 year Arm 1: 66/338 (19.53%) Arm 2: 65/368 (17.66%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Funding source / conflict: Industry, Government, Manufacturer supplied product Original, same study, or follow-up studies: Makrides, 2010[35]; Smithers, 2011[53]; Zhou, 2012[55]; Palmer, 2013[56]; Makrides, 2014 [57]	Infants completers 681 Pregnant age: Treatment: 29.6 Placebo: 29.5 (Treatment: 5.7 Placebo: 5.6) NR Race of Mother: NR (100)	Children's Hospital or Flinders Medical Centre in Adelaide. Exclusion Criteria: NR	and color. Neither the women nor the research staff were aware of the treatment allocated. Arm 2: n-3 LCPUFA group Description: 368 women assigned to fish oil concentrate Brand name: Incromega 500 TG Manufacturer: Croda Chemicals, East Yorkshire, UK Dose: e three 500 mg capsules daily DHA: 800mg EPA: 100mg	
Palmer et al., 2013[56] Study name: DOMInO Study dates: 2006-2011 (allergy follow-up to Domino study) Study design: Trial randomized parallel Location: Australia Funding source / conflict: Industry, Government, Some authors serve on scientific advisory boards for corporations Study follow-up: 3 years Original, same study, or follow-up studies: Makrides, 2010[35]; Smithers, 2011[53]; Palmer, 2012[54]; Zhou, 2012[55]	Study Population: Children with family history of allergy Pregnant enrolled 706 Pregnant completers 638 Infants enrolled 706 Infants completers 638 Pregnant age: DHA: 28.9 Control: 28.9 (DHA: 5.7) Control: 5.6) Infant age: Birth Race of Mother: NR (100)	Inclusion Criteria: Women whose infants had a parent or sibling with a history of any medically diagnosed allergic disease (asthma, allergic rhinitis, eczema) Exclusion Criteria: Already taking a prenatal supplement with DHA Fetus had a known major abnormality, Bleeding disorder in which tuna oil was contraindicated, Taking anticoagulant therapy A documented history of drug or alcohol abuse, Participating in another fatty acid trial, Unable to give written informed consent, or English was not the main language spoken at home	Start time: Pregnant <21 weeks gestation Duration: Pregnant to term Arm 1: Control Description: vegetable oil Dose: 3 500-mg vegetable oil capsules per day Blinding: This was a double-blinded study; all capsules were similar in size, shape and color Arm 2: Fish oil Brand name: Incromega 500 TG, Manufacturer: Croda Chemicals, East Yorkshire, England Dose: 3 500-mg capsules per day DHA: 800 mg per day EPA: 100 mg per day	Outcome: asthma (Primary) Follow-up time: 3 years Arm 1: 5/338 (1.48%) Arm 2: 6/368 (1.63%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Peat et al., 2004[167] Study name: CAPS Study dates: 2000-2003 Study design: Trial randomized factorial design Location: Australia Funding source / conflict: Industry, Government Study follow-up: 3 years Original, same study, or follow-up studies: Mihrshahi, 2003[166]; Mihrshahi, 2006[168]; Brew, 2015[165] Toelle, 2010[169]	Study Population: Pregnant women whose unborn children were at high risk of developing asthma Pregnant enrolled 616 Pregnant withdrawals 90 Pregnant completers 526 Pregnant age: Placebo: 29.1 Diet: 28.6 (Placebo: 5.0 Diet: 5.3) NR Race of Mother: NR (100)	Inclusion Criteria: at least 1 parent or sibling with current asthma or frequent wheeze as assessed by screening questionnaire, fluency in English, a telephone at home, and residence within 30 km of the recruitment center. Exclusion Criteria: a pet cat at home, a vegetarian diet, multiple births, and less than 36 weeks gestation.	Start time: Infants 6 months of age Duration: Infants NR Arm 1: Placebo group Description: The control group received placebo supplement capsules of Sunola oil containing 83% monounsaturated oils (Clover Corp) and were provided with widely used soybean-based polyunsaturated oils and margarines high in omega-6 fatty acids for use in all food preparation Manufacturer: Clover Corp; Goodman Fielder Blinding: The research team responsible for recruitment was blind to the methods of randomization until recruitment was complete. The research nurses and research assistants who undertook the outcome assessments, laboratory analyses, and statistical analyses were blind to the group allocation of the participants. Arm 2: Active intervention group Description: tuna fish oil capsules Manufacturer: Clover Corp; Goodman Fielder Dose: 500 mg tuna fish oil capsules daily Total N-3: 184 mg	Outcome: any asthma (Primary) Follow-up time: 3 years Arm 1: 108/259 (41.7%) Arm 2: 107/267 (40.07%) Outcome: any cough (Primary) Follow-up time: 3 years Arm 1: 157/259 (60.62%) Arm 2: 132/267 (49.44%) Outcome: any wheeze (Secondary) Follow-up time: 3 years Arm 1: 108/259 (41.7%) Arm 2: 107/267 (40.07%)
Toelle et al., 2010[169] Study name: CAPS Study dates: 1997-2008 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Manufacturer supplied product Study follow-up: 8 years	Study Population: Healthy infants Pregnant enrolled 616 Pregnant completers Infants enrolled 616 Infants completers 450 Pregnant age: 28.5 years (5.3 years) Race of Mother: NR (NR)	Inclusion Criteria: Pregnant women whose unborn children were at high risk of developing asthma because of a family history (at least one parent or sibling with symptoms of asthma as assessed by screening questionnaire), reasonable fluency in English, telephone at home, reside within 30 km from center of recruitment Exclusion Criteria: Pet cat at home, families on	Start time: Infants birth Duration: Infants 5 years Arm 1: Control Description: Low-n3 capsules and cooking oils Brand name: Sunola Active ingredients: Capsules: 7% n-6 FA, 82% monounsaturated FA, 9% saturated FA, and 1.7% minor FA; cooking oils: 40% n-6 FA, 20% n-9 FA Dose: Designed to maintain the current n-3 to n-6 ingested FA ratio in the general population (1:15 to 1:20) Blinding: Similar appearance Total N-3: Capsules: 0.3%; cooking oil: 1.2% Arm 2: Omega 3 supplementation Description: High n-3 FA capsules and cooking oils	Outcome: asthma (Primary) Follow-up time: 8 yrs Arm 1: 44/220 (20.0%) Arm 2: 57/230 (24.8%) Outcome: wheeze (Primary) Follow-up time: 8 yrs Arm 1: 51/220 (23.2%) Arm 2: 73/230 (31.7%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Original, same study, or follow-up studies: Mihrshahi, 2003[166]; Mihrshahi, 2004[167]; Mihrshahi, 2006[168]; Brew, 2015[165]		strict vegetarian diet, multiple births, babies born earlier than 36 weeks gestation, birth weight below 2.5 kg, babies requiring surgery, babies requiring hospitalization for more than 1 week, babies with significant neonatal disease, babies with congenital malformations	Active ingredients: Capsules: 6% n-6 polyunsaturated FA, 24% monounsaturated FA, 28% saturated FA, and 5% minor FA; cooking oil: 6% n-6 FA, 40% n-9 FA Blinding: Similar appearance N-6 N-3: 5:1 Total N-3: Capsules: 37%; cooking oil: 6%	

Table 27. Observational studies for respiratory illness

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Lumia, et al., 2011[188] Outcome domain: Respiratory illness Study name: Finnish Type 1 Diabetes Prediction and Prevention Nutrition Study Study dates: 1997-2004 Study design: NR Location: Finland Funding source / conflict: Industry, Government, Multiple foundations and Societies, None Follow-up: 5 years	Study Population: NR Infants enrolled 2908 Infants completers 2679 Pregnant age: 14.8% <25 years at birth 35.4% 25-29 years 30.4% 30-34 years 19.5% =35 years Race of Mother: White European (100%)	Inclusion Criteria: infants at three university hospitals in Finland (Turku, Tampere and Oulu) whose cord blood was screened for HLA-conferred genetic susceptibility to type 1 diabetes (HLA-DQB1) and were found to have high or moderate genetic risk of type 1 diabetes Exclusion Criteria: Severe congenital malformations or diseases, parents of non-Caucasian origin or parents who did not have a working knowledge of Finnish, Swedish or English	Adjustments: Maternal age, mode of delivery, duration of gestation, number of earlier deliveries, birth weight, sex of the child, area of birth, maternal smoking during pregnancy, parental asthma or allergic rhinitis, maternal vocational education, pets at home, farming, contact with cow stable during the first year of life and the duration of total breastfeeding
Miyake, et al., 2009[182] Outcome domain: Respiratory illness Study name: Osaka maternal and child health study Study dates: 2002-2003 Study design: Observational prospective Location: Japan Funding source / conflict: Government, None	Study Population: Healthy infants Pregnant enrolled 1,002 Pregnant completers 763 Infants enrolled 1,002 Infants completers 763 Pregnant age: 30.0 (4.0) Race of Mother: NR (100)	Inclusion Criteria: pregnant women living in Neyagawa City, Osaka Prefecture or the surrounding cities Exclusion Criteria: Not reported	Adjustments: Maternal age, gestation at baseline, residential municipality, family income, maternal and paternal education, maternal and paternal history of asthma, atopic eczema and allergic rhinitis, maternal intake of vitamins D and E during pregnancy, changes in maternal diet in the previous 1 month, season when data at baseline were collected, maternal smoking during pregnancy, baby's older siblings, baby's sex, baby's birth weight, household smoking in the same room as the infant, breastfeeding duration and time of delivery before the third survey
Miyake, et al., 2013[183] Outcome domain: Respiratory illness Study name: Kyushu Okinawa Maternal and Child Health Study Study dates: 2007-2010	Study Population: Healthy infants Pregnant enrolled 1757 Pregnant completers 1354 Infants enrolled 1757 Infants completers 1354 Pregnant age: 31.5 (4.1)	Inclusion Criteria: Women living in one of 7 prefectures on Kyushu Island who became pregnant from 2007-2008 Exclusion Criteria: Failure to complete the study surveys	Adjustments: Maternal age, gestation at baseline, residential municipality, family income, maternal and paternal education, maternal and paternal history of asthma, atopic eczema and allergic rhinitis, maternal intake of vitamins D and E during pregnancy, changes in maternal diet in the previous 1

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Study design: Observational prospective Location: Japan Funding source / conflict: Industry, Government, Multiple foundations and Societies Follow-up: 23-29 months	Race of Mother: NR (100)		month, season when data at baseline were collected, maternal smoking during pregnancy, baby's older siblings, baby's sex, baby's birth weight, household smoking in the same room as the infant, breastfeeding duration and time of delivery before the third survey
Morales, et al., 2012[184] Outcome domain: Respiratory illness Study name: INfancia y Medio Ambiente (INMA) Project Study dates: 2004-2007 Study design: Observational prospective Location: Spain Funding source / conflict: Government Follow-up: 14 months	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 622 Pregnant completers 580 Infants enrolled 622 Infants completers 580 Mother age: 31.6 (4.2) Race of Mother: NR (100)	Inclusion Criteria: to be resident in the study area, to be at least 16 years old, to have a singleton pregnancy, to not have followed any program of assisted reproduction, to wish to deliver in the reference hospital, and to have no communication problems Exclusion Criteria: NR	Adjustments: Child gender, maternal social class, siblings at birth, maternal smoking in pregnancy, and DDE levels in cord blood for wheezing outcome
Newson, et al., 2004[176] Outcome domain: Respiratory illness Study name: Avon Longitudinal Study of Parents and Children (ALSPAC) Study dates: Recruitment: April 1, 1991 to December 31, 1992 Followup: 42 months Study design: Observational prospective Location: UK Funding source / conflict: Government, Multiple foundations and Societies Follow-up: 42 months Original, same study, or follow-up studies: Golding et al., 2001 (ALSPAC)	Study Population: Healthy infants Pregnant enrolled 4136 Infants enrolled 4202 Infants completers 1762 Infant age: Prenatal Race of Mother: NR (100%)	Inclusion Criteria: Pregnant women with expected date of delivery between April 1, 1991, and December 31, 1992, and place of residence within the 3 Bristol-based health districts of the former county of Avon, United Kingdom Exclusion Criteria: NR for enrollment. Exclusion for analysis: multiple pregnancies or in small missing value categories for various confounders.	Adjustments: Child's sex, gestational age at birth, and birth weight, and for the mother's age, education level, housing tenure, parity, ethnicity, and smoking in pregnancy (for variable categories see Table EI in the Journal's Online Repository at http://www.mosby.com/jaci), as well as maternal atopic disease (asthma, eczema, rhinoconjunctivitis), child's head circumference at birth (< 33 cm, 33-34.99 cm, 35-36.99 cm, 37+ cm, unknown), child's crown to heel length at birth (< 48 cm, 48-50.99 cm, 51-53.99 cm, 54+ cm, unknown), mother's body mass index (from prepregnancy self-reported weight and height; < 18.5 kg/m2 , 18.5-24.99 kg/m2 , 25-29.99 kg/m2 , 30+ kg/m2 , unknown), breast-feeding

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Notenboom, et al., 2011[179] Outcome domain: Respiratory illness Study name: KOALA Birth Cohort Study Study dates: Recruitment from October 2000 onwards and Followup: 6-7 years Study design: Observational prospective Location: Netherlands Funding source / conflict: Industry, Government, Multiple foundations and Societies Follow-up: 3 - 84 months	Study Population: Healthy infants Healthy pregnant women Infants enrolled 1275 Infants completers 1253 (samples for 815) Mother age: 32.6 (3.8) Race of Mother: White European (Dutch 96.3%)	Inclusion Criteria: Conventional participants: participation in ongoing study of pelvic girdle pain Alternative participants: frequented locations associated with organic diet and similar lifestyles Subsample: participants recruited from January 2002 onwards who consented to biosampling. Exclusion Criteria: Current multiple pregnancy n=9 Prematurity n=15 Perinatal infant death n=2 Down syndrome n=4 No response after birth n=51	Adjustments: Adjusted for recruitment group, maternal age, maternal ethnicity, maternal education level, maternal smoking during pregnancy, parental history of atopy, term of gestation, season of birth, gender, birth weight, mode of delivery, exposure to environmental tobacco, presence of older siblings and sibling atopy, breastfeeding, child day care, and pets at home
Pike, et al., 2012[186] Outcome domain: Respiratory illness Study name: Southampton Women's Survey Study dates: 2006-2010 Study design: Observational prospective Location: UK Funding source / conflict: Government, Some authors serve on scientific advisory boards for corporations Follow-up: Birth to 6 years	Study Population: Healthy infants Pregnant enrolled Infants enrolled 1485 Infants completers 865 Pregnant age: 30.4 (3.8) Race of Mother: NR (100)	Inclusion Criteria: mothers and children in the Southampton Women's Survey Exclusion Criteria: Infants born = 35 weeks' gestation were excluded to avoid abnormal lung development associated with prematurity	Adjustments: Child's age, maternal asthma, and paternal rhinitis for airway inflammation outcome
Standl, et al., 2014[177] Outcome domain: Respiratory illness Study name: LISAplus Study dates: Recruitment 1997-1999 Study design: Observational prospective Location: Germany	Study Population: Healthy infants Infants enrolled 436 Infants completers 243 Mother age: 32.7 (3.9) NR Infant age: Birth (NR) NR Race of Mother: NR (100)	Inclusion Criteria: NR Exclusion Criteria: Neonates displaying at least one of the following criteria: preterm birth (maturity <37 gestational weeks), low birth weight (<2,500 g), congenital malformation, symptomatic neonatal infection, antibiotic medication, hospitalization or intensive medical care during neonatal period. In addition, newborns from mothers with immune-related diseases (autoimmune disorders, diabetes, hepatitis B), on long-term	Adjustments: Parental education, sex, time of follow-up (2 yr, 6 yr or 10 yr for eczema; 6 yr and 10 yr for asthma, hay fever/allergic rhinitis and aeroallergen sensitization), age, maternal age at birth, parental atopy, total sum of fatty acids

Author, Year, Outcome domain, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Funding source / conflict: Government Follow-up: 10 years		medication or who abuse drugs and/or alcohol, and newborns from parents with a nationality other than German or who were not born in Germany, were excluded.	
Wijga, et al., 2006[175] Outcome domain: Respiratory illness Study name: The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study Study dates: 1995-2000 Study design: Observational prospective Location: Netherlands Funding source / conflict: Industry, Government Follow-up: 4 years	Study Population: NR Pregnant enrolled 276 Pregnant withdrawals 11 Pregnant completers 265 Infants enrolled 276 Infants withdrawals 11 Infants completers 265 Pregnant age: 31.0 (3.9) NR Race of Mother: NR (100)	Inclusion Criteria: Mothers reporting at least 1 of the following: (a history of) asthma, current hay fever, current allergy for pets, or current allergy for house dust or house dust mite were defined as allergic, and mothers reporting that they had none of these were defined as nonallergic. Exclusion Criteria: NR	Adjustments: Sex, number of older siblings, maternal age, maternal smoking during pregnancy, and maternal body mass index before pregnancy
Yu, et al., 2015[185] Outcome domain: Respiratory illness Study dates: Participants recruited between June 2009 and September 2010 Study design: Observational prospective Location: NR Funding source / conflict: Industry, Government	Study Population: Healthy infants Healthy pregnant women Infants enrolled 1162 Infants completers 960 Pregnant age: NR (NR) NR Race of Mother: NR (100%)	Inclusion Criteria: Participants were mother–child pairs in the Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort. Exclusion Criteria: NR	Adjustments: In the models, we adjusted for maternal characteristics including maternal age, ethnicity, gravidity, education level and energy intake. The same was done for infant characteristics including sex, birth weight, gestational age, duration of breast-feeding, family history of allergic diseases (which includes allergic rhinitis, eczema and asthma in first-degree relatives of the children (i.e. father, mother and/or sibling), exposure to environmental tobacco smoking, child day care attendance and having a cat or dog at home up to 18 months of age.

Key Question 3: Maternal or Childhood Adverse Events

- What are the short and long-term risks related to maternal intake of n-3s during pregnancy or breastfeeding on
  - Pregnant women
  - Breastfeeding women
  - Term or preterm human infants at or after birth
- What are the short and long-term risks associated with intakes of n-3s by human infants (as maternal breast milk or infant formula supplemented with n-3 FA)?
- Are adverse events associated with specific sources or doses?

Key Points

Antenatal supplementation

- Among ten RCTs that reported on maternal adverse events associated with prenatal supplementation, three provided no usable data, three reported no difference between intervention groups, four reported increased GI complaints in the n-3 FA supplemented groups; and one reported a statistically insignificant increase in the incidence of preterm birth in the n-3 FA supplemented group. Among five RCTs that reported on infant AEs associated with antenatal maternal supplementation, one study provided no usable data; one study found no difference between groups, except for longer duration of two types of symptoms in infants of supplemented mothers; another study found a decrease in risk for SAEs among infants of supplemented mothers; a fourth found a small but significant increase in risk for respiratory distress among infants of supplemented mothers but no other differences; and a fifth noted one case each of a later infancy neoplasia and intractable seizure disorder in the n-3 FA-supplemented group, neither of which were attributed to prenatal use of the n-3 FA supplements.

Supplementation of preterm infants

- Among four RCTs reporting on AEs in supplemented preterm infants, no differences were observed in SAEs or AEs (except for an increase in gas in one study, compared with placebo). Two reported no differences in adverse outcomes known to be associated with preterm birth, and one reported no differences in such outcomes with the exception of two findings.

Supplementation of healthy term infants

- Among five RCTs reporting on AEs in supplemented healthy term infants, two studies reported a significant increase in non-serious AEs in the placebo group, and only one study, a dose-response assessment of DHA, reported an increase in the incidence of an AE, watery eyes, in infants receiving the middle dose of DHA.

Description of Included Studies

A total of 20 RCTs described or reported assessing adverse events in 20 publications (see Table 28).[29, 31, 32, 35, 58, 98, 107, 108, 111-114, 116, 121, 137, 139, 172, 173] Seven of the studies administered supplements to pregnant or breastfeeding women,[29, 31, 32, 35, 50, 58, 98, 130, 172, 173] Ten administered supplements to infants.[107, 108, 111-114, 116, 121, 137, 139] One study administered supplements to both mothers and infants).[173] This study reported only one adverse event that was not attributed to supplementation with either the intervention or placebo formula. We identified no observational studies that reported on adverse effects of exposure to n-3 FA.

Maternal Supplementation

Maternal Outcomes

Of the studies that conducted maternal interventions and reported on maternal outcomes, two reported no adverse events by study arm[130, 172] and one did not identify the AEs or attribute them to a study arm[98]. Incidence of maternal AEs in four of the remaining five studies did not differ between intervention and placebo groups.

A 2003 study randomized 89 breastfeeding women at risk for postpartum depression to 0.2g/d DHA or placebo in the immediate postpartum period; the duration of the intervention was 4 months. The study reported that no women withdrew because of adverse effects of the supplement.[98]

Another 2003 study randomized 98 pregnant women in Australia to fish oil (3.7 g of n-3 PUFAs with 56.0% as DHA and 27.7% as EPA) or placebo capsules daily from 20 weeks gestation through term.[50] Seven women in the fish oil group and one woman in the placebo group dropped out, complaining of nausea. Three women in the fish oil group and one woman in the placebo group experienced a preterm birth, although the authors did not attribute this outcome to the intervention.

A 2010 study in Sweden randomized 145 pregnant women in the 25th week of gestation to fish oil capsules that provided 1.6g EPA and 1.1g DHA per day or soy bean oil capsules as placebo; supplementation continued through 3.5 months postpartum. This study did not report AEs by study arm.[172, 173]

A 2011 multisite European study randomized 315 pregnant women to receive fish oil alone, fish oil plus 5-MTHF, 5-MTHF alone or placebo daily. This study did not report AEs by study arm.[130]

A 2013 U.S. Phase III RCT randomized 350 pregnant women to supplements containing 40% DHA (percent of total fats by weight) and 5% AA (the placebo contained ALA and DHA). This study found no significant differences between intervention groups in any of 13 categories of maternal AEs and SAEs.[31]

A 2010 multisite Australian trial, the DOMInO trial, randomized 2,399 women at less than 21 weeks gestation to daily supplements of 0.8g/d DHA or placebo through term.[35] The authors reported more gastrointestinal distress but less diarrhea among the women who received DHA-containing supplements. This study also reported no serious adverse events (SAEs) in the mothers.[35]

A 2010 study in Mexico randomized 1,094 pregnant women at 18 to 22 weeks gestation to a supplement of 0.4 g/d algal DHA or a placebo. This study reported no difference in the incidence of vomiting or nausea between the two groups and reported no SAEs among mothers.[32]

A 2010 U.S. study randomized 852 women at high risk of recurrent preterm birth to a daily supplement (1.2g/d EPA: 0.8g/d DHA) or matching placebo from 16 to 22 through 36 weeks of gestation, and reported an increase in gastrointestinal complaints among n-3 supplemented mothers (burping, $p=0.001$, vomiting $p=0.005$, bad taste $p=0.002$).[29]

Infant Outcomes

Among studies with maternal supplementation that reported on infant outcomes, five reported on AEs in infants. One of the four found no differences in a large number of infant birth-associated AEs.[31]

A 2003 study randomized 98 pregnant women in Australia to fish oil (3.7 g of n-3 PUFAs with 56.0% as DHA and 27.7% as EPA) or placebo capsules daily from 20 weeks gestation through term.[50] The authors noted one case each of a later infancy neoplasia and intractable seizure disorder in the fish oil group, neither of which they attributed to prenatal use of n-3 FA supplements.

A 2010 study in Mexico randomized 1,094 pregnant women at 18 to 22 weeks gestation to a supplement of 0.4 g/d algal DHA or a placebo. The effects of maternal supplementation on infant health and adverse health outcomes were assessed at birth [32] and at 1, 3, and 6 months.[58] At birth, total AEs and SAEs (including congenital anomalies) did not differ between groups of infants.[32] Maternal reports of symptoms of illnesses and duration of illnesses, including fever, vomiting, diarrhea, rash and other illnesses did not differ between groups at 1, 3, or 6 months of age. However, the relative risk of longer duration of rash was greater for infants of DHA-supplemented mothers than for infants of control mothers at 1 month (RR1.22[1.05, 1.41]); the relative risk for longer duration of "other illnesses" was less for infants of DHA-supplemented mothers at 3 months (RR 0.77[0.62, 0.95]), and at 6 months, the relative risk for longer duration of vomiting was greater (RR1.74[1.19, 2.54]) and for rash (RR 0.77[0.64, 0.94]) and other illnesses (0.75[0.59, 0.94]) was less for infants of DHA-supplemented mothers.[58]

A 2010 multisite Australian trial, the DOMInO trial, randomized 2,399 women at less than 21 weeks gestation to daily supplements of 0.8g/d DHA or placebo through term.[35] The authors reported fewer SAEs among infants of n-3 FA supplemented mothers than among infants of mothers who received the placebo supplements during the first 18 months of life, including a decreased risk for any admission to a neonatal intensive care unit (RR 0.57[0.34, 0.97]) and decreased risk for death (RR0.33[0.11, 1.03]). No difference in the risk for major congenital anomalies was observed between the groups.[35]

A 2010 U.S. study randomized 852 women at high risk of recurrent preterm birth to a daily supplement (1.2g/d EPA: 0.8g/d DHA) or matching placebo from 16 to 22 through 36 weeks of gestation. This study observed an increase in the risk for respiratory distress at birth among infants of the n-3 FA supplemented mothers compared with infants of mothers given the placebo supplement, but no other differences between the groups.[29]

Infant Supplementation

Among studies of infant supplementation alone, four enrolled preterm infants, and five enrolled healthy term infants. All randomized infants to a supplement containing combinations of DHA and AA.

Preterm Infants

A small study conducted in Taiwan that randomized 27 larger preterm infants to receive formula supplemented with 0.05% DHA and 0.1% AA or the identical formula without LCPUFA reported no SAEs in either group over the first year of life.[137]

A multisite Australian study that randomized 657 preterm infants to higher-concentration DHA formula (1.0%DHAand 0.6% AA) or lower-concentration DHA formula (0.6% DHA 0.6% AA) compared adverse birth outcomes associated with prematurity between groups, and observed no difference in rates of mortality, necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), interventricular hemorrhage, seizures, blindness, hearing loss, of need for oxygen.[116]

A 2005 U.S. study that randomized preterm infants to one of three infant formulas supplemented with algal DHA (0.017g/100 ml) and AA (0.034 g/100ml), the same concentrations of fish DHA and algal AA, or placebo oils also reported no difference among the groups with respect to parental reports of fussiness, diarrhea, or constipation (data not shown), but more gas than usual among the algal DHA and fish DHA-supplemented groups of infants at 40 weeks and 44 weeks post-menstrual age ($p<0.05$) but no differences at 53 or 57 weeks.[108] This study also found no differences in multiple adverse outcomes that are associated with preterm birth.

A 2008 study in Norway that randomized preterm infants to a supplement added to breast milk (0.032g DHA and 0.031 g AA or placebo per100 ml milk) found no difference in "registered" AEs between the groups.[107] However, the study reported a non-statistically significant increase in two adverse outcomes associated with preterm birth in the infants who received supplemented milk: longer duration of need for both nasal continuous positive airway pressure treatment (28 vs 13 days) and oxygen (13 vs 8 days).

Healthy Term Infants

Included studies of healthy term infants recruited, randomized, and initiated interventions in the first week of life.

A 2005 U.S. study randomized 103 healthy term infants (born at one of two hospitals) to two commercial infant formula products: Enfamil with iron supplemented with DHA (0.36% of total fatty acids) and AA (0.72% of total fatty acids) or not supplemented.[111] Withdrawal from the study due to gastrointestinal intolerance of the study formula or to illness not attributable to the formula was assessed over 12 months; at no time did withdrawal from the supplemented formula group due to gastrointestinal effects significantly exceed that of the group receiving control formula. Likewise, withdrawal due to other infant conditions was the same across study groups.

A 2007 multisite U.S. study randomized 244 healthy term infants to receive a soy formula fortified with 0.017g DHA/100 kcal from algal oil and 0.034g AA/100 kcal or a control formula for 4 months.[114] No significant differences were observed between groups for AEs except for the following: gastrointestinal reflux was higher in the controls than in the supplemented group ($p = 0.009$); the incidence of metabolic or nutritional difficulties (weight loss, poor weight gain, and Type 1 glutaric acidemia) was higher in controls than in the supplemented group ($p = 0.013$). The numbers of SAEs were the same for each group, and none were attributed to the study products.

A 2008 Canadian study randomized 30 healthy term infants to one of two formulas: S-26 Gold supplemented with 0.2% DHA and 0.34% AA (by weight) or the same formula without LCPUFA.[112] The authors reported no difference between the groups in the incidence of non-serious AEs (e.g., gas, spit-ups, cramps, vomiting, mucus or blood in stools) as reported by mothers or in laboratory values at 2 or 6 weeks.

The 2010 DIAMOND study, a multisite U.S. study, randomized healthy term infants to receive formula supplemented with one of three levels of DHA (0.32%, 0.64%, and 0.96%) and 0.64% AA. No differences were observed in the proportions of infants with at least one AE; in any of the 86 symptoms assessed, with the exception of watery eyes (increased only in the 0.64% DHA group); and in the numbers with at least one SAE.[121] The association between one case of sepsis in an infant in the 0.64% DHA group and diet could not be definitively established.

A 2014 study in Serbia randomized 213 healthy term infants to one of two types of formula: a standard formula fortified with DHA and AA (0.011g/100kcal each) or the same formula without LCPUFA (a reference group was breastfed).[113] At 4 months of age, the incidence of total AEs was nearly 50% higher in the infants receiving the control formula (45 percent) than in the infants receiving the fortified formula (24%, p=0.003). The proportion of infants who experienced non-serious AEs was three times higher in the control group as in the fortified formula group (41.3 percent vs. 13.6 percent), although the proportions of AE by type were similar across the two groups (e.g., 50 percent were respiratory tract infections, 24 percent were skin infection/eczema, and 10 percent were gastrointestinal problems). The proportion of infants who experienced an SAE was higher in the intervention group than in the control group (10.2 percent vs. 3.3 percent), but the authors attributed only one SAE per group (a combination of gastrointestinal complaints) to formula consumption.

Table 28. Adverse events

Author, Year, Study	Intervention group and Adverse Event	
Dunstan, et al., 2003[50]	Intervention: Pregnant women Maternal nausea Fish oil 7/52 Control 1/46 Preterm birth Fish oil 3/52 Control 1/46 Neoplastic condition of infancy Fish oil 1/42 Control 0/43 Intractable infantile seizure disorder Fish oil 1/42 Control 0/43	
Carlson et al., 2013[31]	<u>Maternal Serious Adverse Events</u> Miscarriage DHA 4/154 Control 3/147 Other prenatal maternal hospitalization DHA 14/154 Control 15/147 Postpartum hospitalization DHA 1/154 Control 3/147 <u>Infant Serious Adverse Events</u> Hospitalization and death DHA 26/154 Control 31/147 Congenital anomalies DHA 5/154 Control 2/147 Non-serious Adverse Events Body DHA 81/154 Control 83/147 Cardiovascular and blood DHA 80/154 Control 82/147 Eye, Ear, Nose, Throat DHA 16/154 Control 8/147	Gastrointestinal DHA 59/154 Control 69/147 Head, Neck, Mental well-being DHA 38/154 Control 19/147 Infant DHA 110/154 Control 120/147 Metabolic and Nutrition DHA 38/154 Control 39/147 Unable to Categorize DHA 3/154 Control 3/147 Pregnancy, Delivery DHA 89/154 Control 80/147 Respiratory DHA 29/154 Control 26/147 Skin DHA 11/154 Control 10/147 Urogenital DHA 70/154 Control 85/147

Author, Year, Study	Intervention group and Adverse Event
Imhoff-Kunsch et al., 2011[58]	Intervention: congenital anomalies at birth DHA 16/547 (2.93%) control 15/547 (2.74%) infant deaths DHA 4/547 (0.73%) control 8/547 (1.46%) nausea DHA 184/547 (33.7%) control 166/547 (30.3%) serious adverse event DHA 25/547 (4.57%) control 21/547 (3.84%) stillbirths DHA 2/547 (0.37%) control 3/547 (0.55%) vomiting DHA 147/547 (26.9%) control 130/547 (23.8%)
Agostoni et al., 2009[139]	Intervention: Healthy term infants any adverse event Intervention 0/580 (0%) control 0/580 (0%)

Author, Year, Study	Intervention group and Adverse Event
Fleddermann et al., 2014[113] Name of study: BeMIM (Belgrade-Munch Infant Milk Tri	Intervention: Healthy term infants formula associated serious AE Breast-fed 0/45 (0%) Control 1/92 (1.09%) Intervention 1/88 (1.14%) gastrointestinal Breast-fed 2/45 (4.44%) Control 6/92 (6.52%) Intervention 1/88 (1.14%) not formula associated serious AE Breast-fed 4/45 (8.89%) Control 2/92 (2.17%) Intervention 8/88 (9.09%) others Breast-fed 5/45 (11.11%) Control 3/92 (3.26%) Intervention 3/88 (3.41%) respiratory Breast-fed 18/45 (40%) Control 21/92 (22.83%) Intervention 6/88 (6.82%) skin Breast-fed 14/45 (31.11%) Control 7/92 (7.61%) Intervention 1/88 (1.14%) total AE Breast-fed 45/45 (100%) Control 41/92 (44.57%) Intervention 21/88 (23.86%) total non-serious AE Breast-fed 41/45 (22.2%) Control 38/92 (41.3%) Intervention 12/88 (13.6%) total serious AE Breast-fed 4/45 (2.2%) Control 3/92 (3.3%) Intervention 9/88 (10.2%) urinary tract Breast-fed 2/45 (4.44%) Control 1/92 (1.09%) Intervention 1/88 (1.14%)

Author, Year, Study	Intervention group and Adverse Event
Birch et al., 2010[121] Name of study: Diamond	Intervention: Infant at least one adverse event 0.32 % DHA 76/83 (91.57%) 0.64 % DHA 80/84 (95.24%) 0.96% DHA 80/87 (91.95%) control 75/85 (88.24%) at least one serious adverse event 0.32 % DHA 6/83 (7.23%) 0.64 % DHA 6/84 (7.14%) 0.96% DHA 6/87 (6.9%) control 7/85 (8.24%) infant watery eyes 0.32 % DHA 1/83 (1.2%) 0.64 % DHA 4/84 (4.76%) 0.96% DHA 0/87 (0%) control 0/85 (0%) report of sepsis 0.32 % DHA 0/83 (0%) 0.64 % DHA 1/84 (1.19%) 0.96% DHA 0/87 (0%) control 0/85 (0%)
Field et al., 2008[112]	Intervention: Infant "no difference among groups in the incidence of minor adverse events (gas, spit-ups, cramps, vomiting and mucus or blood in stools) ./. (.%)
Carlson et al., 2013[31]	
Furuhjelm et al., 2011[172]	Intervention: Maternal discontinuation due to abdominal pain 3/145 (2.07%) discontinuation due to inability to swallow capsule 9/145 (6.21%) discontinuation due to nausea 6/145 (4.14%)

Author, Year, Study	**Intervention group and Adverse Event**
Makrides et al., 2010[35] Name of study: DOMInO	Intervention: Maternal infant at least one adverse event (admission to level III (intensive care) hospital treatment, major congenital abnormality, or death) DHA 36/1197 (3.01%) control 54/1202 (4.49%) infant death DHA 4/1197 (0.33%) control 12/1202 (1%) infant major congenital abnormality DHA 15/1197 (1.25%) control 11/1202 (0.92%) infant with any admission to neonatal intensive care DHA 21/1197 (1.75%) control 37/1202 (3.08%) mother any level III antenatal hospitalization DHA 2/1197 (0.17%) control 2/1202 (0.17%) mother death DHA 0/1197 (0%) control 0/1202 (0%)
Llorente et al., 2003[98] Name of study: Unnamed Trial A	Intervention: Maternal no withdrawals due to adverse events DHA 0/44 (0%) placebo 0/45 (0%)
Ramakrishnan et al., 2010[32] Name of study: POSGRAD	Intervention: Maternal infant born with congenital anomalies (spina bifida, heart malformations, considered unrelated to intervention) DHA 16/547 (2.93%) control 15/547 (2.74%) infant death DHA 4/547 (0.73%) control 8/547 (1.46%) stillbirths DHA 2/547 (0.37%) control 3/547 (0.55%) total serious adverse events DHA 25/547 (4.57%) control 21/547 (3.84%) women reported nausea DHA 184/547 (33.7%) control 166/547 (30.3%) women reported vomiting DHA 147/547 (26.9%) control 130/547 (23.8%)

Author, Year, Study	Intervention group and Adverse Event
Harper et al., 2010[29]	Intervention: Maternal admission to intensive/intermediate care nursery omega3 110/427 (25.9%) placebo 99/410 (24.6%) bronchopulmonary dysplasia omega3 9/425 (2.1%) placebo 6/403 (1.5%) interventricular hemorrhage, any grade omega3 10/427 (2.4%) placebo 9/410 (2.2%) interventricular hemorrhage, grade 3-4 omega3 5/427 (1.2%) placebo 3/410 (0.7%) necrotizing enterocolitis omega3 3/427 (0.7%) placebo 4/410 (1%) patent ductus arteriosus omega3 11/427 (2.6%) placebo 7/410 (1.7%) pregnancy loss or neonatal death omega3 16/434 (3.7%) placebo 17/418 (4.1%) proven sepsis omega3 5/427 (1.2%) placebo 3/410 (0.7%) received surfactant omega3 38/425 (8.9%) placebo 29/403 (7.2%) respiratory distress syndrome omega3 59/425 (13.9%) placebo 35/403 (8.7%) retinopathy of prematurity omega3 5/427 (1.2%) placebo 4/410 (1%) transient tachypnea omega3 31/425 (7.3%) placebo 24/403 (6%)
Furuhjelm et al., 2009[173]	Intervention: Maternal and infant infant born with an atrioventricular defect and a coarctation of the aorta and needed surgery Intervention 1/52 (1.92%) control 0/65 (.%)
Fang et al., 2005[137]	Intervention: Preterm infants serious AE Neoangelac 0/11 (0%) Neoangelac Plus 0/16 (0%)

Author, Year, Study	Intervention group and Adverse Event
Clandinin et al., 2005[108]	Intervention: Preterm infants adverse events for nervous system control 19/119 (16%) fish-DHA 8/130 (6%) bronchopulmonary dysplasia algal-DHA 16/112 (15%) control 17/119 (15%) fish-DHA 21/130 (17%) confirmed sepsis algal-DHA 19/112 (17%) control 16/119 (13%) fish-DHA 19/130 (15%) death during initial hospitalization control 2/119 (1.68%) fish-DHA 3/130 (2.31%) interventricular hemorrhage algal-DHA 14/112 (13%) control 32/119 (29%) fish-DHA 33/130 (27%) necrotizing enterocolitis algal-DHA 6/112 (5%) control 3/119 (3%) fish-DHA 7/130 (5%) retinopathy of prematurity algal-DHA 35/112 (47%) control 31/119 (42%) fish-DHA 53/130 (58%)

Author, Year, Study	Intervention group and Adverse Event
Henriksen et al., 2008[107] Name of study: Unnamed Trial D	Intervention: Preterm infants NEC, treated, proven control 0/73 (0%) intervention 1/68 (1.5%) NEC, treated, suspected control 0/73 (0%) intervention 1/68 (1.5%) died before discharge control 2/73 (3%) intervention 0/68 (0%) intracranial hemorrhage, grade 1 control 7/73 (10%) intervention 6/68 (9%) intracranial hemorrhage, grade 2 control 5/73 (7%) intervention 3/68 (5%) intracranial hemorrhage, grade 3-4 control 1/73 (1.5%) intervention 2/68 (3%) need for respiratory support control 29/73 (40%) intervention 31/68 (46%) periventricular leukomalacia, 1 or 2 cysts on 1 side control 0/73 (0%) intervention 3/68 (4.5%) periventricular leukomalacia, >2 cysts or bilateral control 1/73 (1.5%) intervention 1/68 (1.5%) retinopathy, any retinopathy control 13/73 (18%) intervention 8/68 (12%) retinopathy, treated retinopathy control 3/73 (4%) intervention 3/68 (4%)

Author, Year, Study	**Intervention group and Adverse Event**
Makrides et al., 2009[116] Name of study: DINO	Intervention: Preterm infants Death high DHA 9/322 (8.89%) standard DHA 9/335 (2.8%) blindness high DHA 0/322 (5.07%) standard DHA 1/335 (0%) hearing loss high DHA 0/322 (0.3%) standard DHA 1/335 (0%) interventricular hemorrhage high DHA 45/322 (2.09%) standard DHA 44/335 (13.98%) necrotizing enterocolitis high DHA 14/322 (2.69%) standard DHA 7/335 (4.35%) need for oxygen treatment high DHA 60/322 (0.3%) standard DHA 84/335 (18.63%) retinopathy of prematurity high DHA 74/322 (13.13%) standard DHA 73/335 (22.98%) seizures high DHA 7/322 (21.79%) standard DHA 17/335 (2.17%)

Author, Year, Study	Intervention group and Adverse Event
Hoffman et al., 2008[114]	Intervention: Term infants diarrhea DHA+ARA 5/96 (5.21%) control 8/86 (9.3%) fussiness DHA+ARA 6/96 (6.25%) control 6/86 (6.98%) gastroesophageal reflux DHA+ARA 3/96 (3.13%) control 13/86 (15.12%) poor weight gain DHA+ARA 0/96 (0%) control 2/86 (2.33%) serious AE unrelated to intervention DHA+ARA 6/96 (6.25%) control 6/86 (6.98%) type 1 glutaric acidemia DHA+ARA 0/96 (0%) control 1/86 (1.16%) vomiting DHA+ARA 4/96 (4.17%) control 8/86 (9.3%) weight loss DHA+ARA 0/96 (0%) control 3/86 (3.49%)
Birch et al., 2005[111]	Intervention: Term infants withdrawal due to gastrointestinal intolerance LCP 17 wk 0/46 (0%) LCP 39 wk 1/44 (2.27%) LCP 52 wk 0/42 (0%) LCP 6 wk 4/47 (8.51%) control 17 wk 2/46 (4.35%) control 39 wk 0/46 (0%) control 52 wk 0/44 (0%) control 6 wk 3/48 (6.25%) withdrawal due to infant illness unrelated to formula LCP 17 wk 1/46 (2.17%) LCP 39 wk 1/44 (2.27%) LCP 52 wk 0/42 (0%) LCP 6 wk 0/47 (0%) control 17 wk 0/46 (0%) control 39 wk 0/46 (0%) control 52 wk 1/44 (2.27%) control 6 wk 0/48 (0%)

Discussion

Overall Summary of Key Findings

For this systematic review, we identified 74 RCTs (in 75 publications) and 43 eligible prospective longitudinal studies and nested case-control studies that were eligible for inclusion based on the prespecified inclusion criteria. Most of the RCTs evaluated the effects of marine oil supplements on prenatal weight gain (risk for low birth weight) and length of gestation (risk for preterm birth) or the effects of DHA with or without AA as supplements or added to infant formulas on infant neural and cognitive development. Most observational studies assessed the association between the status of particular n-3 FA and developmental outcomes.

Within each category of analysis (by outcome, target of intervention, n-3 FA, and study design), studies diverged greatly with respect to the sources, doses, and durations of interventions; definitions or tests used to measure outcomes; and follow-up times. For outcomes such as visual, neurological, and cognitive development, by necessity, the tests used over time (in studies with multiple follow-ups) changed to match maturity level. As a result, it was challenging to identify groups of studies that were sufficiently similar to pool, even with studies from the original report. In addition, many RCTs employed and reported the results of numerous outcome measures, which were often internally inconsistent or showed no apparent pattern over time. The majority of studies did not find statistically significant findings. A small number of observational studies that were excluded from the original report met the inclusion criteria for the current report, and the observational studies identified for the current report seldom assessed outcomes that were similar to those assessed in RCTs. Additional challenges are described in the Limitations section below.

The original report found inconsistent effects of prenatal maternal supplementation with DHA on length of gestation and the risk for preterm birth and a consistent finding of no effects of prenatal maternal supplementation with EPA+DHA among a large number of RCTs. The current report found similar findings for these outcomes in RCTs.

For the current report, pooled analysis of 11 RCTs among healthy pregnant women found a significant increase in length of gestations among mothers who received algal DHA or DHA-enriched fish oil (WMD +0.34 [95% CI 0.02, 0.67] weeks) compared to placebo. Pooled analysis of 7 RCTs showed no significant effect of DHA or DHA-enriched fish oil on the incidence of preterm birth.

Pooled analysis of 5 RCTs showed that maternal fish oil supplementation (EPA+DHA) among healthy pregnant women had no significant effects on gestational age. Pooled analysis of 9 RCTs (in four publications) found no effects of EPA+DHA supplementation on the incidence of preterm birth. Prospective studies are sparse and found no consistent associations of maternal exposures with outcomes related to length of gestation or preterm birth.

The original report did not find a significant effect of maternal n-3 FA supplementation on the risk for low birth weight or SGA or a clear association of any maternal biomarkers with risk for low birth weight or birth weight itself. For the current report, we found a moderate level of evidence that maternal supplementation with DHA may increase birth weight, and a low level of evidence that maternal supplementation with EPA+DHA may not have significant effects on birth weight. Pooled analysis of 12 RCTs showed significantly higher birth weights among infants (mixed term and preterm) whose health pregnant women received algal DHA or DHA-enriched fish oil compared with placebo (WMD [95% CI]=90.12 [2.63, 177.62] grams). Pooled analysis of five RCTs found no effect of maternal EPA+DHA supplementation on infant birth weight. One RCT that assessed the effects of ALA on infant birth weight showed no effects. These findings are consistent with prospective studies, which found that higher maternal blood DHA concentrations were associated with higher birth weight.

There is also a low level of evidence that maternal supplementation with EPA+DHA may not have significant effects on risk for delivering a low birth weight infant among at-risk pregnant women, but the evidence is insufficient for the effects of maternal supplementation with DHA on risk for delivering a low birth weight infant among healthy pregnant women. Pooled analysis of four RCTs showed no significant effects of DHA+EPA supplementation (doses ranged from 2.0 to 3 g/d) on the incidence of small for gestational age between DHA+EPA supplementation and control groups (OR [95% CI]=1.00, CI[0.70, 1.43]). Two RCTs identified for the current study that assessed the effects of DHA alone or DHA-enriched fish oil both showed no significant effects on the risk for delivering a low birth weight infant among women who were not at risk. Observational studies were sparse and showed mostly no associations between n-3 intake or biomarkers and these outcomes.

The outcome of risk for antenatal and postnatal depression was a new one for this review. Three of the four RCTs that assessed the effects of prenatal supplementation with DHA alone, DHA+AA, or EPA-enriched fish oil or postnatal supplementation with DHA alone found no effects on risk for developing perinatal depression among healthy pregnant women. Prospective studies found inconsistent associations of maternal n3FA levels and risk of developing perinatal depression.

The original report found no consistent effect of maternal supplementation with n-3FA on the risk for gestational hypertension or preeclampsia. Pooling one study identified for the current report and two studies from the original report that randomized high-risk women to DHA supplements or placebo resulted in no difference in the risk for gestational hypertension or preeclampsia (OR 0.94[0.66, 1.34], I^2=0% (n=2,818); pooling studies of women not at high risk wo were randomized to fish oil or placebo also showed no effect (OR 1.04 [0.76 , 1.42], $I^{2=}$ 0%).

The original report found no, or inconsistent, effects of maternal supplementation or infant formula fortification on postnatal growth patterns. For the current report, pooled analysis of five RCTs of prenatal supplementation with DHA and EPA or fish oil showed no significant effects on weight, length, or head circumference at 18 months. Pooled analysis of three studies of fortification of infant formula with DHA and AA also showed no effects on postnatal weight and length at 4 months among preterm infants.

The original report found no consistent effect of maternal or infant supplementation with n-3 FA on neurological developmental outcomes and inconsistent associations with biomarkers. Likewise, RCTs identified for the current report found no consistent effects of n-3 FA alone or in combination with n-6 FA on any of these outcomes compared with placebo. Two studies reported a positive effect of formula supplemented with DHA and AA on Bayley's PDI scores (an index of motor development) in preterm infants at 12 and 18 months, and two RCTs reported positive effects on brainstem maturation but mixed effects on gross motor control in term infants supplemented with DHA and similarly mixed effects of DHA plus AA.

The original report found inconsistent effects of maternal and infant supplementation with n-3 FA on visual acuity development and inconsistencies between behavioral measures and electrophysiological measures (VEP). The current report identified one RCT that found that DHA supplementation of breast-feeding mothers resulted in improvement in one VEP outcome at 4 and 8 months of age but not at 5 years of age. We pooled five studies (four from the original report and one newly identified) that assessed the effects of supplementing infant formula with any n-3 FA on visual acuity development in preterm infants at 4 and 6 months and saw no significant effect of the intervention over that of placebo, although the effect approached borderline significance. Pooling studies (eight from the original report and two identified for the current report) of the effects of supplementing infant formula with any n-3 FA or with DHA plus AA on visual acuity among term infants showed small but significant effects at 2 months using behavioral methods, and at 4 and 12 months using VEP. Thus, results across time and outcome measure were inconsistent.

The original report found inconsistent effects of n-3 FA supplementation on cognitive development. We identified ten RCTs of pregnant women that reported cognitive outcomes in their offspring (including the only RCT identified in the prior systematic review); only two reported significant results. Six RCTs, including two from the previous AHRQ review, reported on supplementation for lactating women; none reported significant results. The prior AHRQ review included six RCTs in pre-term infants that reported cognitive outcomes, while the current one identified an additional six reports on five RCTs. Seven RCTs of pre-term infants reported the Bayley MDI score at 18 to 24 months of age; the pooled difference between the intervention and placebo groups was significant. The other RCTs reported mixed results. Two studies found no lasting differences during longterm (8 to 10 years) followup. Regarding healthy infants, the prior AHRQ review reported that six of eight RCTs did not find a significant difference between intervention and placebo groups in Bayley MDI scores. The current review identified five additional reports on four RCTs that measured cognitive outcomes. The pooled difference in MDI scores at 18 months was not significant when 3 RCTs were pooled. The RCTs that could not be pooled reported insignificant results regarding cognitive outcomes. Among six observational studies identified for the current report, only one association was noted: In one study that controlled for 18 potential confounders, low levels of AA were associated with lower performance IQ and high levels of adrenic acid were associated with lower verbal IQ at age 8; low levels of DHA were associated with lower verbal and full scale IQ, however, the authors caution that the effect sizes were small. In sum, there is moderate evidence that maternal n-3 supplementation has no effect on cognitive outcomes of offspring, while there is low strength evidence that supplementing formula for per-term infants may have a positive effect on cognitive outcomes at 18 months. However, there is insufficient evidence regarding long-term difference in cognitive outcomes. Developmental outcomes newly included for the current report were the risk for Autism Spectrum Disorders (ASD), Learning Disorders, and Attention Deficit Hyperactivity Disorder (ADHD). Two RCTs were identified that assessed the association between n-3 FA and the risk for ASD; one studied supplements for pregnant women and the other supplemented formula for pre-term infants. Both found no association with diagnosis of ASD. One large observational study on this topic was identified; women with the highest quartile of total PUFA intake while pregnant were at lower risk of having a child with ASD than women in the lowest quartile (RR 0.67; 95% CI 0.49, 0.92), after controlling for many important potential confounders. The authors advised that the results should be interpreted with caution, given the small number of cases (317 cases with ASD, 17,728 comparison mothers). Regarding ADHD, two RCTs of pre-term infants and one RCT of pregnant women measured attention or reported diagnoses of ADHD at long-term follow-up; each reported no association between supplementation and these outcomes.

Additional outcomes newly included in the current report were risks for atopic dermatitis/eczema, risks for allergies, and risks for respiratory illnesses, including asthma. A number of studies were conducted in mothers or infants at high familial risk for allergies or asthma. Three of four prenatal and three postnatal n-3 FA supplementation studies showed no significant effects on the risk for atopic dermatitis/eczema. Six of seven prospective observational studies also found no associations between n-3 FA exposures and risk for atopic dermatitis/eczema; however studies that assessed the association of n-3 FA biomarkers with this risk found inconsistent associations with higher plasma levels of DHA, erythrocyte EPA, AA levels, and EPA/AA ratios. Metaanalysis of three RCTs that assessed the effect of maternal supplementation with DHA plus EPA showed a reduction in the risk for food allergies that was not statistically significant. Prospective observational studies showed no consistent associations of maternal or infant n-3 FA exposures with risk for allergies. Among seven RCTs that assessed the effect of prenatal n-3 FA supplementation on the risk for respiratory illnesses, only two reported significant effects, decreases in the risk for asthma, but these effects were not consistent over time. A metaanalysis of three postnatal interventions that assessed the effects of fortified formula on risk for wheeze found no significant summary effect. Prospective observational studies and biomarker studies reported inconsistent associations between various postnatal n-3 FA and n-6 FA exposures and risk for respiratory illnesses.

The original report identified 21 RCTs that reported on adverse events with n-3 FA supplementation in pregnant women, breastfeeding mothers, and preterm and term infants. Overall they found that n-3 FA supplements and fortified formulas were well tolerated. Pregnant and breastfeeding women reported no serious adverse events, and adverse events in these groups were limited to mild GI symptoms. Among both preterm and term infants, adverse events were largely limited to GI symptoms also, with most serious adverse events attributable to morbidities associated with prematurity. The current report identified 18 RCTs that reported on adverse events. The profile of both non-serious and serious adverse events in this report was identical to that of the original report. None of the observational studies identified for the current report described adverse events.

Too few studies assessed the effects of increasing doses of n-3 FA using similar populations and outcome measures to enable dose-response or threshold estimation.

Few studies stratified outcomes according to risk groups, so it was usually not possible to assess whether the effectiveness of omega-3 interventions depended on level of risk. In addition, no studies stratified outcomes by baseline n-3 FA status, so it is not possible to assess whether adequacy of n-3 FA status might account for differences in outcomes across (or lack of outcomes within) studies.

Limitations

Overall, both RCTs and observational studies included in this review had numerous quality concerns that could increase the risk for bias. Across RCTs, the most common risk-of-bias limitation was a lack of intention-to-treat analyses (54 percent of the included RCTs analyzed data per protocol). Of 95 included articles reporting on RCTs, 36 percent failed to describe allocation concealment sufficiently to determine whether it was adequate (and many studies failed to describe recruitment methods). Blinding of study participants contributed only slightly to potential risk of bias because participants were usually infants or children and outcomes were usually clinically apparent or assessed in a clinical laboratory. Thirty-seven percent of RCTs were at risk of attrition bias due to overall dropout rates greater than 20 percent, although most studies reported similar dropout rates between groups. Although 87 percent of the included RCTs reported similar baseline demographic characteristics between groups, 57 percent did not report baseline n-3 FA intake or status. This omission is a critical concern because baseline n-3 FA status likely affects response to changes in n-3 FA intake.

Across observational studies, the most common risk of bias limitation was the lack of representativeness of the cohorts to the population of interest: 35 percent were judged to be select populations or only somewhat representative. In most cases, these populations were described as having high intakes of fish; in several cases, the populations were at higher than average risk for the outcome of interest or another condition. Another reporting inadequacy related to the ranges and distribution of n-3 FA exposures: Of included observational studies, most of the n-3 FA dietary intake assessments included only dietary sources (not n-3 FA supplements).

Few studies reported adverse events, but among the 20 studies that did report adverse events, 60 percent did not predefine or prespecify adverse events to be queried, and none used a recognized categorization system to prespecify or sort categories or levels of intensity of adverse events reported. Only 35 percent reported an active mode of collection of adverse event information, and of the studies that reported serious adverse events (or lack thereof), most did not define "serious adverse event." Of additional concern, studies of preterm infants often comingled morbidities associated with prematurity (such as bronchopulmonary dysplasia and retinopathy of prematurity) and adverse events that might be associated with the intervention. Only one study that met inclusion criteria considered whether mercury exposure could account for the findings on the effects of fish oil intake, but the findings were equivocal.

The population profiles differed somewhat between RCTs and observational studies. Understandably, a number of the RCTs were conducted in women at risk for premature birth, gestational hypertension, a low birth weight infant, or women with a personal or family history of allergy or asthma. However, most observational studies examining the associations between dietary n-3 FA intake or biomarkers of n-3 FA intake and birth, respiratory, allergy, or developmental outcomes were conducted in generally healthy populations. Most RCTs were also small in size, although most reported doing power calculations. Observational studies that enrolled fewer than 250 were excluded by design.

Study interventions or measured exposures tended to be highly heterogeneous. Studies that labeled themselves as studies of DHA alone often included some amount of EPA as well as n-6 FA (usually AA). Fish oil studies did not always report the oil's concentration of n-3 and n-6 FA in addition to the one of interest. Few studies assessed the effects of EPA alone and only one study assessed the effects of ALA alone. Of most concern was the heterogeneity in the description of the n-3 and n-6 FA contents of infant formulas and the systematic lack of assessment of formula intake (realizing the difficulty of this measurement in human infants). Few trials compared n-3 FA dose, formulation (e.g., ratio of EPA to DHA), or source. No trial compared different n-3 to n-6 FA ratios of supplements or intake. None of the observational studies attempted to determine a threshold effect of any associations between n-3 FA and the outcome of interest. Some observational studies failed to report median or range data of n-3 FA levels within quantiles, confidence intervals (or equivalent) of association hazard ratios, or conducted only linear analyses across a full range of n-3 FA values. In addition, studies varied in the range of n-3 FA status (e.g., intake level) within each study. The applicability of many of the observational studies to the U.S. population may also be limited by the higher baseline intakes of fish and other n-3 FA-containing foods and supplements among the populations in these studies.

Among studies that assessed associations between biomarkers of n-3 FA status and an outcome of interest, so many different n-3 FA biomarkers were investigated, that it was impossible to make comparisons across studies.

Another limitation of many of the studies was the inability or failure to control for potentially confounding factors. Observational studies often corrected for a large number of potential confounders, but many important factors could not be or were not measured; this issue is magnified for long-term follow up studies of cognitive development, where environmental factors were seldom considered. RCTs that reported cognitive outcomes at long-term follow up also rarely controlled for potential confounders, although they did report baseline data on characteristics such as SES and parent education, which were usually statistically similar among placebo and intervention groups.

For the outcomes related to infant and child development (except for growth patterns), tests used to measure most outcomes were numerous and heterogeneous across studies regardless of the study designs, and follow-up times varied widely. As a result, studies for a number of outcomes of interest could not be pooled, either with studies identified for the original report or with newly identified studies. In addition, the multiplicity of measures all but ensured that some outcome measure would produce a significant effect. Understandably, studies of cognitive, neurological, and visual acuity development with multiple follow-up points were required to use age/stage-appropriate outcome measures, but they seldom attempted to account for these changes in outcome measures.

The RCTs and observational studies differed in a number of ways, making it difficult to compare outcomes across the two study designs. Of note, the doses of n-3 FA supplements in RCTs were often much higher than the highest intake reported for observational studies. Furthermore, not all observational studies explicitly included n-3 FA supplements in their assessment of intake, and almost none of the RCTs attempted to account for background fish or n-3 FA intake as an effect modifier. For a very small number of RCTs where no significant differences in outcomes were observed between intervention and placebo treatments, posthoc analysis found an association between a biomarker of n-3 FA and the outcome of interest. This observation would seem to suggest that the apparent lack of effect of the intervention on the outcome of interest might be attributable to the participants having had adequate baseline n-3 FA status. However, the number of studies that conducted these follow-up analyses was too small to draw definitive conclusions. Likewise, very few RCTs assessed reported baseline dietary intakes of n-3 FA or biomarker status.

Finally, due to the significant heterogeneity across studies, the interpretation of overall meta-analysis results is limited. Only a small number of RCTs conducted dose response assessments (usually with poor results). For those reasons, we did not attempt to do dose-response meta-analysis of observational studies and performed only a small number of meta-regressions on dose-response across RCTs.

Future Research Recommendations

Future RCTs should be designed to determine whether particular populations or individuals are more likely to benefit from n-3 FA supplements or fortified formulas, e.g., individuals with relatively low baseline intakes of n-3 FA.

Therefore, studies need to measure—and match intervention groups according to—baseline n-3 FA biomarker status (although the current report has not clearly revealed the most relevant biomarkers). Researchers need to reach consensus on standardized formulations and on reporting of concentrations for interventions. The results of this review should help guide these decisions.

Studies also need to ascertain whether n-3 FA are more effective in individuals at increased risk for particular conditions (such as low birth weight, preterm birth, gestational hypertension, or for infants, risk for delayed visual acuity development or atopy).

Some recent evidence suggests that individuals' abilities to benefit from dietary supplementation with n-3 FA (or breastfeeding) is influenced by polymorphisms within the gene encoding FADs2, an enzyme involved in the desaturation of fatty acids to convert precursors to LCPUFAs such as DHA. If these findings are confirmed, future studies may need to perform genetic profiles on potential participants and to exclude those who are genetically incapable of responding to supplementation.

Finally, identifying the most promising and clinically relevant outcome measures will be important to expanding the strength of the evidence base for the effectiveness of supplemental n-3 FA for maternal and childhood outcomes. The findings of large cohort studies are still needed to assess the potential role of n-3 FA status in the risk for conditions such as autism spectrum disorder, learning disabilities, and ADHD; however, it may be necessary first to identify clear intermediate risk factors for these conditions, because the length of follow-up needed for diagnosis of the conditions themselves greatly increases the potential interference of other confounding factors.

Conclusions

Maternal Exposures and Birth Outcomes

Strength of evidence (SoE) is low for a small positive effect of algal docosahexaenoic acid (DHA) or DHA-enriched fish oil on length of gestation compared with placebo; strength of evidence is low regarding an apparent lack of effect of DHA or DHA-rich fish oil on risk for preterm birth. Strength of evidence is insufficient to draw conclusions about effects or associations for other n-3 FA alone or in combination. Observational studies did not show consistent associations of n-3 FA exposures (intake measurements or biomarkers) with these outcomes.

SoE is also moderate for a positive effect of algal DHA or DHA-enriched fish oil on birth weight but strength of evidence is insufficient to draw conclusions for the effects of most n-3 FA interventions on low birth weight or small-for-gestational age (SGA) infants; maternal n-3 FA biomarkers were significantly associated with birth weight, and low SoE supports an association of low early pregnancy plasma EPA and risk for SGA.

A low SoE supports a lack of effect of DHA or DHA-rich fish oil on (or association of n-3 FA with) risk for gestational hypertension SoE is insufficient to draw conclusions about the effects of other n-3 FA interventions, either pre- or postnatal.

A moderate SoE supports a lack of effect of DHA supplementation on the risk for gestational hypertension or preeclampsia among high-risk pregnant women. SoE is insufficient to draw conclusions regarding the effects of other interventions.

Infant and Child Outcomes

A moderate SoE supports a lack of effect of prenatal maternal supplementation with fish oil or DHA plus EPA on postnatal growth patterns (attainment of weight, length, and head circumference); a low SoE supports a lack of effect of pre- and postpartum maternal supplementation on these outcomes. SoE is insufficient to draw conclusions about the effects of other pre- or postnatal maternal interventions. A low SoE supports a lack of effect of DHA plus AA-fortified infant formulas on growth patterns of preterm or term infants. SoE is insufficient regarding effects of other n-3 FA or supplementation at other times on growth patterns.

A moderate SoE supports a lack of consistent effect of prenatal DHA on development of visual acuity in infants. SoE is insufficient to draw conclusions regarding the effects of other n-3 FA supplementation of pregnant or breastfeeding women on visual acuity. A low SoE supports a lack of effect of supplementation of infant formula with any n-3 FA on visua acuity measured in preterm infants at 4 or 6 months corrected age. A moderate SoE supports an effect of supplementation of infant formula with any n-3 FA on VEP-measured visual acuity development in term infants at 4 and 12 months of age but not on visual acuity measured using behavioral methods. A low SoE supports a small positive effect of supplementation of term infant formula with DHA plus AA on VEP but not on visual acuity measured using behavioral methods in term infants at 4 and 12 months.

A low SoE supports inconsistent effects of prenatal DHA on any measure of neurological development; insufficient SoE supports conclusions regarding the effects of any other n-3 FA supplementation of pregnant or breastfeeding mothers, or supplementation of preterm or term infants on measures of neurological development or associations of prenatal n-3 FA biomarker status and n-3 FA intakes with infant neurological development.

Regarding cognitive developmental outcomes, a moderate SoE supports a lack of effect of supplementation of pregnant women with either DHA plus AA or DHA plus EPA on cognitive outcomes in offspring. A low SoE supports lack of consistent effect of n-3 supplementation for full term infants on cognitive outcomes; there is moderate SoE that supplementing pre-term infants' formula with DHA plus AA may have a positive effect on infant cognition. There is insufficient evidence that any n-3 infant supplements are associated with long-term cognitive outcomes.

A low SoE supports the conclusion that n-3 FA status is unrelated to risk for autism spectrum disorders or ADHD.

A low SoE supports inconsistent effects of prenatal or postnatal n-3 FA supplementation on the risk for atopic dermatitis/eczema and allergies and associations of biomarkers and intakes with these outcomes. A moderate SoE supports a lack of effect of prenatal and postnatal infant n-3 FA supplementation on the risk for asthma and other respiratory illnesses. A low level of evidence supports inconsistent associations between n-3 FA exposures and risk for respiratory illnesses.

Table 29 summarizes the findings for which we identified a low, moderate, or high strength of evidence (SoE) for an effect or no effect of n-3 FA.

Adverse Events

A moderate SoE supports a lack of serious adverse events (AEs) among pregnant women and infants who consume supplemental n-3 FA or foods fortified with n-3 FA; a moderate SoE supports a lack of non-serious AEs, with the exception of an increased risk for mild gastrointestinal symptoms, among pregnant women and infants who consume supplemental n-3 FA.

Overall Conclusions

Most studies identified for this report examined the effects of marine oil (or other combinations of DHA and EPA) supplements on pregnant or breastfeeding women or the effects of infant formula fortified with DHA plus arachidonic acid. With the exception of small effects on birth weight and length of gestation (confirming the findings of the original report), n-3 FA supplementation or fortification has no consistent evidence of effects on peripartum maternal or infant health outcomes. No effects of n-3 FA were seen on gestational hypertension, peripartum depression, or postnatal growth. Apparent effects of n-3 FA supplementation were inconsistent across assessment methods and followup times for outcomes related to infant visual acuity and cognitive development and prevention of allergy and asthma. Evidence was insufficient to draw conclusions regarding effects of n-3 FA on or associations of n-3 FA exposures with autism spectrum disorders, ADHD, and learning disabilities. Future RCTs need to assess standardized preparations of n-3 and n-6 FA, using a select group of clinically important outcomes, on populations with baseline n-3 FA intakes typical of those of most western populations.

Table 29. Conclusions with strength of evidence for an effect or lack of effect

Outcome	Intervention/Exposure	Study Design[a]	Strength of Evidence[b]	Conclusion[c]
Maternal outcomes				
Length of gestation	Healthy pregnant women: n-3 FA[d] supplementation	12 RCTs 4 observational studies	Moderate	RCTs: Increase in gestational length compared with placebo Meta-analysis of 12 RCTs in update: WMD 0.33 (95% CI 0.04, 0.62) weeks. Observational studies: No associations. Original report: mixed findings .
Length of gestation	Healthy pregnant women: Algal DHA or DHA-enriched fish oil supplementation	11 RCTs 4 observational studies	Moderate	RCTs: Increase in gestational length compared with placebo Meta-analysis of 11 RCTs in update: WMD 0.34 (95% CI 0.02, 0.67) weeks Observational studies: No associations. Original report: mixed findings
Length of gestation	Healthy pregnant women: EPA+DHA fish oil supplementation	7 RCTs 4 observational studies	Low	RCTs: No significant effects on gestational length compared with placebo Observational studies: 3 of 4 found no association. Original report: no effects found[e]
Risk for preterm birth	Healthy pregnant women: Algal DHA or DHA-enriched fish oil supplementation	7 RCTs	Low	RCTs: No significant effects on the incidence of preterm birth compared with placebo Meta-analysis of 7 RCTs: OR 0.87 (95% CI 0.66, 1.15)
Risk for preterm birth	At-risk pregnant women: EPA+DHA fish oil supplementation	9 RCTs 2 observational studies	Low	RCTs:No significant effects on the incidence of preterm birth compared with placebo Meta-analysis of 9 RCTs: 0.86 (95% CI 0.65, 1.15) Observational studies

Outcome	Intervention/Exposure	Study Design[a]	Strength of Evidence[b]	Conclusion[c]
				showed mixed results.
Birth weight	Healthy pregnant women: n-3 FA* supplementation	16 RCTs 10 observational studies	Moderate	RCTs: Significant Increase in birth weight compared with placebo Meta-analysis of 16 RCTs in update: WMD 74.8 (95% CI 12.4, 137.17) grams. Observational studies of dietary intake, supplement use, and biomarkers generally showed positive associations with birth weight. Original report: Mixed findings
Birth weight	Healthy pregnant women: Algal DHA or DHA-enriched fish oil supplementation	12 RCTs 3 observational studies	Moderate	RCTs: Significant Increase in birth weight compared with placebo Meta-analysis of 12 RCTs: WMD 90.12 (95% CI 2.62, 177.62) grams Observational studies showed associations between DHA intake and biomarkers and birth weight. Original report: mixed findings
Birth weight	Healthy pregnant women: EPA+DHA fish oil supplementation	5 RCTs 4 observational studies	Low	RCTs: No significant effects on birth weight compared with placebo Meta-analysis of 5 RCTs: WMD 37.89 (95% CI -19.53, 95.31) grams Observational studies showed mixed associations with birth weight. Original report: no effects
Low birth weight	Healthy pregnant women: Algal DHA or DHA-enriched fish oil supplementation	4 RCTs	Low	RCTs: No significant effects on risk of low birth weight compared with placebo Meta-analysis of 4 RCTs: OR 0.72 (95% CI 0.43, 1.11)
SGA / IUGR	At-risk pregnant women: EPA+DHA or fish oil supplementation	4 RCTs 2 observational studies	Low	RCTs: No significant effects on SGA/IUGR compared

Outcome	Intervention/Exposure	Study Design[a]	Strength of Evidence[b]	Conclusion[c]
				with placebo Observational studies: no consistent association with SGA Meta-analysis of 4 RCTs: OR 1.00 (95% CI 0.70, 1.43)
Gestational hypertension	Normal-risk pregnant women: DHA supplementation	3 RCTs	Low	RCTs: No significant effect on risk for gestational hypertension in normal risk women Meta-analysis of 3 RCTs OR 0.94 (95% CI 0.66, 1.34)
Gestational hypertension	High-risk pregnant women: Marine oil supplementation	3 RCTs	Moderate	RCTs: No significant effect on risk for gestational hypertension among high-risk women Meta-analysis of 3 RCTs OR 1.04 (95% CI 0.76 , 1.42)
Peripartum depression	Pregnant women: Prenatal DHA, DHA-rich fish oil, DHA+AA, EPA+DHA/fish oil, or any n-3 FA	4 RCTs 8 observational studies	Low	RCTs: Nosignificant effect on risk for peripartum depression across studies. Observational studies showed no associations with risk for depression.[e]
Infant and child outcomes				
Postnatal growth patterns	Pregnant women: Fish oil or DHA+EPA supplementation	7 RCTs 2 observational studies	Moderate	RCTs: No significant effect on postnatal growth patterns among healthy term infants. Observational studies: Consistent with RCTs[e]
Postnatal growth patterns	Breastfeeding women: Supplementation with any n-3FA	6 RCTs 1 observational study	Low	RCTs: No- significant effect on postnatal growth patterns Observational study: consistent with RCTs[e]
Postnatal growth patterns	Preterm or term infants: Feeding infant formula fortified with DHA+AA	47 RCTs	Low	RCTs: No significant effect on postnatal growth patterns[e]
Visual acuity	Pregnant women: Supplementation with DHA-enriched fish oil	4 RCTs	Low	RCTs: No significant effect on development of visual acuity in infants.[e]
Visual acuity	Preterm infants: Feeding infant formula supplemented with any n-3 FA	5 RCTs	Low	VEP RCTs: No significant effect in preterm infants 4 months

Outcome	Intervention/Exposure	Study Design[a]	Strength of Evidence[b]	Conclusion[c]
				corrected age WMD -0.06 (−0.12; 0.01)
Visual acuity	Preterm infants: Feeding infant formula supplemented with any n-3 FA	5 RCTs	Low	VEP RCTs: No significant effect on development of visual acuity in preterm infants 6 months corrected age WMD -0.04 (-0.09, 0.01)
Visual acuity	Term infants: Feeding infant formula supplemented with any n-3 FA	6 RCTs	Low	Behavioral measures RCTs: Significant effect at 2 months WMD 0.07 (0.00, 0.14) six RCTs
Visual acuity	Term infants: Feeding infant formula supplemented with any n-3 FA	6 RCTs	Low	VEP RCTs: No significant effect at 2 months WMD 0.07[-0.03, 0.17], six RCTs
Visual acuity	Term infants: Feeding infant formula supplemented with any n-3 FA	6 RCTs	Low	Behavioral measures RCTs: No significant effect at 4 months WMD -0.05 (-0.08, 0.01) six RCTs
Visual acuity	Term infants: Feeding infant formula supplemented with any n-3 FA	6 RCTs	Moderate	VEP RCTs: Significant effect at 4 months WMD -0.10(-0.14, -0.07), six RCTs
Visual acuity	Term infants: Feeding infant formula supplemented with any n-3 FA	8 RCTs	Low	Behavioral measures RCTs:No significant effect of n-3 FA at 12 months WMD -0.10 (-0.14, -0.07)
Visual acuity	Term infants: Feeding infant formula supplemented with any n-3 FA	8 RCTs	Moderate	VEP RCTs: Significant effect of n-3 FA at 12 months WMD -0.14 (-0.17, -0.12)
Visual acuity	Term infants: Feeding DHA plus AA-fortified infant formula	7 RCTs	Low	VEP RCTs: Significant effect of DHA+AAat 4 months. WMD -0.10 (-0.14, -0.07)
Visual acuity	Term infants: Feeding DHA plus AA-fortified infant	6 RCTs	Moderate	VEP RCTs: Significant effect of

Outcome	Intervention/Exposure	Study Design[a]	Strength of Evidence[b]	Conclusion[c]
	formula			DHA+AA at 12 months WMD -0.14 (-0.17, -0.12)
Neurological development	Pregnant women: Supplementation with any n-3 FA	17 RCTs 5 observational studies	Low	RCTs: No significant effects on measures of neurological development across studies (insufficient numbers of studies of any outcomes to pool) consistent with observational studies.[e]
Cognitive development	Pregnant women: Supplementation with DHA+EPA or DHA + AA	10 RCTs	Moderate	RCTs: No significant effects on cognitive development across studies[e]
Cognitive development	Preterm infants: Supplementation with any n-3 FA	11 RCTs	Moderate	RCTs: Significant increase in cognitive (MDI) scores WMD 2.24; (95% CI 0.05, 4.43)
Cognitive development	Term infants: Supplementation with DHA+ AA	12 RCTs	Low	RCTs: No significant effect on cognitive development at 18-24 months WMD 0.75, 95% CI -9.29, 10.79
Autism Spectrum Disorders (ASD)	Pregnant women or preterm infants: Supplementation with DHA	2 RCTs 1 observational study	Low	RCTs: No significant effect on risk for ASD; association shown for intake of n-3 FA in observational study[e]
ADHD	Pregnant women or preterm infants: Supplementation with DHA	3 RCTs	Low	RCTs: No significant effect on risk for ADHD[e]
Atopic dermatitis/ eczema	Pregnant women: Supplementation with any n-3 FA or exposures as assessed by biomarkers	4 RCTs	Low	RCTs: No significant (and inconsistent) effects on risk for atopic dermatitis/eczema
Atopic dermatitis/ eczema	Breastfeeding women or infants: Supplementation of mothers or infants through formula fortification with any n-3 FA or exposure as assessed with biomarkers	3 RCTs 7 observational studies	Low	RCTs: No significant (and inconsistent) effects on risk for atopic dermatitis/eczema across RCTs, consistent with observational studies[e]
Allergies	Pregnant women: Supplementation with any n-3 FA or exposures as assessed by biomarkers	3 RCTs 4 observational studies (including 3 biomarker studies)	Low	RCTs: No significant effect on the risk for food allergy at 12 months OR 0.54 (95% CI 0.05, 6.2); Observational studies: no consistent association of biomarkers and risk for

Outcome	Intervention/Exposure	Study Design[a]	Strength of Evidence[b]	Conclusion[c]
				allergy
Allergies	Breastfeeding women or infants: Supplementation of mothers or infants through formula fortification with any n-3 FA or exposure as assessed by biomarkers	3 RCTs 2 observational studies	Low	RCTs: No significant effect on the risk for food or dust mite allergy and no association of breastmilk or infant biomarkers and risk for allergies across observational studies[e]
Asthma and other respiratory illnesses	Pregnant women: Supplementation with any n-3 FA	6 RCTs	Moderate	RCTs: No significant effect on the risk for asthma and other respiratory illnesses Meta-analysis of 3 RCTs OR 0.95 95% CI 0.77, 1.16
Asthma and other respiratory illnesses	Breastfeeding women or infants: Supplementation of mothers or infants through formula fortification with any n-3 FA	3 RCTs	Moderate	RCTs: No significant effect on the risk for asthma and other respiratory illnesses[e]
Asthma and other respiratory illnesses	Pregnant women or infants: Any n-3 FA exposures	10 observational studies	Low	Observational Studies: Inconsistent associations with risk for respiratory illnesses across studies. [e]
Asthma and other respiratory illnesses: Wheeze	Breastfeeding women or infants: Supplementation of mothers or infants through formula fortification with DHA	3 RCTs 5 observational studies 4 biomarkers studies	Low	RCTs: No significant effect on risk for wheeze at 12 months; meta-analysis of 3 RCTs: OR 1.06 (95% CI 0.73,1.54) Observational studies: showed Inconsistent associations with risk for wheeze across studies
Adverse events				
Maternal adverse events Non-serious	Pregnant or breastfeeding women: Supplementation with n-3 FA in the form of fish oil	9 RCTs	Moderate	RCTs: Increased risk for mild gastrointestinal symptoms but no other consistent non-serious adverse events. [e]
Maternal adverse events serious	Pregnant or breastfeeding women: Supplementation with n-3 FA in the form of fish oil	4 RCTs	Moderate	RCTs: No significant difference in risk for serious adverse events.[e]
Infant adverse events non-serious	Healthy term infants or preterm infants: Supplementation with n-3 FA in the form of fish oil alone or added to infant	13 RCTs	Moderate	RCTs:Increased risk for mild gastrointestinal symptoms across studies but no other consistent non-serious

Outcome	Intervention/Exposure	Study Design[a]	Strength of Evidence[b]	Conclusion[c]
	formula			adverse events.[e]
Infant adverse events serious	Healthy term infants: Supplementation with n-3 FA in the form of fish oil	6 RCTs	Moderate	RCTs:No significant difference in risk for serious adverse events.[e]
Infant adverse events serious	Preterm infants: Supplementation with n-3 FA in the form of fish oil	RCTs	Low	RCTs:No significant difference in risk for serious events associated with preterm birth.[e]

AA = arachidonic acid; ALA = alpha linolenic acid; CI = confidence interval; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; IUGR = intrauterine growth retardation; n-3 FA = omega-3 fatty acid; OR odds ratio; RCT = randomized controlled trial; SGA = small for gestational age; VEP = visual evoked potentials; WMD = weighted mean difference

[a]Figures represent numbers of studies considered as evidence in drawing the conclusion;
[b]Strength of evidence (SoE) was assessed using a modification of the GRADE method; the assessments for each domain considered in assigning the overall SoE grade are provided in Appendix G for each outcome; RCT outcomes were compared with observational study outcomes, when available, to contribute to the "consistency" domain; [c]Meta-analysis results are shown for all outcomes for which studies were pooled; remaining conclusions are based on trends across studies;
[d]Any n-3 FA refers to a pooled analysis of studies that employed any or unspecified n-3 FA;
[e]RCTs determined to be too heterogeneous to permit pooling.

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Abbreviations/Acronyms

Abbreviation	Meaning
ALA	A-linolenic acid
AA	Arachidonic Acid
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
ASD	Autism Spectrum Disorder
BDI	Beck Depression Inventory
BMI	Body mass index
CI	Confidence Interval
DHA	Docosahexaenoic acid
DPA	Docosapentaenoic acid
EAR	Estimated Average Requirement
EEG	Electroencephalogram
EFA	Essential fatty acid
EPA	Eicosapentaenoic acid
EPC	Evidence-based Practice Center
EPDS	Edinburgh Pregnancy Depression Scale
FOS	Fructooligosaccharide
GHTN	Gestational hypertension
Hg	Mercury
HR	Hazard ratio
IUGR	Intrauterine growth retardation
KQ	Key Question
LBW	Low birth weight
LCPUFA	Long-chain polyunsaturated fatty acid
MA	Meta-analysis
MDI	Mental Development Index
Mg	Milligram
n-3 FA	Omega-3 fatty acid(s)
n-6 FA	Omega-6 fatty acid(s)
NOS	Newcastle-Ottawa Scale or Neurological Optimality Score
NR	Not reported
ODS	Office of Dietary Supplements
OR	Odds ratio
PDI	Psychomotor Development Index
PE	Preeclampsia or eclampsia
PPD	Post- or peripartum depression
PUFA	Polyunsaturated fatty acid
RBC	Red blood cell
RCT	Randomized controlled trial
RoB	Risk of bias
RR	Risk ratio
SD	Standard deviation
SDA	Stearidonic acid

SGA	Small for gestational age
SBP	Systolic blood pressure
SR	Systematic review
TEP	Technical Expert Panel
UK	United Kingdom

Appendix A. Search Strategy

DATABASE SEARCHED & TIME PERIOD COVERED:
PsycINFO – 1/1/2000-8/24/2015

LANGUAGE:
English

SEARCH STRATEGY:
[TI (omega 3 or omega-3 or omega3 OR polyunsaturated or pufa or dha or epa or "long chain" or long-chain or longchain OR Docosapentanoic or docosapentaenoic or docosahexanoic or docosahexaenoic or dpa or dha OR eicosapentanoic or eicosapentaenoic or icosapent*) OR SU (omega 3 or omega-3 or omega3 OR polyunsaturated or pufa or dha or epa or "long chain" or long-chain or longchain OR Docosapentanoic or docosapentaenoic or docosahexanoic or docosahexaenoic or dpa or dha OR eicosapentanoic or eicosapentaenoic or icosapent*) OR AB (omega 3 or omega-3 or omega3 OR polyunsaturated or pufa or dha or epa or "long chain" or long-chain or longchain OR Docosapentanoic or docosapentaenoic or docosahexanoic or docosahexaenoic or dpa or dha OR eicosapentanoic or eicosapentaenoic or icosapent*)
OR
TI (((fatty acid or fatty acids*) and essential) OR "fish oil" or "fish oils" or linolenic or alpha-linolenic OR alphalinolenic or alpha-linolenic OR linolenate or cervonic or timnodonic or stearidonic) OR SU (((fatty acid or fatty acids*) and essential) OR "fish oil" or "fish oils" or linolenic or alpha-linolenic OR alphalinolenic or alpha-linolenic OR linolenate or cervonic or timnodonic or stearidonic) OR AB (((fatty acid or fatty acids*) and essential) OR "fish oil" or "fish oils" or linolenic or alpha-linolenic OR alphalinolic or alpha-linolenic OR linolenate or cervonic or timnodonic or stearidonic)
OR
((n 3 or n3 or n-3) and (oil or oils or pufa or fatty acid or fatty acids)) OR ((menhaden or flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed or perilla or shiso) and (oil or oils)) OR walnut* or butternut*or soybean* or "pumpkin seed" or pumpkinseed* OR "cod liver oil" or "codliver oil" or "marine oil" or "marine oils" or "marine fat") OR SU (((n 3 or n3 or n-3) and (oil or oils or pufa or fatty acid or fatty acids)) OR ((menhaden or flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed or perilla or shiso) and (oil or oils)) OR walnut* or butternut*or soybean* or "pumpkin seed" or pumpkinseed* OR "cod liver oil" or "codliver oil" or "marine oil" or "marine oils" or "marine fat") OR AB (((n 3 or n3 or n-3) and (oil or oils or pufa or fatty acid or fatty acids)) OR ((menhaden or flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed or perilla or shiso) and (oil or oils)) OR walnut* or butternut*or soybean* or "pumpkin seed" or pumpkinseed* OR "cod liver oil" or "codliver oil" or "marine oil" or "marine oils" or "marine fat")
OR
TI (salmon or mackerel or herring or tuna or halibut or seaweed or anchov* or sardine* OR Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega or Lovaza or Vascepa or icosapent ethyl OR ((fish n3 consum*) or (fish n3 intake) or (fish n3 diet*)) OR mediterranean n3 diet*) OR SU (salmon or mackerel or herring or tuna or halibut or seaweed or anchov* or sardine* OR Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega or Lovaza or Vascepa or icosapent ethyl OR ((fish n3 consum*) or (fish n3 intake) or (fish n3 diet*)) OR mediterranean n3 diet*) OR AB (salmon or mackerel or herring or tuna or halibut or seaweed or anchov* or sardine* OR Ropufa

or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega or Lovaza or Vascepa or icosapent ethyl OR ((fish n3 consum*) or (fish n3 intake) or (fish n3 diet*)) OR mediterranean n3 diet*)]
AND
[TI (growth OR ((child* n3 development) or gestational age or premature infant or low birth weight OR (gestat* and (age* or durat* or week*)) OR prematur* or preterm or pre-term OR (low n3 (birthweight or weight))) OR SU (growth OR ((child* n3 development) or gestational age or premature infant or low birth weight OR (gestat* and (age* or durat* or week*)) OR prematur* or preterm or pre-term OR (low n3 (birthweight or weight))) OR SU (growth OR ((child* n3 development) or gestational age or premature infant or low birth weight OR (gestat* and (age* or durat* or week*)) OR prematur* or preterm or pre-term OR (low n3 (birthweight or weight))) OR AB (growth OR ((child* n3 development) or gestational age or premature infant or low birth weight OR (gestat* and (age* or durat* or week*)) OR prematur* or preterm or pre-term OR (low n3 (birthweight or weight)))
OR
TI (newborn or neonat* OR Retinopathy n3 Prematurity OR retrolental fibroplasia* OR ADHD or attention deficit disorder* OR atopic n3 dermatitis) OR SU (newborn or neonat* OR Retinopathy n3 Prematurity OR retrolental fibroplasia* OR ADHD or attention deficit disorder* OR atopic n3 dermatitis) OR AB (newborn or neonat* OR Retinopathy n3 Prematurity OR retrolental fibroplasia* OR ADHD or attention deficit disorder* OR atopic n3 dermatitis)
OR
TI (autism OR autistic OR asperger* OR ados OR hypersensitiv* OR allerg* OR (Fetal AND growth AND retard*) OR (Embryo* AND Fetal Development) OR (Fetus OR ((fetal OR fetus OR intrauterine) AND (growth OR develop*)))) OR SU (autism OR autistic OR asperger* OR ados OR hypersensitiv* OR allerg* OR (Fetal AND growth AND retard*) OR (Embryo* AND Fetal Development) OR (Fetus OR ((fetal OR fetus OR intrauterine) AND (growth OR develop*)))) OR AB ((autism OR autistic OR asperger* OR ados OR hypersensitiv* OR allerg* OR (Fetal AND growth AND retard*) OR (Embryo* AND Fetal Development) OR (Fetus OR ((fetal OR fetus OR intrauterine) AND (growth OR develop*))))
OR
TI (Preeclamp* OR pre-eclamp* OR (Pregnan* AND Toxemi*) OR ((Gestation* OR pregnan*) AND (hypertens* OR toxemi*)) OR (gestat* AND (child* OR newborn* OR infan* OR neonat* OR baby OR babies OR pediatr* OR paediatr*)) OR (depression AND (postpartum OR postnatal OR post-partum OR post-natal OR post partum OR post natal OR ante-natal OR antenatal OR ante natal)) OR (grow* near/3 (child* OR infant* OR infancy))) OR SU (Preeclamp* OR pre-eclamp* OR (Pregnan* AND Toxemi*) OR ((Gestation* OR pregnan*) AND (hypertens* OR toxemi*)) OR (gestat* AND (child* OR newborn* OR infan* OR neonat* OR baby OR babies OR pediatr* OR paediatr*)) OR (depression AND (postpartum OR postnatal OR post-partum OR post-natal OR post partum OR post natal OR ante-natal OR antenatal OR ante natal)) OR (grow* near/3 (child* OR infant* OR infancy))) OR AB (Preeclamp* OR pre-eclamp* OR (Pregnan* AND Toxemi*) OR ((Gestation* OR pregnan*) AND (hypertens* OR toxemi*)) OR (gestat* AND (child* OR newborn* OR infan* OR neonat* OR baby OR babies OR pediatr* OR paediatr*)) OR (depression AND (postpartum OR postnatal OR post-partum OR post-natal OR post partum OR post natal OR ante-natal OR antenatal OR ante natal)) OR (grow* near/3 (child* OR infant* OR infancy)))
OR
TI ((congenital AND (vision near/3 disorder*)) OR ((learning near/3 disorder*) OR dyslexi* OR discalculi*) OR ((respiratory near/3 illness) OR asthma* OR wheez* OR respiratory syncitial virus)) OR SU ((congenital AND (vision near/3 disorder*)) OR ((learning near/3 disorder*) OR dyslexi* OR discalculi*) OR ((respiratory near/3 illness) OR asthma* OR wheez* OR respiratory syncitial virus)) OR AB ((congenital AND (vision near/3 disorder*)) OR ((learning near/3 disorder*) OR dyslexi* OR discalculi*) OR ((respiratory near/3 illness) OR asthma* OR wheez* OR respiratory syncitial virus))]

AND
Population Group: Human
Search modes - Find all search terms

==

DATABASE SEARCHED & TIME PERIOD COVERED:
Medline on OVID – 1/1/2000-8/25/2015

LANGUAGE:
English

SEARCH STRATEGY:
1 exp Growth/ or exp Gestational Age/ or Infant, Premature/ or Infant, Low Birth Weight/

2 limit 1 to (english language and yr="2014 - 2015")

3 (gestat* and (age* or durat* or week*)).mp.

4 limit 3 to (english language and yr="2014 - 2015")

5 (prematur* or preterm or pre-term).mp.

6 limit 5 to (english language and yr="2014 - 2015")

7 ((Infant* or baby) adj3 (low adj3 (birthweight or weight))).mp.

8 limit 7 to (english language and yr="2014 - 2015")

9 ((Infant$ or baby or birth) adj3 (prematur$ or gestational age)).mp.

10 limit 9 to (english language and yr="2014 - 2015")

11 (newborn or neonatal).mp.

12 limit 11 to (english language and yr="2014 - 2015")

13 Retinopathy of Prematurity/

14 limit 13 to (english language and yr="2014 - 2015")

15 retrolental fibroplasia$.mp.

16 limit 15 to (english language and yr="2014 - 2015")

17 Retinopathy of Prematurity.tw.
18 limit 17 to (english language and yr="2014 - 2015")

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19 Attention Deficit Disorder with Hyperactivity/ or ADHD.mp. or attention deficit disorder*.mp.

20 limit 19 to (english language and yr="2014 - 2015")

21 Dermatitis, Atopic/ or (atopic adj3 dermatitis).mp.

22 limit 21 to (english language and yr="2014 - 2015")

23 (autism or autistic).mp. or Autistic Disorder/ or asperger*.mp. or Asperger Syndrome/

24 limit 23 to (english language and yr="2014 - 2015")

25 ados.mp.

26 limit 25 to (english language and yr="2014 - 2015")

27 Hypersensitivity/ or allerg*.mp.

28 limit 27 to (english language and yr="2014 - 2015")

29 Fetal Growth Retardation/

30 limit 29 to (english language and yr="2014 - 2015")

31 exp Embryo/ and Fetal Development/

32 limit 31 to (english language and yr="2014 - 2015")

33 exp Fetus/

34 limit 33 to (english language and yr="2014 - 2015")

35 ((fetal or fetus or intrauterine) adj3 (growth or develop$)).mp.

36 limit 35 to (english language and yr="2014 - 2015")

37 Pre-Eclampsia/

38 limit 37 to (english language and yr="2014 - 2015")

39 (Preeclamp$ or pre-eclamp*).mp.

40 limit 39 to (english language and yr="2014 - 2015")

41 (Pregnan$ adj10 Toxemia$).mp.

42 limit 41 to (english language and yr="2014 - 2015")

43 ((gestation$ or pregnan$) and (hypertens$ or toxemia$)).mp.

44 limit 43 to (english language and yr="2014 - 2015")

45 (gestat$ and (child$ or newborn$ or infan$ or neonat$ or baby or babies or pediatr$ or paediatr$)).mp.

46 limit 45 to (english language and yr="2014 - 2015")

47 Depression, Postpartum/ or (depression adj3 (postpartum or postnatal or post-partum or post-natal or post partum or post natal or ante-natal or antenatal or ante natal)).mp.

48 limit 47 to (english language and yr="2014 - 2015")

49 (grow* adj3 (child* or infant* or infancy)).mp.

50 limit 49 to (english language and yr="2014 - 2015")

51 congenital.mp. and (Vision Disorders/ or (vision adj3 disorder*).mp.) {Including Related Terms}

52 limit 51 to (english language and yr="2014 - 2015")

53 Learning Disorders/ or (learning adj3 disorder*).mp. or dyslexi*.mp. or discalculi*.mp.

54 limit 53 to (english language and yr="2014 - 2015")

55 ((respiratory adj3 illness) or asthma* or wheez* or respiratory syncitial virus).mp.

56 limit 55 to (english language and yr="2014 - 2015")

57 2 or 4 or 6 or 8 or 10 or 12 or 14 or 16 or 18 or 20 or 22 or 24 or 26 or 28 or 30 or 32 or 34 or 36 or 38 or 40 or 42 or 44 or 46 or 48 or 50 or 52 or 54 or 56

58 exp fatty acids, omega-3/

59 limit 58 to (english language and yr="2014 - 2015")

60 fatty acids, essential/ or linolenic acids/ or exp fish oils/

61 limit 60 to (english language and yr="2014 - 2015")

62 (omega 3 or omega-3 or omega3).mp.

63 limit 62 to (english language and yr="2014 - 2015")

64 (polyunsaturated fat$ or pufa or dha or epa or long chain or longchain).mp.

65 limit 64 to (english language and yr="2014 - 2015")

66 Docosapenta?noic.mp.

67 limit 66 to (english language and yr="2014 - 2015")

68 DPA.mp.

69 limit 68 to (english language and yr="2014 - 2015")

70 ((omega-3 or omega 3 or omega3) and fatty acid$).mp.

71 limit 70 to (english language and yr="2014 - 2015")

72 ((n 3 or n3 or n-3) and (oil$ or pufa or fatty acid$ or omega 3)).mp.

73 limit 72 to (english language and yr="2014 - 2015")

74 Docosahexaenoic Acids/

75 limit 74 to (english language and yr="2014 - 2015")

76 docosahexa?noic.mp.

77 limit 76 to (english language and yr="2014 - 2015")

78 Eicosapentaenoic Acid/

79 limit 78 to (english language and yr="2014 - 2015")

80 eicosapenta?noic.mp.

81 limit 80 to (english language and yr="2014 - 2015")

82 icosapent?enoic.mp.

83 limit 82 to (english language and yr="2014 - 2015")

84 (alpha linolenic or alphalinolenic or alpha-linolenic).mp.

85 limit 84 to (english language and yr="2014 - 2015")

86 (linolenate or cervonic or timnodonic or stearidonic).mp.

87 limit 86 to (english language and yr="2014 - 2015")

88 menhaden oil$.mp.

89 limit 88 to (english language and yr="2014 - 2015")

90 ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed or perilla or shiso) adj2 oil$).mp.

91 limit 90 to (english language and yr="2014 - 2015")

92 (walnut$ or butternut$ or soybean$ or pumpkin seed$).mp.

93 limit 92 to (english language and yr="2014 - 2015")

94 (fish adj2 oil$).mp.

95 limit 94 to (english language and yr="2014 - 2015")

96 (cod liver oil$ or codliver oil$ or marine oil$ or marine fat$).mp.

97 limit 96 to (english language and yr="2014 - 2015")

98 (salmon or mackerel or herring or tuna or halibut or seaweed or anchov$ or sardine$).mp.

99 limit 98 to (english language and yr="2014 - 2015")

100 (Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega or Lovaza or Vascepa or icosapent ethyl).mp.

101 limit 100 to (english language and yr="2014 - 2015")

102 (fish consumption or fish intake or (fish adj2 diet$)).mp.

103 limit 102 to (english language and yr="2014 - 2015")

104 (mediterranean adj diet$).mp.

105 limit 104 to (english language and yr="2014 - 2015")

106 ((red blood cell or phospholipid or plasma fatty acid or plasma or phospholipid or triacylglycerol or cholesteryl or ester or adipos$ or fatty acid or erythrocyte or ghost or platelet or granulocyte or neutrophil or mononuclear or LDL or HDL) and (DHA or docosahexa?noic or EPA or eicosapenta?noic or SDA or stearidonic or omega)).mp.

107 limit 106 to (english language and yr="2014 - 2015")

108 59 or 61 or 63 or 65 or 67 or 69 or 71 or 73 or 75 or 77 or 79 or 81 or 83 or 85 or 87 or 89 or 91 or 93 or 95 or 97 or 99 or 101 or 103 or 105 or 107

109 57 and 108

110 (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt.

111 limit 110 to (english language and yr="2014 - 2015")

112 (exp clinical trial/ or evaluation studies or follow-up studies or prospective studies or exp randomized controlled trials/ or exp Randomized Controlled Trials as Topic/) {Including Related Terms}

113 limit 112 to (english language and yr="2014 - 2015")

114 exp random allocation/ or exp double-blind method/ or exp single-blind method/

115 limit 114 to (english language and yr="2014 - 2015")

116 exp placebos/ or exp longitudinal studies/ or exp cohort studies/

117 limit 116 to (english language and yr="2014 - 2015")

118 ("prospective studies" or "prospective study").af.

119 limit 118 to (english language and yr="2014 - 2015")

120 Cross-Sectional Studies.sh.

121 limit 120 to (english language and yr="2014 - 2015")

122 (clin$ adj trial$).af.

123 limit 122 to (english language and yr="2014 - 2015")

124 ((evaluation adj3 study) or (evaluation adj3 studies)).af.

125 limit 124 to (english language and yr="2014 - 2015")

126 (followup or follow-up or (follow$ adj2 up)).af. NOTE: SEARCH ENGINE DID NOT ACCEPT THIS AS A PHRASE

127 limit 126 to (english language and yr="2014 - 2015")

128 (follow-up or "follow up").af. NOTE: SEARCH ENGINE DID NOT ACCEPT THIS AS A PHRASE

129 limit 128 to (english language and yr="2014 - 2015")

130
("following up" or "followed up").af. NOTE: SEARCH ENGINE DID NOT ACCEPT THIS AS A PHRASE

131 limit 130 to (english language and yr="2014 - 2015")

132 ((prospective adj3 study) or (prospective adj3 studies)).af.

133 limit 132 to (english language and yr="2014 - 2015")

134 (prospective adj3 observational).af.

135 limit 134 to (english language and yr="2014 - 2015")

136 (multicenter or multi-center).af.

137 limit 136 to (english language and yr="2014 - 2015")

138 (random$ or rct$).af.

139 limit 138 to (english language and yr="2014 - 2015")

140 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).af.

141 limit 140 to (english language and yr="2014 - 2015")

142 (placebo$ or comparative study or longitudinal or cohort* or observational or cross section$ or cross-section$ or food frequency questionnaire$).af.

143 limit 142 to (english language and yr="2014 - 2015")

144 "before-and-after".af. NOTE: SEARCH ENGINE DID NOT ACCEPT THIS AS A PHRASE

145 limit 144 to (english language and yr="2014 - 2015")

146 ((before adj2 after) or single-arm or "single arm").af.

147 limit 146 to (english language and yr="2014 - 2015")

148 (single-arm or "single arm").af.

149 limit 148 to (english language and yr="2014 - 2015")

150 "before-and-after".af. NOTE: SEARCH ENGINE DID NOT ACCEPT THIS AS A PHRASE

151 limit 150 to (english language and yr="2014 - 2015")

152 111 or 113 or 115 or 117 or 119 or 121 or 123 or 125 or 127 or 129 or 131 or 133 or 135 or 137 or 139 or 141 or 143 or 145 or 147 or 149 or 151

153 109 and 152

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DATABASE SEARCHED & TIME PERIOD COVERED:
Embase – 1/1/2000-8/25/2015

LANGUAGE:
English

SEARCH STRATEGY:
#1 'body growth'/exp OR 'body growth' OR 'child development'/exp OR 'child development' OR 'gestational age'/exp OR 'gestational age' OR 'prematurity'/exp OR 'prematurity' OR 'low birth weight'/exp OR 'low birth weight'

#2 gestat* AND (age* OR durat* OR week*)

#3 premature* OR preterm OR 'pre term'

#4 infant* OR 'baby'/exp OR baby AND low AND ('birthweight'/exp OR birthweight OR 'weight'/exp OR weight)

#5 'newborn'/exp OR newborn OR neonat*

#6 'retrolental fibroplasia'/exp OR 'retrolental fibroplasia' OR 'attention deficit disorder'/exp OR 'attention deficit disorder' OR 'atopic dermatitis'/exp OR 'atopic dermatitis' OR 'autism'/exp OR 'autism' OR 'hypersensitivity'/exp OR 'hypersensitivity'

#7 retrolental AND fibroplas* OR retinopathy NEAR/2 prematurity OR ('attention'/exp OR attention AND deficit AND ('disorder'/exp OR disorder)) OR 'adhd'/exp OR adhd OR atopic NEAR/3 dermatitis OR 'autism'/exp OR autism OR autistic OR asperger* OR ados OR allerg*

#8 retrolental AND fibroplas* OR retinopathy NEAR/2 prematurity OR ('attention' OR 'attention'/exp OR attention AND deficit AND ('disorder' OR 'disorder'/exp OR disorder)) OR 'adhd' OR 'adhd'/exp OR adhd OR atopic NEAR/3 dermatitis OR 'autism' OR 'autism'/exp OR autism OR autistic OR asperger* OR ados OR allerg*

#9 'intrauterine growth retardation'/exp OR 'intrauterine growth retardation' OR 'prenatal development'/exp OR 'prenatal development' OR 'fetus'/exp OR 'fetus' OR 'preeclampsia'/exp OR 'preeclampsia' OR 'puerperal depression'/exp OR 'puerperal depression'

#10 (fetal OR fetus OR intrauterine) NEAR/3 (growth OR develop*)

#11 preeclamp* OR 'pre eclampsia'/exp OR 'pre eclampsia'

#12 pregnan* NEAR/10 toxemi*

#13 gestation* OR pregnan* AND (hypertens* OR toxemi*)

#14 gestation* AND (child* OR newborn* OR infan* OR neonat* OR 'baby'/exp OR baby OR babies OR pediatr* OR paediatr*)

#15 depression NEAR/3 (postpartum OR postnatal OR 'post partum' OR 'post natal' OR antenatal OR 'ante natal')

#16 grow* NEAR/3 (child* OR infant* OR infancy)

#17 'visual disorder'/exp OR 'visual disorder' AND congenital

#18 congenital AND ('vision'/exp OR vision OR visual) AND disorder*

#19 'learning disorder'/exp OR 'learning disorder' OR learning NEAR/3 disorder* OR dyslexi* OR discalculi*

#20 respiratory NEAR/3 illness OR respiratory NEAR/3 disease* OR respiratory NEAR/3 condition* OR asthma* OR wheez* OR (respiratory AND syncytial AND ('virus'/exp OR virus))

#21 infant* OR 'baby'/exp OR baby AND (premature* OR gestational) AND ('age'/exp OR age)

#22 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21

#23 #3 AND (2014:py OR 2015:py)

#24 #3 AND (2014:py OR 2015:py) AND [english]/lim

#25 'icosapentaenoic acid'/exp OR 'icosapentaenoic acid'

#26 'docosahexaenoic acid'/exp OR 'docosahexaenoic acid'

#27 'omega 3 fatty acid'/exp OR 'omega 3 fatty acid'

#28 'essential fatty acid'/exp OR 'essential fatty acid'

#29 'fish oil'/exp OR 'fish oil'

#30 'omega 3'/exp OR 'omega 3' OR ('omega'/exp OR omega AND 3) OR omega3 OR (polyunsaturated AND fat*) OR pufa OR dha OR epa OR dpa OR (long AND chain) OR 'long chain'

#31 'docosapentaenoic acid'/exp OR 'docosapentaenoic acid' OR docosapent* OR docosahex* OR eicosapent* OR icosapent*

#32 n3 OR 'n 3' OR (n AND 3) AND (oil* OR pufa OR fatty) AND acid*

#33 alpha AND linolenic OR alphalinolenic OR 'alpha linolenic'

#34 linolenate* OR cervonic OR timnodonic OR stearidonic

#35 menhaden NEAR/3 oil*

#36 flax* OR 'linseed' OR 'linseed'/exp OR linseed OR ('rape' OR 'rape'/exp OR rape AND ('seed' OR 'seed'/exp OR seed)) OR 'rapeseed' OR 'rapeseed'/exp OR rapeseed

#37 'canola' OR 'canola'/exp OR canola OR soy OR soybean* OR 'walnut' OR 'walnut'/exp OR walnut

#38 'mustard' OR 'mustard'/exp OR mustard AND ('seed' OR 'seed'/exp OR seed)

#39 'perilla' OR 'perilla'/exp OR perilla OR shiso

#40 walnut* OR butternut* OR soybean* OR ('pumpkin' OR 'pumpkin'/exp OR pumpkin AND ('seed' OR 'seed'/exp OR seed)) OR pumpkinseed*

#41 fish NEAR/2 oil*

#42 cod AND ('liver' OR 'liver'/exp OR liver) AND oil* OR (codliver AND oil*) OR (marine AND oil*) OR (marine AND ('fat'/exp OR fat))

#43 'salmon' OR 'salmon'/exp OR salmon OR mackerel OR 'herring' OR 'herring'/exp OR herring OR 'tuna' OR 'tuna'/exp OR tuna OR 'halibut' OR 'halibut'/exp OR halibut OR 'seaweed' OR 'seaweed'/exp OR seaweed OR anchov* OR sardine*

#44 ropufa OR 'maxepa' OR 'maxepa'/exp OR maxepa OR 'omacor' OR 'omacor'/exp OR omacor OR 'efamed' OR 'efamed'/exp OR efamed OR resq OR epagis OR almarin OR coromega OR 'lovaza' OR 'lovaza'/exp OR lovaza OR 'vascepa' OR 'vascepa'/exp OR vascepa OR ('icosapent' OR 'icosapent'/exp OR icosapent AND ethyl)

#45 fish NEAR/2 consum* OR fish NEAR/2 intake OR fish NEAR/2 diet

#46 'mediterranean diet'/exp OR 'mediterranean diet'

#47 red AND ('blood' OR 'blood'/exp OR blood) AND ('cell' OR 'cell'/exp OR cell) OR ('plasma' OR 'plasma'/exp OR plasma AND fatty AND ('acid' OR 'acid'/exp OR acid)) OR 'plasma' OR 'plasma'/exp OR plasma OR 'phospholipid' OR 'phospholipid'/exp OR phospholipid OR 'triacylglycerol' OR 'triacylglycerol'/exp OR triacylglycerol OR cholesteryl OR 'ester' OR 'ester'/exp OR ester OR adipos* OR (fatty AND ('acid' OR 'acid'/exp OR acid)) OR 'erythrocyte' OR 'erythrocyte'/exp OR erythrocyte OR ghost OR 'platelet' OR 'platelet'/exp OR platelet OR 'granulocyte' OR 'granulocyte'/exp OR granulocyte OR 'neutrophil' OR 'neutrophil'/exp OR neutrophil OR mononuclear OR 'ldl' OR 'ldl'/exp OR ldl OR 'hdl' OR 'hdl'/exp OR hdl AND (dha OR docosahexa?noic OR epa OR eicosapenta?noic OR sda OR stearidonic OR 'omega' OR 'omega'/exp OR omega)

#48 #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47

#49 #22 AND #48

#50 #34 AND (2014:py OR 2015:py)

#51 #34 AND (2014:py OR 2015:py) AND [english]/lim

#52 #34 AND (2014:py OR 2015:py) AND [humans]/lim

NUMBER OF RESULTS: 56

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DATABASE SEARCHED & TIME PERIOD COVERED:
Cochrane Databases – 1/1/2000-8/26/2015

LANGUAGE:
English

SEARCH STRATEGY:
#1 MeSH descriptor: [Fatty Acids, Omega-3] explode all trees

#2 MeSH descriptor: [Fatty Acids, Essential] explode all trees

#3 MeSH descriptor: [Linolenic Acids] explode all trees

#4 MeSH descriptor: [Fish Oils] explode all trees

#5 MeSH descriptor: [Docosahexaenoic Acids] explode all trees

#6 MeSH descriptor: [Eicosapentaenoic Acid] explode all trees

#7 omega 3 or omega-3 or omega3:ti,ab,kw (Word variations have been searched)

#8 polyunsaturated or pufa or dha or epa or "long chain" or long-chain or longchain:ti,ab,kw (Word variations have been searched)

#9 Docosapentanoic or docosapentaenoic or docosahexanoic or docosahexaenoic or dpa or dha:ti,ab,kw (Word variations have been searched)

#10 icosapentanoic or eicosapentaenoic or icosapent*:ti,ab,kw (Word variations have been searched)

#11 (fatty acid or fatty acids*) and essential:ti,ab,kw (Word variations have been searched)

#12 "fish oil" or "fish oils" or linolenic or alpha-linolenic:ti,ab,kw (Word variations have been searched)

#13 alphalinolenic or alpha-linolenic:ti,ab,kw (Word variations have been searched)

#14 linolenate or cervonic or timnodonic or stearidonic:ti,ab,kw (Word variations have been searched)

#15 (n 3 or n3 or n-3) and (oil or oils or pufa or fatty acid or fatty acids):ti,ab,kw (Word variations have been searched)

#16 menhaden or flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy:ti,ab,kw (Word variations have been searched)

#17 soybean or walnut or mustard seed or perilla or shiso:ti,ab,kw (Word variations have been searched)

#18 walnut* or butternut* or soybean* or "pumpkin seed" or pumpkinseed*:ti,ab,kw (Word variations have been searched)

#19 "cod liver oil" or "codliver oil" or "marine oil" or "marine oils" or "marine fat":ti,ab,kw (Word variations have been searched)

#20 salmon or mackerel or herring or tuna or halibut or seaweed or anchov* or sardine*:ti,ab,kw (Word variations have been searched)

#21 Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega or Lovaza:ti,ab,kw (Word variations have been searched)

#22 Vascepa or icosapent ethyl:ti,ab,kw (Word variations have been searched)

#23 (fish near/3 consum*) or (fish near/3 intake) or (fish near/3 diet*):ti,ab,kw (Word variations have been searched)

#24 mediterranean near/3 diet*:ti,ab,kw (Word variations have been searched)

#25 red blood cell or phospholipid or plasma fatty acid or plasma or phospholipid or triacylglycerol:ti,ab,kw (Word variations have been searched)

#26 cholesteryl or ester or adipos* or fatty acid or erythrocyte or ghost or platelet or granulocyte:ti,ab,kw (Word variations have been searched)

#27 neutrophil or mononuclear or LDL or HDL:ti,ab,kw (Word variations have been searched)

#28 EPA or SDA or stearidonic or omega:ti,ab,kw (Word variations have been searched)

#29 #25 or #26 or #27

#30 #29 and #28

#34 MeSH descriptor: [Growth] explode all trees

#35 MeSH descriptor: [Child Development] explode all trees

#36 MeSH descriptor: [Gestational Age] explode all trees

#37 MeSH descriptor: [Infant, Premature] explode all trees

#38 MeSH descriptor: [Infant, Premature] explode all trees

#39 MeSH descriptor: [Infant, Low Birth Weight] explode all trees

#40 MeSH descriptor: [Retinopathy of Prematurity] explode all trees

#41 MeSH descriptor: [Attention Deficit Disorder with Hyperactivity] explode all trees

#42 MeSH descriptor: [Dermatitis, Atopic] explode all trees

#43 MeSH descriptor: [Autistic Disorder] explode all trees

#44 MeSH descriptor: [Hypersensitivity] explode all trees

#45 MeSH descriptor: [Fetal Growth Retardation] explode all trees

#46 MeSH descriptor: [Embryonic and Fetal Development] explode all trees

#47 MeSH descriptor: [Fetus] explode all trees

#48 MeSH descriptor: [Pre-Eclampsia] explode all trees

#49 MeSH descriptor: [Depression, Postpartum] explode all trees

#50 MeSH descriptor: [Vision Disorders] explode all trees

#51 growth or (child* next/3 development) or gestational age or premature infant or low birth weight:ti,ab,kw (Word variations have been searched)

#52 gestat* and (age* or durat* or week*):ti,ab,kw (Word variations have been searched)

#53 prematur* or preterm or pre-term:ti,ab,kw (Word variations have been searched)

#54 low near/3 (birthweight or weight):ti,ab,kw (Word variations have been searched)

#55 newborn or neonat*:ti,ab,kw (Word variations have been searched)

#56 Retinopathy near/3 Prematurity:ti,ab,kw (Word variations have been searched)

#57 retrolental fibroplasia*:ti,ab,kw (Word variations have been searched)

#58 ADHD or attention deficit disorder*:ti,ab,kw (Word variations have been searched)

#59 atopic near/3 dermatitis:ti,ab,kw (Word variations have been searched)

#60 autism or autistic or asperger*:ti,ab,kw (Word variations have been searched)

#61 ados or hypersensitiv* or allerg*:ti,ab,kw (Word variations have been searched)

#62 Fetal and growth and retard*:ti,ab,kw (Word variations have been searched)

#63 Embryo* and Fetal Development:ti,ab,kw (Word variations have been searched)

#64 Fetus or ((fetal or fetus or intrauterine) and (growth or develop*)):ti,ab,kw (Word variations have been searched)

#65 (Preeclamp* or pre-eclamp*) or (Pregnan* and Toxemi*):ti,ab,kw (Word variations have been searched)

#66 (Gestation* or pregnan*) and (hypertens* or toxemi*):ti,ab,kw (Word variations have been searched)

#67 gestat* and (child*or newborn* or infan* or neonat*or baby or babies or pediatr* or paediatr*):ti,ab,kw (Word variations have been searched)

#68 depression and (postpartum or postnatal or post-partum or post-natal or post partum or post natal or ante-natal or antenatal or ante natal):ti,ab,kw (Word variations have been searched)

#69 grow* near/3 (child* or infant* or infancy):ti,ab,kw (Word variations have been searched)

#70 congenital and (vision near/3 disorder*):ti,ab,kw (Word variations have been searched)

#71 (learning near/3 disorder*) or dyslexi* or discalculi*:ti,ab,kw (Word variations have been searched)

#72 (respiratory near/3 illness) or asthma* or wheez* or respiratory syncitial virus:ti,ab,kw (Word variations have been searched)

#73 #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50

#74 #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72

#75 #73 or #74

#76 #33 and #75

LIMITED TO 2014-2015

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PUBMED "SIMILAR ARTICLE" SEARCH ON BABIN 2000:
Alpha linolenic acid in cholesterol esters: a marker of alphalinolenic acid intake in newborns.
Babin F, Rodriguez A, Sarda P, Vandeputte B, Mendy F, Descomps B.

Eur J Clin Nutr. 2000 Nov;54(11):840-3.
PMID: 11114678

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WEB OF SCIENCE FORWARD SEARCH ON BABIN 2000:

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SCOPUS FORWARD SEARCH ON BABIN 2000:

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DATABASE SEARCHED & TIME PERIOD COVERED:
CAB ABSTRACTS – 1/1/2000-8/28/2015

LANGUAGE:
English

SEARCH STRATEGY:
ti(omega-3 OR omega3 OR "omega 3" OR "essential fatty acid" OR "essential fatty acids" OR linolenic OR "fish oil" OR "fish oils" OR polyunsaturated OR pufa OR dha OR epa OR long chain OR longchain OR Docosapentanoic OR Docosapentaenoic OR Docosahexaenoic OR Eicosapentaenoic OR icosapentaenoic OR ((n 3 OR n3 OR n-3) AND (oil OR pufa OR fatty acid OR omega 3)) OR alpha linolenic OR alphalinolenic OR alpha-linolenic OR linolenate OR cervonic OR timnodonic OR stearidonic OR butternut OR soybean OR pumpkin seed OR menhaden OR flax OR flaxseed OR flax seed OR linseed OR rape seed OR rapeseed OR canola OR soy OR soybean OR walnut OR mustard seed OR perilla OR shiso OR walnut OR "cod liver oil" OR "codliver oil" OR "marine oil" OR "marine oils" OR "marine fat" OR salmon OR mackerel OR herring OR tuna OR halibut OR seaweed OR anchov* OR sardine* OR Ropufa OR MaxEPA OR Omacor OR Efamed OR ResQ OR Epagis OR Almarin OR Coromega OR Lovaza OR Vascepa OR icosapent ethyl OR (fish AND (consum* OR intake OR diet*)) OR “mediterranean diet” OR ((“Red blood cell” OR “red blood cells” OR phospholipid* OR plasma OR triacylglycerol OR cholesteryl OR ester OR adipos* OR fatty acid OR fatty acids OR erythrocyte OR ghost OR platelet* OR granulocyte OR neutrophil OR mononuclear OR LDL OR HDL) AND (EPA OR SDA OR stearidonic OR omega*)))
AND
ti(("Child Development" OR (gestat* AND (age* OR durat* OR week*)) OR prematur* OR preterm OR pre-term OR ((Infant* OR baby) AND (birthweight OR birth-weight OR weight)) OR newborn OR neonatal OR (grow* AND (child* OR infant* OR infancy)) OR "Retinopathy of Prematurity" OR "retrolental fibroplasia" OR ADHD OR attention deficit disorder* OR "atopic dermatitis" OR (congenital AND ("vision disorder")) OR "learning disorder" OR "learning disorders" OR dyslexi* OR discalculi* OR "respiratory illness" OR asthma* OR wheez* OR respiratory syncitial virus OR autism OR autistic OR Asperger* OR ados OR hypersensitiv* OR allerg* OR (Fetal AND growth AND retard*) OR ((embryo* OR Fetus OR fetal OR fetus OR intrauterine) AND (growth OR develop*)) OR Preeclamp* OR pre-eclamp* OR ((Gestation* OR pregnan*) AND (hypertens* OR toxemi*)) OR (gestat* AND (child*or newborn* OR infan* OR neonat*or baby OR babies OR pediatr* OR paediatr*)) OR (depression AND (postpartum OR postnatal OR post-partum OR post-natal OR post partum OR post natal OR ante-natal OR antenatal OR ante natal)) OR (grow* AND (child* OR infant* OR infancy))))

Appendix B. List of Excluded Studies

This appendix lists all studies (publications) that were identified in our literature searches that were subsequently excluded during abstract or full-text screening. Among these excluded publications were some that were included in the original report. Most of the studies included in the original report were subsequently included in our analyses, but for the sole purpose of tracking the article flow from our literature searches and the reasons for exclusion, we counted the publications from the original report that appeared in our searches as having been excluded.

Studies included in the original report that were also identified in our searches – N=31

1. Agostoni C, Marangoni F, Giovannini M, et al. Prolonged breast-feeding (six months or more) and milk fat content at six months are associated with higher developmental scores at one year of age within a breast-fed population. Adv Exp Med Biol. 2001;501:137-41. PMID: 11787675.

2. Auestad N, Halter R, Hall RT, et al. Growth and development in term infants fed long-chain polyunsaturated fatty acids: a double-masked, randomized, parallel, prospective, multivariate study. Pediatrics. 2001 Aug;108(2):372-81. PMID: 11483802.

3. Auestad N, Scott DT, Janowsky JS, et al. Visual, cognitive, and language assessments at 39 months: a follow-up study of children fed formulas containing long-chain polyunsaturated fatty acids to 1 year of age. Pediatrics. 2003 Sep;112(3 Pt 1):e177-83. PMID: 12949309.

4. Birch EE, Birch DG, Hoffman DR, et al. Dietary essential fatty acid supply and visual acuity development. Invest Ophthalmol Vis Sci. 1992 10/1992;33(11):3242-53.

5. Birch EE, Garfield S, Hoffman DR, et al. A randomized controlled trial of early dietary supply of long-chain polyunsaturated fatty acids and mental development in term infants. Dev Med Child Neurol. 2000 Mar;42(3):174-81. PMID: 10755457.

6. Birch EE, Hoffman DR, Castaneda YS, et al. A randomized controlled trial of long-chain polyunsaturated fatty acid supplementation of formula in term infants after weaning at 6 wk of age. Am J Clin Nutr. 2002 Mar;75(3):570-80. PMID: 11864865.

7. Carlson SE, Werkman SH, Rhodes PG, et al. Visual-acuity development in healthy preterm infants: effect of marine-oil supplementation. Am J Clin Nutr. 1993 7/1993;58(1):35-42.

8. de Groot RH, Hornstra G, van Houwelingen AC, et al. Effect of alpha-linolenic acid supplementation during pregnancy on maternal and neonatal polyunsaturated fatty acid status and pregnancy outcome. Am J Clin Nutr. 2004 Feb;79(2):251-60. PMID: 14749231.

9. Fewtrell MS, Abbott RA, Kennedy K, et al. Randomized, double-blind trial of long-chain polyunsaturated fatty acid supplementation with fish oil and borage oil in preterm infants. J Pediatr. 2004 Apr;144(4):471-9. PMID: 15069395.

10. Fewtrell MS, Morley R, Abbott RA, et al. Double-blind, randomized trial of long-chain polyunsaturated fatty acid supplementation in formula fed to preterm infants. Pediatrics. 2002 Jul;110(1 Pt 1):73-82. PMID: 12093949.

11. Ghys A, Bakker E, Hornstra G, et al. Red blood cell and plasma phospholipid arachidonic and docosahexaenoic acid levels at birth and cognitive development at 4 years of age. Early Hum Dev. 2002 Oct;69(1-2):83-90. PMID: 12324186.

12. Helland IB, Saugstad OD, Smith L, et al. Similar effects on infants of n-3 and n-6 fatty acids supplementation to pregnant and lactating women. Pediatrics. 2001 Nov;108(5):E82. PMID: 11694666.

13. Helland IB, Smith L, Saarem K, et al. Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. Pediatrics. 2003 Jan;111(1):e39-44. PMID: 12509593.

14. Hoffman DR, Birch EE, Birch DG, et al. Impact of early dietary intake and blood lipid composition of long-chain polyunsaturated fatty acids on later visual development. J Pediatr Gastroenterol Nutr. 2000 Nov;31(5):540-53. PMID: 11144440.

15. Innis SM, Adamkin DH, Hall RT, et al. Docosahexaenoic acid and arachidonic acid enhance growth with no adverse effects in preterm infants fed formula. J Pediatr. 2002 May;140(5):547-54. PMID: 12032520.

16. Innis SM, Gilley J, Werker J. Are human milk long-chain polyunsaturated fatty acids related to visual and neural development in breast-fed term infants? J Pediatr. 2001 Oct;139(4):532-8. PMID: 11598600.

17. Koletzko B, Sauerwald U, Keicher U, et al. Fatty acid profiles, antioxidant status, and growth of preterm infants fed diets without or with long-chain polyunsaturated fatty acids. A randomized clinical trial. Eur J Nutr. 2003 Oct;42(5):243-53. PMID: 14569405.

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No interventions of interest - N=7

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Appendix C. Evidence Table for Randomized Controlled Trials

Table C1. Evidence table for randomized controlled trials

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Agostoni et al., 2009[139] Study name: NR Study dates: Enrollment occurred May and June 2005; 1-year follow-up Study design: Trial randomized parallel Location: Italy Funding source / conflict: Manufacturer supplied product	Study Population: Healthy infants Infants enrolled 1160 Infants withdrawals 69 Infants completers 1091 Mother age: 32 years (4.5 years) NR Infant age: intervention began 1 day after discharge (NA) NA Race of Mother: White European (100%)	Inclusion Criteria: weight at birth 2500 g or more, gestational age between 37 and 42 completed weeks, single birth, absence of neonatal or birth abnormalities, Apgar score 7 or higher at 5 min, and white parents. Exclusion Criteria: presence of neonatal diseases requiring hospitalization for 7 days or more; involvement of neonate in another clinical study; unknown father; and parents unable to understand the protocol requirements, to fill out the infant's diary, or to understand and speak the Italian language adequately.	Start time: Infants 1 day after discharge from birth hospital Duration: Infants 1 year Arm 1: placebo Description: oral liquid Manufacturer: Humana Italia SpA Active ingredients: 400 IU vitamin D3 Viability: Parents were advised to store the bottles in a dry and fresh environment. Dose: 1 mL once per day Blinding: Intervention and placebo preparations were identical in aroma, taste, and texture Total N-3: 0 Arm 2: Human Italia SpA Active ingredients: 400 IU vitamin D3 Viability: Parents were advised to store the bottles in a dry and fresh environment. Dose: 1 mL once per day DHA: 20 mg DHA/ml	Outcome domain: Neurological development Outcome: age achieving gross motor: hands-and-knees crawling (weeks) (Primary) Follow-up time: varies Arm 1: Sample size 476; mean 39.4; SD (6.2) Arm 2: Sample size 482; mean 38.9; SD (6.4) Outcome: age achieving gross motor: sitting without support (weeks) (Primary) Follow-up time: varies Arm 1: Sample size 542; mean 28.3; SD (4.2) Arm 2: Sample size 551; mean 26.8; SD (4.2) Outcome: age achieving gross motor: standing alone (weeks) (Primary) Follow-up time: varies Arm 1: Sample size 542; mean 50.1; SD (8.1) Arm 2: Sample size 549; mean 49.2; SD (7.6) Outcome: age achieving gross motor: walking alone (weeks) (Primary) Follow-up time: varies Arm 1: Sample size 542; mean 55.8; SD (6.7) Arm 2: Sample size 549; mean 54.9; SD (6.8)
Almaas et al., 2015[126] Study name: Unnamed	Study Population: Preterm infants Low birth weight infants	Inclusion Criteria: Very low birth weight infants (birth weight <1500 g)	Start time: Infants (intervention began when the infant received most of his nutrients enterally: >100ml human milk/kg body weight/day	Outcome domain: Cognitive development Outcome: Weschler Abbreviated Scale of Intelligence: Full Scale IQ (Secondary)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Trial D Study dates: 2003-2014 Study design: Trial randomized parallel Location: Norway Funding source / conflict: Government, None Study follow-up: 8 years Original, same study, or follow-up studies: Henriksen, 20008[107]; Ane, 2011[125]	Infants enrolled 129 Infants completers 98 Mother age: Median: Intervention: 31 years Control: 32 years 28-35 years Infant age: Median Gestational age: Control: 28.9 weeks Intervention: 28.4 weeks Gestational age: 26.6-30.9 weeks Race of Mother: NR	Exclusion Criteria: Major congenital abnormalities and cerebral hemorrhage	Duration: Infants Until discharge or bottle of study oil was empty (average 63 days of age) Arm 1: Control Description: Study oil: soy oil and medium chain triglycerides Active ingredients: 127mg linolenic acid/100 ml milk(27.1% total fatty acids) Dose: 0.5 ml study oil/100 ml human milk Blinding: Study oils packed in numbered bottles in hospital pharmacy Maternal conditions Infant conditions ALA: 16mg/100 ml milk; 3.4% total fatty acids Current smoker 15% Low birth weight 100% Other conditions 1 Small for gestational age: 30% Arm 2: Intervention Description: DHA and AA-containing oil Manufacturer: Martek Biosciences Active ingredients: 88mg/100 ml linoleic acid per 100 ml milk (18.8%) Dose: 0.5 ml study oil per 100 ml milk, ad lib Maternal conditions Infant conditions DHA: 32mg/100ml milk (6.9%) AA: 31 mg/100 ml milk (6.7% total fatty acids Current smoker 19% Low birth weight 100% Other conditions 1 Small for gestational age: 29%	Follow-up time: 8 years Arm 1: Sample size 52; mean 93.9; SD (10) Arm 2: Sample size 45; mean 92.7; SD (8.8) Outcome: Weschler Abbreviated Scale of Intelligence: Verbal IQ (Secondary) Follow-up time: 8 years Arm 1: Sample size 52; mean 90.3; SD (12.5) Arm 2: Sample size 45; mean 88.8; SD (10.3) Outcome: Weschler Abbreviated Scale of Intelligence: performance IQ (Secondary) Follow-up time: 8 years Arm 1: Sample size 52; mean 95.9; SD (14.4) Arm 2: Sample size 45; mean 95.0; SD (12.6)
Ane C. Westerberg et	Study Population:	Inclusion Criteria: All	Start time: Infants at start of enteral feeding	Outcome domain: Cognitive development

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
al., 2011[125] Study name: Unnamed Trial D Study dates: Enrollment: December 2003 and October 2005 Study design: Trial randomized parallel Location: Norway Funding source / conflict: Multiple foundations and Societies, Manufacturer supplied product Study follow-up: 20 months	Preterm infants Infants enrolled 141 Infants completers 92 Mother age: Intervention: 30.8 years Control: 31.7 years (Intervention: 4.9 years Control: 5.0 years) 28-35 years Infant age: Mean Gestational age: Intervention: 28.7 weeks Control: 28.9 weeks (Intervention: 2.9 weeks Control: 2.7 weeks) Gestational age: 26.6-30.9 weeks Race of Mother: NR Baseline biomarker information: DHA: intervention[64.2 (23.5) mg/mL] and control group [61.3 (18.7)mg / mL], AA: intervention[205.6 (52.8) mg/mL] and control group [199.6 (48.7)mg / mL],	VLBW infants (<1500g) born between December 2003 and November 2005 at Rikshospitalet-Radiumhospitalet Medical Center, Akershus University Hospital, Buskerud Hospital, and Vestfold Hospital in Norway Exclusion Criteria: Major congenital abnormalities or cerebral hemorrhage (grade 3 or 4) as determined through ultrasonography	Duration: Infants until discharge or until the study oil bottle was empty (mean duration of supplementation was 63 days) Arm 1: Placebo Description: Soy oil Active ingredients: 127mg linolenic acid/100 ml milk(27.1% total fatty acids) Dose: 0.5 ml study oil/100 ml human milk Blinding: Study oils packed in numbered bottles in hospital pharmacy ALA: 16mg/100 ml milk; 3.4% total fatty acids Arm 2: DHA + AA group Description: DHA and AA-containing oil Manufacturer: Martek Active ingredients: 88mg/100 ml linoleic acid per 100 ml milk (18.8%) Dose: 0.5 ml study oil per 100 ml milk, ad lib Maternal conditions ALA: 11mg/100 ml milk; 3.4% total fatty acids DHA: 32mg/100ml milk (6.9%) AA: 31 mg/100 ml milk (6.7% total fatty acids Current smoker 22% during pregnancy	Outcome: Bayley Mental Development Index (MDI) (Secondary) Follow-up time: 20 months Arm 1: Sample size 42; mean 82.9; SD (13.3) Arm 2: Sample size 40; mean 83.5; SD (10.5)
Atwell et al., 2013[119]	Study Population: Preterm infants	Inclusion Criteria: Infants were eligible if	Start time: Infants birth	Outcome domain: respiratory illness Outcome: one or more hospitalizations for

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study name: DINO Study dates: 2001-2005 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies, Manufacturer supplied product, Some authors serve on scientific advisory boards for corporations Study follow-up: 18 months corrected age Original, same study, or follow-up studies: Smithers, 2008[104]; Makrides, 2009[116]; Smithers, 2010[117]; Manley, 2011[118]; Collins, 2011[105]; Collins, 2015[120]	Infants enrolled 657 Infants completers 648 Infant age: birth Race of Mother: White European (90.5%) Other race/ethnicity (9.5%)	born before 33 weeks' gestation Exclusion Criteria: Infants in other trials of fatty acid supplementation, or with major congenital or chromosomal abnormalities, or maternal contraindication for tuna oil ingestion (allergy or coagulopathy) were excluded.	Duration: Infants to 40 weeks' postmenstrual age (term) Arm 1: Standard DHA Description: Placebo/control group (soy oil) Dose: 6 soy oil capsules/ daily Blinding: capsules given to breastfeeding mothers or added to formula DHA: 0.35% in preterm formula Arm 2: High DHA Description: DHA maternal supplements or supplemented preterm formula Dose: 6 tuna oil capsules daily DHA: 900 mg in capsules or 1% infant formula	lower respiratory conditions (Secondary) Follow-up time: 18 months Arm 1: 82/335 (24.48%) Arm 2: 72/322 (22.36%)
Bergmann et al., 2012[52] Study name: NR Study dates: 2000-2009 Study design: Trial	Study Population: Healthy infants Pregnant enrolled 144 Pregnant completers 115	Inclusion Criteria: Healthy pregnant Caucasian women who were at least 18 years and willing to breastfeed for at least 3 months were	Start time: Pregnant 21 weeks gestation Duration: Pregnant 21 weeks until 3 months after delivery Arm 1: Vitamins and minerals ("basic") Description: Control 1	Outcome domain: growth Outcome: BMI (kg/m2) (Secondary) Follow-up time: 6 yrs Arm 1: Sample size 74; mean 15.5; SD (1.3) Arm 2: Sample size 41; mean 15.7; SD (1.5)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
randomized parallel Location: Germany Funding source / conflict: NR, None, Manufacturer supplied product Study follow-up: 6 years Original, same study, or follow-up studies: Bergmann, 2012[41]	Infants enrolled 123 Infants completers 115 Pregnant age: 30.9 years (4.89) Infant age: 21 weeks gestation Race of Mother: White European (100) Baseline biomarker information: In previous study, see refid 2803	enrolled at 21 weeks of gestation Exclusion Criteria: Mothers: increased risk of premature delivery or multiple pregnancy, allergy to cow milk protein, lactose intolerance, diabetes, smoking, consumption of alcohol (>20 g/week), or participation in another study Infants: Premature at birth (<37 weeks' gestation), had any major malformations, or were hospitalized for more than one week	Manufacturer: Nestle Arm 2: Basic supplements plus a prebiotic fructooligosaccharide (FOS) Description: Control 2 Manufacturer: Nestle Arm 3: Basic supplements, FOS, and fish oil Description: Intervention Manufacturer: Nestle DHA: 200 mg EPA: 60 mg	Outcome: head circumference (cm) (Secondary) Follow-up time: 6 yrs Arm 1: Sample size 74; mean 52.7; SD (1.3) Arm 2: Sample size 41; mean 52.5; SD (1.6) Outcome: height (cm) (Secondary) Follow-up time: 6 yrs Arm 1: Sample size 74; mean 119.6; SD (4.6) Arm 2: Sample size 41; mean 119.2; SD (5.3) Outcome: weight (kg) (Secondary) Follow-up time: 6 yrs Arm 1: Sample size 74; mean 22.3; SD (2.9) Arm 2: Sample size 41; mean 22.4; SD (3.1)
Birch et al., 2005[111] Study name: NR Study dates: Not reported Study design: Trial randomized parallel Location: US Funding source /	Study Population: Healthy infants Infants enrolled 103 Infants completers 86 Pregnant age: 31 years (4 years) Infant age: 3.6 _x0004_days (1.3 days) 1-5 days	Inclusion Criteria: All were born at 37– 40 wk after conception. Only singleton births with birth weight appropriate for gestational age Exclusion Criteria: Family history of milk protein allergy, genetic or familial eye disease, vegetarian or vegan	Start time: Infants 1-5 days Duration: Infants 52 wks Arm 1: Control Description: Commercial infant formula Brand name: Enfamil with Iron Manufacturer: Mead Johnson Nutritionals, Evansville, IN Active ingredients: Linoleic acid-8.48g/L (14.6%); 14.7 g protein/L, 37.5 g fat/L, 69.0 g carbohydrate/L Blinding: Each diet was masked by 2 color and	Outcome domain: Visual function Reason results are not reported: data only reported on graph Outcome: (Primary) Outcome domain: growth Reason results are not reported: data only reported on graph Outcome: (Secondary)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
conflict: Government, Manufacturer supplied product	Race of Mother: NR	maternal dietary patterns, maternal metabolic disease or infection, jaundice, perinatal asphyxia, meconium aspiration, or any perinatal event that resulted in placement of the infant in the neonatal intensive care unit.	2 number codes, for a total of 4 possible diet assignments. The randomization schedule had random-length blocks (block length varied from 6 to 12) and was provided in individual sealed envelopes to the study site. ALA: 1.5% of total fatty acids Arm 2: LCPUFA-supplemented formula Description: Commercial formula supplemented with LCPUFA Brand name: Enfamil with Iron plus DHASCO and ARASCO Manufacturer: Formula: Mead Johnson; DHA+ARA: Martek Biosciences Active ingredients: 15% linoleic acid,14.7 g /L protein, 37.5 g /L fat, 69.0 g /L carbohydrate ALA: 1.5% of total fatty acids DHA: 0.36% of total fatty acids AA: 0.72% of total fatty acids	
Birch et al., 2007[146] Study name: Birch Study dates: 1993-1999 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product	Study Population: Healthy infants, Pregnant women whose unborn children were at high risk of developing asthma Infants enrolled 79+40BF Infants completers 52+32BF Infant age: birth (0-5 days) Race of Mother: NR	Inclusion Criteria: All participants were born at 37 to 40 weeks postmenstrual age. Only singleton births with birthweights appropriate for gestational age Exclusion Criteria: family history of milk-protein allergy, genetic or familial eye disease (e.g. hereditary retinal disease, strabismus), vegetarian or vegan	Start time: Infants birth (0-5 days) Duration: Infants 17 weeks Arm 1: Control Description: standard infant formula without added n-3 FA Brand name: Enfamil with Iron Manufacturer: Mead Johnson Nutritionals Active ingredients: linoleic acid: 15% of total fats ALA: 1.5% of total fats Arm 2: DHA Description: infant formula fortified with DHA Brand name: Enfamil with Iron, supplemented	Outcome domain: Cognitive development Outcome: Wechsler Preschool and Primary Scale of Intelligence: Full-Scale IQ (Secondary) Follow-up time: 4 years Arm 1: Sample size 19; mean 101.0; SE (2.6) Arm 2: Sample size 16; mean 105.9; SE (3.9) Arm 3: Sample size 32; mean 107.5; SE (3.1) Outcome: Wechsler Preschool and Primary Scale of Intelligence: Performance IQ (Secondary) Follow-up time: 4 years Arm 1: Sample size 19; mean 104.2; SE

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study follow-up: 4 years		maternal dietary patterns, maternal metabolic disease, anemia, or infection, presence of a congenital malformation or infection, jaundice, perinatal asphyxia, meconium aspiration, and any perinatal event which resulted in placement of the infant in the neonatal intensive care unit	with DHASCO Manufacturer: Formula: Mead Johnson; DHA: Martek Biosciences Active ingredients: linoleic acid: 15% of total fats ALA: 1.5% DHA: 0.36% Arm 3: DHA+ARA Description: infant formula fortified with DHA and ARA Brand name: Enfamil with Iron, fortified with DHASCO and ARASCO Manufacturer: Formula: Mead-Johnson; DHA, ARA: Martek Biosciences Active ingredients: linoleic acid 15% ALA: 1.5% DHA: 0.36% AA: 0.72%	(2.7) Arm 2: Sample size 16; mean 108.1; SE (3.8) Arm 3: Sample size 32; mean 108.6; SE (3.3) Outcome: Wechsler Preschool and Primary Scale of Intelligence: Verbal IQ (Secondary) Follow-up time: 4 years Arm 1: Sample size 19; mean 98.8; SE (2.6) Arm 2: Sample size 16; mean 102.7; SE (4.1) Arm 3: Sample size 32; mean 104.5; SE (2.9) Outcome domain: Visual function Outcome: Visual acuity Left Eye (log minimum angle of resolution in minutes of arc) (Primary) Follow-up time: 4 years Arm 1: Sample size 19; mean 0.05; SE (0.016) Arm 2: Sample size 16; mean 0.02; SE (0.018) Arm 3: Sample size 17; mean 0.03; SE (0.017) Outcome: Visual acuity Right Eye (log minimum angle of resolution in minutes of arc) (Primary) Follow-up time: 4 years Arm 1: Sample size 19; mean 0.08; SE (0.022) Arm 2: Sample size 16; mean 0.02; SE (0.019) Arm 3: Sample size 17; mean 0.03; SE

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(0.017)
Birch et al., 2010[121] Study name: Diamond Study dates: 2003-2006 Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Some authors employed by industry (companies that make the supplements) Original, same study, or follow-up studies: Drover, 2011[122]; Drover. 2012[123]; Colombo, 2013[124]; Currie, 2015[115]	Study Population: Healthy infants Infants enrolled 343 Infants completers 244 Pregnant age: NR Mother age: NR Infant age: 1-9 days Race of Mother: NR	Inclusion Criteria: Healthy term formula-fed, singleton-birth infants born in any of 5 hospitals Exclusion Criteria: Infants who had received human milk within 24 h of randomization or who had diseases or congenital abnormalities likely to interfere with normal growth and development or with the normal maturation of visual or cognitive function, poor formula intake, or known or suspected intolerance to cow milk infant formula were excluded from the study. Also excluded were infants born to mothers with chronic illness, such as HIV disease, renal or hepatic disease, type 1 or type 2 diabetes, alcoholism, or substance abuse	Start time: Infants 4-9 days of age Duration: Infants 12 months Arm 1: Control Brand name: Enfamil with IRon Manufacturer: Mead-Johnson Nutrition, Evansville IN Arm 2: 0.32% DHA Brand name: Enfamil LIPIL Manufacturer: Mead-Johnson; DHA and ARA from algal and fungal oils manufactured by Martek Biosciences Dose: not specified Blinding: not specified DHA: 0.32% or 17mg/100kcal AA: 0.64% FA or 34mg/100kcal Arm 3: 0.64% DHA Brand name: not specified Manufacturer: not specified DHA: 34mg/100kg AA: 0.64% FA or 34mg/100kcal Arm 4: 0.96% DHA Brand name: not specified Manufacturer: not specified DHA: 51mg/100kg AA: 0.64% FA or 34mg/100kcal	Outcome domain: Visual function Reason results are not reported: data only reported on graph Outcome: (Primary)
Bouwstra et al., 2003[62]	Study Population:	Inclusion Criteria:	Start time: Infants Birth	Outcome domain: Neurological

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study name: Groningen LCPUFA study Study dates: 1997-1999 Study design: Trial randomized parallel Location: Netherlands Funding source / conflict: Industry Study follow-up: 3 months Original, same study, or follow-up studies: Bouwstra, 2005[63]; de Jong, 2010[64]; de Jong, 2012[65]; van Goor, 2010[36]; Goor, 2011[66]	Healthy infants Infants enrolled 472 Infants completers 397 Mother age: 31 (5) NR Infant age: Gestational age 39.6 wk (1.3) NR Race of Mother: White European (100)	healthy term infants Exclusion Criteria: infants who had a congenital disorder that interfered with adequate functioning in daily life, infants from multiple births, infants whose mothers did not have mastery of the Dutch language or suffered from significant illness or disability, adopted and foster infants, and formula-fed infants who had received human milk for >5 d.	Duration: Infants 2 months Arm 1: Control formula Description: Standard formula with no supplemental LCPUFA Brand name: Nutrilon premium Manufacturer: Zoetermeer, Netherlands Active ingredients: linoleic acid (11mol%); ALA 1.27 mol% Dose: ad lib Blinding: not reported Maternal conditions Current smoker 32% during pregnancy Maternal abuse of alcohol/psychotropic drugs Alcohol USE during pregnancy 10% Arm 2: LCPUFA formula Description: LCPUFA formula fortified with n-3s and n-6s Brand name: NR Maternal conditions DHA: 0.30% (by wt) AA: h 0.45% (by wt) Current smoker 32% smoked during pregnancy Maternal abuse of alcohol/psychotropic drugs 13% used alcohol during pregnancy Arm 3: breastfed group Description: breastfed, no formula, not randomized here - used as reference group Maternal conditions Current smoker 28% smoked during pregnancy Maternal abuse of alcohol/psychotropic drugs 38% consumed alcohol during pregnancy	development Outcome: mildly abnormal general movements (Primary) Follow-up time: 3 months Arm 1: 41/131 (31.0%) Arm 2: 23/119 (19.0%) Outcome: normal-optimal general movements (Primary) Follow-up time: 3 months Arm 1: 28/131 (21.0%) Arm 2: 21/119 (18.0%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Bouwstra et al., 2005[63] Study name: Groningen LCPUFA study Study dates: 1997-2002 Study design: Trial randomized parallel Location: Netherlands Funding source / conflict: Industry Study follow-up: 18 months Original, same study, or follow-up studies: Bouwstra, 2003[62]; de Jong, 2010[64]; de Jong, 2012[65]; van Goor, 2010[36]; Goor, 2011[66]	Study Population: Healthy infants Infants enrolled 472 Infants completers 446 Mother age: 31 years (5 years) NR Infant age: birth Race of Mother: White European (100%)	Inclusion Criteria: healthy term infants Exclusion Criteria: infants who had a congenital disorder that interfered with adequate functioning in daily life, infants from multiple births, infants whose mothers did not have mastery of the Dutch language or suffered from significant illness or disability, adopted and foster infants, and formula-fed infants who had received human milk for >5 d.	Start time: Infants Birth Duration: Infants 2 months Arm 1: Control group Description: Standard formula Brand name: Nutrilon premium Manufacturer: Zoetermeer, Netherlands Active ingredients: linoleic acid (11mol%); ALA 1.27 mol% Dose: ad lib Maternal conditions Current smoker 31% during pregnancy Maternal abuse of alcohol/psychotropic drugs Alcohol USE during pregnancy 8% Arm 2: LCPUFA formula Description: LCPUFA formula Dose: ad lib Maternal conditions DHA: 0.30% DHA AA: 0.45% AA Current smoker 31% during pregnancy Maternal abuse of alcohol/psychotropic drugs 9% used alcohol during pregnancy Arm 3: breast feeding group Description: breast fed, no formula Maternal conditions Current smoker 19% smoked during pregnancy Maternal abuse of alcohol/psychotropic drugs 24% used alcohol during pregnancy	Outcome domain: Cognitive development Outcome: Bayley Scales of Infant Development (Mental Development Index) (Secondary) Follow-up time: 18 months Arm 1: Sample size 155; mean 105.4; SD (15) Arm 2: Sample size 135; mean 102.7; SD (15.4) Outcome domain: Neurological development Outcome: Bayley PDI (Secondary) Follow-up time: 18 months Arm 1: Sample size 169; mean 100.9; SD (13.6) Arm 2: Sample size 146; mean 99.4; SD (13.4) Outcome: neurological optimality score (Secondary) Follow-up time: 18 months Arm 1: Sample size 169; median 52.0; 5, 95 percentile Arm 2: Sample size 146; median 52.0; 5, 95 percentile Outcome: number of children with minor neurological dysfunction (Secondary) Follow-up time: 18 months Arm 1: 8/169 (5.0%) Arm 2: 10/146 (7.0%)
Brew et al., 2015[165] Study name: CAPS	Study Population: Healthy infants	Inclusion Criteria: parent or an older sibling had a history of	Start time: Infants Birth Duration: Infants 8 years	Outcome domain: Cognitive development Outcome: National Assessment Program Literacy and Numeracy (NAPLAN):

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study dates: September 1997 to 1999-2008 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government Study follow-up: 3, 5, 7, and 9 years of school Original, same study, or follow-up studies: Mihrshahi, 2003[166]; Mihrshahi, 2004[167]; Mihrshahi, 2006[168]; Toelle, 2010[169]	Infants enrolled 616 Infants completers 239 Pregnant age: 29.8 (4.90) Infant age: NR Race of Mother: NR (NR) Baseline biomarker information: Total n-3 PUFA (DHA+EPA+DPA+ALA) as % of total fatty acids at 4 ages (on a bar chart): 18 months: Intervention 72% Controls: 48% 3 years Intervention 64% Controls: 46% 5 years Intervention 62% Controls: 50% 8 years: Intervention 50% Controls: 45% Baseline Omega-3 intake: 500 mg of tuna fish oil, daily, which comprised 37% LCPUFA (including 135 mg of DHA and 32 mg of EPA per capsule) and 6% omega-6 PUFA (linoleic acid,	asthma or recurrent wheezing, and that the child was born at 436 weeks of gestation Exclusion Criteria: NR	Arm 1: Intervention Description: d 500 mg of tuna fish oil 37% LCPUFA Manufacturer: Nu-Mega Industries Pty Ltd, Brisbane, Australia DHA: 135 mg EPA: 32 mg AA: 6% of omega 3PUFA (linoleic acid, arachidonic acid, docosapentaenoic acid) Arm 2: Control Description: a daily Sunola oil capsule Manufacturer: Nu-Mega Industries ALA: 0.3%	numeracy score (difference in NAPLAN units) (Secondary) Follow-up time: 10-11 years 239; difference in means -13.7; 95% CI Follow-up time: 12-13 years 239; difference in means -11.7; 95% CI Follow-up time: 14-15 years 239; difference in means -24.1; 95% CI Follow-up time: 8-9 years 239; difference in means -25.4; 95% CI Outcome: National Assessment Program Literacy and Numeracy (NAPLAN): reading score (difference in NAPLAN units) (Secondary) Follow-up time: 10-11 years 239; difference in means -3.2; 95% CI Follow-up time: 12-13 years 239; difference in means -7.0; 95% CI Follow-up time: 14-15 years 239; difference in means -19.9; 95% CI Follow-up time: 8-9 years 239; difference in means -27.03; 95% CI

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	arachidonic acid and docosapentaenoic acid)			
Campoy et al., 2011[141] Study name: NR Study dates: NR, <2011 Study design: Trial randomized factorial design Location: Germany, Spain, Hungary Funding source / conflict: Government, None Study follow-up: 6.5 years Original, same study, or follow-up studies: Escolano-Margarit, 2011[130]	Study Population: Healthy pregnant women Pregnant enrolled 315 Pregnant completers 154 Pregnant age: 31 years (NR) Race of Mother: White European (99%) Baseline biomarker information: From Krauss, 2007 mean DHA Placebo group 5.95 Fish oil group 5.75 5-MHTF (folic acid) group 5.68 Fish oil + 5-MHTF group 5.89 mean EPA Placebo group 0.28 Fish oil group 0.18 5-MHTF (folic acid) group 0.17 Fish oil + 5-MHTF group 0.22	Inclusion Criteria: health pregnant women, singleton pregnancy, gestation 20 week at enrollment, body weight between 50 and 92 kg at study entry, and intention to deliver in one of the obstetrical centers Exclusion Criteria: serious chronic illness (e.g., diabetes, hepatitis, or chronic enteric disease), use of FO supplements since the beginning of pregnancy or folate or vitamin B-12 supplements after gestation week 16	Start time: Pregnant 22 weeks gestation Infants 22 weeks gestation Duration: Pregnant until birth Infants until birth Arm 1: placebo Description: milk-based supplement Brand name: Blemil Plus Manufacturer: Ordesa Laboratorios, Barcelona, Spain) Active ingredients: vitamins and minerals in amounts meeting the recommended intakes during the second half of pregnancy for European women Dose: one daily dose of 15 g Blinding: supplements were not distinguishable with respect to the appearance of the sachets or to their contents Maternal conditions Current smoker during pregnancy 8.9% Arm 2: fish oil Description: fish oil in milk-based supplement Manufacturer: Pronova Biocare, Lysaker, Norway Active ingredients: vitamins and minerals in amounts meeting the recommended intakes during the second half of pregnancy for European women Dose: one 15 g dose Maternal conditions DHA: 500 mg EPA: 100 mg	Outcome domain: Cognitive development Outcome: Kauffman Assessment Battery for Children: Mental Processing Composite (Secondary) Follow-up time: 6.5 years Arm 1: Sample size 45; median 110.0; IQR (14.5) Arm 2: Sample size 37; median 110.0; IQR (11) Arm 3: Sample size 35; median 108.0; IQR (12) Arm 4: Sample size 37; median 108.0; IQR (10.5) Outcome: Kauffman Assessment Battery for Children: Sequential Processing Scale (Secondary) Follow-up time: 6.5 years Arm 1: Sample size 45; median 106.0; IQR (19) Arm 2: Sample size 37; median 108.0; IQR (12) Arm 3: Sample size 35; median 104.0; IQR (14) Arm 4: Sample size 37; median 104.0; IQR (17) Outcome: Kauffman Assessment Battery for Children: Simultaneous Processing Scale (Secondary) Follow-up time: 6.5 years Arm 1: Sample size 45; median 112.0; IQR (11.5) Arm 2: Sample size 37; median 112.0; IQR (10.5)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			Current smoker during pregnancy 18.9% Arm 3: folic acid Description: 400 ug 5-MTHF Manufacturer: BASF, Ludwigshafen, Germany Active ingredients: vitamins and minerals in amounts meeting the recommended intakes during the second half of pregnancy for European women Dose: one 15 g dose Maternal conditions Current smoker during pregnancy 17.1% Arm 4: folic acid + fish oil Description: 400 _x0001_g 5-MTHF +fish oil Manufacturer: BASF, Ludwigshafen, Germany Active ingredients: vitamins and minerals in amounts meeting the recommended intakes during the second half of pregnancy for European women Dose: one 15 g dose Maternal conditions DHA: 500 mg EPA: 100 mg Current smoker during pregnancy 18.9%	Arm 3: Sample size 35; median 109.0; IQR (14) Arm 4: Sample size 37; median 110.0; IQR (10.5)
Carlson et al., 1996[160] Study name: NR Study dates: NR (<1995) Study design: Trial randomized parallel	Study Population: Preterm infants Infants enrolled 59 Infants completers 27 Infant age: 3 days (NR) 2 to 5 days Race of Mother: NR	Inclusion Criteria: infants weighing between 747 and 1275 g at birth who achieved full enteral feeding of 418 kJ (100 kcal)/kg/d by 6 wk of age and tolerated enteral feeding thereafter	Start time: Infants 3 days after birth Duration: Infants 2 months Arm 1: Placebo Description: standard formula Brand name: Similac Special Care Manufacturer: Ross Products Division, Abbott Laboratories Infant conditions	Outcome domain: Cognitive development Outcome: Fagan Test of Intelligence: time/look (seconds) (Secondary) Follow-up time: 12 months Arm 1: Sample size 12; mean 1.3; SD (0.1) Arm 2: Sample size 15; mean 1.13; SD (0.07) Outcome: Fagan Test of Intelligence: looks to familiar (number) (Secondary)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Location: US Funding source / conflict: Government, Manufacturer supplied product Study follow-up: 12 months	(100)	Exclusion Criteria: intraventricular or periventricular hemorrhage > grade 2, a history of maternal cocaine or alcohol abuse, congenital anomalies likely to affect long-term growth and development, or intrauterine growth retardation defined as a weight for gestational age below the 5th percentile	ALA: 2.4 g / 100 g Other dose 1: linolenic acid 21.2 g/ 100 g Pre-term birth 100% Other conditions 1 bronchopulmonarydysplasia (BPD) or chronic lung disease of % Arm 2: DHA supplement Description: formula supplemented with DHA from marine oil Brand name: Similac Special Care (plus marine oil) Manufacturer: Ross Products Division, Abbott Laboratories Infant conditions ALA: 2.4 g / 100 g DHA: 0.20 g / 100g EPA: 0.06 g / 100 g Other dose 1: linolenic acid 21.2 g/ 100 g Pre-term birth 100% Other conditions 1 bronchopulmonarydysplasia (BPD) or chronic lung disease of- %	Follow-up time: 12 months Arm 1: Sample size 12; mean 17.5; SD (1.4) Arm 2: Sample size 15; mean 21.5; SD (1.3) Outcome: Fagan Test of Intelligence: looks to novel (number) (Secondary) Follow-up time: 12 months Arm 1: Sample size 12; mean 22.9; SD (1.5) Arm 2: Sample size 15; mean 25.3; SD (1.6) Outcome: Fagan Test of Intelligence: novel time (% of total) (Secondary) Follow-up time: 12 months Arm 1: Sample size 12; mean 64.0; SD (1.9) Arm 2: Sample size 15; mean 59.7; SD (1.7) Outcome: Fagan Test of Intelligence: time to familiar (seconds) (Secondary) Follow-up time: 12 months Arm 1: Sample size 12; mean 16.9; SD (1) Arm 2: Sample size 15; mean 19.3; SD (0.9) Outcome: Fagan Test of Intelligence: time to novel (seconds) (Secondary) Follow-up time: 12 months Arm 1: Sample size 12; mean 33.1; SD (1.4) Arm 2: Sample size 15; mean 31.5; SD (1.5) Outcome: Fagan Test of Intelligence: time/familiar look (seconds) (Secondary) Follow-up time: 12 months Arm 1: Sample size 12; mean 1.04; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(0.11) Arm 2: Sample size 15; mean 0.95; SD (0.08) Outcome: Fagan Test of Intelligence: time/novel look (seconds) (Secondary) Follow-up time: 12 months Arm 1: Sample size 12; mean 1.49; SD (0.09) Arm 2: Sample size 15; mean 1.28; SD (0.06) Outcome: Fagan Test of Intelligence: total looks (number) (Secondary) Follow-up time: 12 months Arm 1: Sample size 12; mean 40.4; SD (2.7) Arm 2: Sample size 15; mean 46.8; SD (2.7) Outcome: Fagan Test of Intelligence: total time (seconds) (Secondary) Follow-up time: 12 months Arm 1: Sample size 12; mean 50.0; SD (1.6) Arm 2: Sample size 15; mean 50.8; SD (1.7)
Carlson et al., 2013[31] Study name: NR Study dates: 2006.01-2011.10 Study design: Trial randomized parallel Location: US	Study Population: Healthy pregnant women Pregnant enrolled 350 Pregnant withdrawals 49 Pregnant completers 301 Pregnant age: placebo: 24.8; DHA: 25.3	Inclusion Criteria: English speaking, between 8 and 20 wk of gestation, between 16 and 35.99 y of age, and planning to deliver at a hospital in the Kansas City metropolitan area Exclusion Criteria:	Start time: Pregnant 99.6/102.9 day Duration: Pregnant enrollment to birth Arm 1: Placebo Description: half soybean and half coin oil Manufacturer: DSM Nutritional Products) Active ingredients: a-linolenic acid Dose: 3 *capsule 200/day Blinding: both DHA and placebo capsules were orange flavored	Outcome domain: Birth weight Outcome: birth weight (g) (Primary) Follow-up time: birth Arm 1: Sample size 147; mean 3187.0; SD (602) Arm 2: Sample size 154; mean 3359.0; SD (524) Outcome domain: Gestational hypertension preeclampsia eclampsia Outcome: preeclampsia (Secondary)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Funding source / conflict: Government, Manufacturer supplied product	(placebo 4.7; DHA 4.9) Race of Mother: Black (46%;37%) Non-black (54%; 63%) Baseline biomarker information: RBC-phospholipid-DHA (placebo group 4.3 +- 1.3; 4.3 +- 1.1) Baseline Omega-3 intake: Voluntary DHA intake from supplement (placebo group 15%, DHA group 9%)	carrying more than one fetus, had preexisting diabetes mellitus or systolic blood pressure $140 mm Hg at enrollment, or had any serious health condition likely to affect the prenatal or postnatal growth and development of their offspring, including cancer, lupus, hepatitis, HIV/AIDS, or a diagnosed alcohol or chemical dependency, or if the initial screening based on their self-reported weight and height suggested a BMI (in kg/m2 >=40).	Arm 2: DHA Description: marine algae-oil source of DHA Manufacturer: DHASCO; DSM Nutritional Products, formerly Martek Biosciences) Dose: 200 mg capsule, 3 times a day DHA: 200mg/capsule * 3	Follow-up time: during pregnancy Arm 1: 2/147 (1.3%) Arm 2: 2/154 (1.3%) Outcome domain: LBW Outcome: birthweight <1500g (Secondary) Follow-up time: birth Arm 1: 5/147 (3.4%) Arm 2: 0/154 (0.0%) Outcome: birthweight <2500g (Secondary) Follow-up time: birth Arm 1: 13/147 (9.0%) Arm 2: 6/154 (3.9%) Outcome domain: duration of gestation Outcome: gestational age (days) (Primary) Follow-up time: birth Arm 1: Sample size 147; mean 272.8; SD (17) Arm 2: Sample size 154; mean 275.7; SD (11.2) Outcome: incidence of premature birth (Secondary) Follow-up time: birth Arm 1: 13/147 (8.8%) Arm 2: 12/154 (7.8%)
Cheatham et al., 2011[129] Study name: Danish National Birth Cohort-Lactating Women Study dates: 1998-2007 Study design:	Study Population: Healthy infants Pregnant enrolled 150 Pregnant completers 98 Infants enrolled 98 Infants completers 92	Inclusion Criteria: Described in Ref. 26 All the children who participated in the 9 month follow-up visit (n = 149) were invited to participate in the 7 year follow-up study.	Start time: Pregnant birth Duration: Pregnant 9 months Arm 1: Fish oil Manufacturer: m BASF Health and Nutrition A/S, Ballerup, Denmark DHA: 0.62 g EPA: 0.79 g	Outcome domain: Cognitive development Outcome: Stroop scores (Secondary) Follow-up time: 7.5 years Arm 1: Sample size 28; mean -0.21; SD (0.1) Arm 2: Sample size 35; mean -0.23; SD (0.14) Outcome: Woodcock Johnson Test: Standardized speed of processing

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Observational prospective Location: Denmark Funding source / conflict: Government Study follow-up: 7 years Original, same study, or follow-up studies: Lauritzen, 2004[127]; Lauritzen, 2005[102]; Lauritzen, 2005[128]	Infant age: 7.5 Race of Mother: NR (100)	Exclusion Criteria: Living outside Zealand	Total N-3: 1.5 g/d LCPUFA Arm 2: Olive oil Manufacturer: m BASF Health and Nutrition A/S, Ballerup, Denmark	(Secondary) Follow-up time: 7.5 years Arm 1: Sample size 27; mean 1.02; SD (0.26) Arm 2: Sample size 36; mean 0.96; SD (0.26)
Clandinin et al., 2005[108] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: Canada Funding source / conflict: Industry	Study Population: Preterm infants Infants enrolled 361 preterm+105 term breastfed Infants completers 179 preterm and 76/105 term breastfed Infant age: 30.6 weeks postmenstrual age 24-36 weeks postmenstrual age Race of Mother: NR (100)	Inclusion Criteria: Phase I: gestational age <35 weeks PMA and received <10 total days of enteral feedings of >30 mL/kg per day. Infants initially fed human milk were not enrolled unless formula was started within 10 days after completing the first day of human milk feeding Phase II: completion of phase I and >=80% enteral intake from study formula during hospitalization and 100% of caloric intake	Start time: Infants 10 days of age Duration: Infants 118 weeks Arm 1: Control Description: Non-supplemented premature, discharge, and term formula Dose: Ad lib Blinding: Not reported Infant conditions Pre-term birth 119 (100%) Arm 2: Algal-DHA Description: supplemented premature infant formula supplemented with DHA from algal oil Manufacturer: Martek Biosciences Dose: ad lib DHA: 17mg/100kcal (0.33% by weight) EPA: 0.1% by weight AA: 34mg/100kcal (0.67% by weight)	Outcome domain: Cognitive development Outcome: Bayley Scale of Infant Development II (Mental developmental index) (Unspecified) Follow-up time: 118 weeks Arm 1: Sample size 54; mean 77.0; SE (2) Arm 2: Sample size 44; mean 83.0; SE (2) Arm 3: Sample size 60; mean 87.0; SE (2) Arm 4: Sample size 58; mean 98.0; SE (2) Outcome domain: Neurological development Outcome: Bayley Scale of Infant Development II (Physical developmental index) (Unspecified) Follow-up time: 118 weeks Arm 1: Sample size 54; mean 83.0; SE (2) Arm 2: Sample size 46; mean 88.0; SE (2) Arm 3: Sample size 59; mean 88.0; SE (2) Arm 4: Sample size 59; mean 98.0; SE (2)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		from study formula at completion of phase 1. Birth weight<1500g Exclusion Criteria: congenital abnormalities of the gastrointestinal tract, hepatitis, hepatic or biliary pathology, necrotizing enterocolitis confirmed before enrollment, or history of underlying disease or congenital malformation likely to interfere with evaluation	Arm 3: Fish-DHA Description: Premature infant formula supplemented with DHA from tuna fish oil Manufacturer: Martek Biosciences Dose: ad lib DHA: 17mg DHA/100 kcal AA: 34mg/100 kcal Arm 4: Reference Description: Breast fed term infants	Outcome domain: growth Reason results are not reported: data only reported on graph Outcome: (Unspecified)
Collins et al., 2011[105] Study name: DINO Study dates: 2001-2007 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Manufacturer supplied product Study follow-up: 18	Study Population: Preterm infants Postpartum women Breast-feeding women Pregnant enrolled 545 Infants enrolled 657 Infants completers 598 Pregnant age: high DHA group 29.9; standard DHA group 30.2 (high DHA group 5.8; standard DHA group 5.4)	Inclusion Criteria: infant born <33 weeks gestation Exclusion Criteria: Infants were excluded if they had major congenital or chromosomal abnormalities; were a multiple birth where not all live births were eligible; were in other trials of fatty acid supplementation or had a lactating mother where tuna oil was	Start time: Infants birth Duration: NR Arm 1: standard DHA Description: placebo soya oil capsules for lactating women and/or standard pre-term formula Manufacturer: Capsule: Clover Corporation; Formula: Mead Johnson Nutritionals and Nutricia Australasia Dose: 6*500mg placebo soya oil capsules Blinding: All capsules were similar in size, shape and colour. Formula was packaged by colour code. Parents, clinicians and all research personnel were blinded to the participant's study group	Outcome domain: growth Outcome: head circumference (cm) (Secondary) Follow-up time: 12 months Arm 1: Sample size 231; mean 46.2; SD (1.8) Arm 2: Sample size 225; mean 46.1; SD (1.8) Follow-up time: 18 months Arm 1: Sample size 305; mean 47.8; SD (1.7) Arm 2: Sample size 282; mean 47.8; SD (1.8) Follow-up time: 4 months Arm 1: Sample size 312; mean 41.8; SD (1.7) Arm 2: Sample size 289; mean 41.6; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
months Original, same study, or follow-up studies: Smithers, 2008[104]; Makrides, 2009[116]; Smithers, 2010[117]; Manley, 2011[118]; Atwell, 2013[119]; Collins, 2015[120]	Infant age: 4 day high DHA 3-6; standard 2-5 Race of Mother: NR (100)	contraindicated (bleeding disorders, anticoagulants).	 Arm 2: High DHA Description: tuna oil capsules or DHA pre-term formula Manufacturer: Capsule: Clover Corporation; Formula: Mead Johnson Nutritionals and Nutricia Australasia Dose: six 500 mg DHA-rich tuna oil capsules per day	(1.7) Outcome: length (cm) (Secondary) Follow-up time: 12 months Arm 1: Sample size 239; mean 74.1; SD (3.7) Arm 2: Sample size 226; mean 74.3; SD (3.6) Follow-up time: 18 months Arm 1: Sample size 306; mean 81.2; SD (3.9) Arm 2: Sample size 286; mean 81.9; SD (4) Follow-up time: 4 months Arm 1: Sample size 311; mean 61.2; SD (3.4) Arm 2: Sample size 294; mean 61.3; SD (3.2) Outcome: weight (g) (Secondary) Follow-up time: 12 months Arm 1: Sample size 240; mean 9195.0; SD (1410) Arm 2: Sample size 231; mean 9317.0; SD (1455) Follow-up time: 18 months Arm 1: Sample size 306; mean 10775.; SD (1520) Arm 2: Sample size 292; mean 11029.; SD (1764) Follow-up time: 4 months Arm 1: Sample size 316; mean 6203.0; SD (1059) Arm 2: Sample size 299; mean 6218.0; SD (1013)
Collins et al., 2015[120]	Study Population: Preterm infants	Inclusion Criteria: infants born at <33	Start time: Infants within 5 days of 1st enteral feeding	Outcome domain: ADHD Outcome: ADHD Conners 3 AI-parent:

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study name: DINO Study dates: 2001-2013 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Industry, Government Study follow-up: 7 years Original, same study, or follow-up studies: Smithers, 2008[104]; Makrides, 2009[116]; Smithers, 2010[117]; Manley, 2011[118]; Collins, 2011[105]; Atwell, 2013[119]; Collins, 2015[120]	Infants enrolled 657 Infants completers 604 Infant age: median 30 weeks gestational age 28-31 weeks Race of Mother: NR (100)	weeks' gestation from five Australian tertiary hospitals between 2001 and 2005 Exclusion Criteria: a major congenital or chromosomal abnormality, multiple birth in which not all live-born infants were eligible, enrollment in other trials of fatty acid supplementation, or if fish oil was contraindicated in the lactating mother	Duration: Infants to expected due date Arm 1: standard DHA Description: DHA supplementation of infant formula or breastfeeding mothers to achieve DHA concentrations of term formula fed infants DHA: ___20 mg/kg/ day of DHA Arm 2: High DHA Description: DHA supplementation of infant formula or breastfeeding mothers to achieve DHA concentration of breastmilk DHA: ___50 mg/kg/ day of DHA	ADHD t score (total score) (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 64.4; SD (18.7) Arm 2: Sample size 291; mean 65.6; SD (18.5) Outcome: number with ADHD (parent reported) (Secondary) Follow-up time: 7 years Arm 1: 7/298 (2.3%) Arm 2: 9/285 (3.16%) Outcome domain: Autism Outcome: number with autism spectrum disorder Follow-up time: 7 years Arm 1: 9/298 (3.0%) Arm 2: 10/285 (3.5%) Outcome domain: Cognitive development Outcome: Weschler Abbreviated Scale of Intelligence: Full Scale IQ (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 98.5; SD (14.9) Arm 2: Sample size 291; mean 98.3; SD (14) Outcome: Weschler Abbreviated Scale of Intelligence: Performance IQ (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 98.5; SD (13.6) Arm 2: Sample size 291; mean 98.5; SD (14.5) Outcome: Weschler Abbreviated Scale of Intelligence: Verbal IQ (Secondary)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Follow-up time: 7 years Arm 1: Sample size 313; mean 98.8; SD (15.8) Arm 2: Sample size 291; mean 98.0; SD (14.2) Outcome domain: Neurological development Outcome: Rey Auditory Verbal Learning Test: Delayed recall raw score (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 7.2; SD (3) Arm 2: Sample size 291; mean 7.3; SD (3.5) Outcome: Rey Auditory Verbal Learning Test: Delayed recognition correct words (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 13.1; SD (3) Arm 2: Sample size 291; mean 13.3; SD (2.6) Outcome: Rey Auditory Verbal Learning Test: Total (trials 1-5) correct words (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 34.8; SD (10.8) Arm 2: Sample size 291; mean 34.4; SD (12.1) Outcome: Rey Auditory Verbal Learning Test: Total intrusions (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 2.5; SD (4) Arm 2: Sample size 291; mean 2.1; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(3.5) Outcome: Rey Auditory Verbal Learning Test: Total repetitions (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 3.7; SD (4.1) Arm 2: Sample size 291; mean 4.0; SD (4.5) Outcome: Rey Auditory Verbal Learning Test: Trial 1 correct words (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 4.3; SD (2) Arm 2: Sample size 291; mean 4.4; SD (2) Outcome domain: Visual function Outcome: Test of visual perception skills: figure ground standard score (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 9.6; SD (4.3) Arm 2: Sample size 291; mean 9.4; SD (3.8) Outcome: Test of visual perception skills: visual closure standard score (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 8.0; SD (3.7) Arm 2: Sample size 291; mean 7.6; SD (3.6) Outcome: Test of visual perception skills: visual discrimination standard score (Secondary) Follow-up time: 7 years Arm 1: Sample size 313; mean 8.1; SD (3.6) Arm 2: Sample size 291; mean 8.1; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(3.1)
Colombo et al., 2013[124] Study name: Diamond Study dates: 09/03/03-09/25/05 Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Government, Manufacturer supplied product Study follow-up: 18 months-6 years Original, same study, or follow-up studies: Birch, 2010[121]; Drover, 2011[122]; Drover. 2012[123]; Currie, 2015[115]	Study Population: Healthy infants Infants enrolled 159 Infants completers 81 Pregnant age: 24.1 (5.1) Race of Mother: White European (34.9) Black (63.9) Other race/ethnicity (1.2)	Inclusion Criteria: Healthy, full term formula-fed singleton infants, 37-42 weeks gestation, 2490-4200 g birth weight, born in Kansas City between 9/3/03 and 9/25/05 Exclusion Criteria: Receipt of human milk within 24 h of randomization; maternal and newborn health conditions known to interfere with normal growth and development (e.g., intrauterine growth restriction) or with normal cognitive function (e.g., congenital anomalies or established genetic diagnoses associated with intellectual disability), poor formula intake, or intolerance to cow milk infant formula; mothers with physician-documented chronic illness (e.g., HIV, renal or hepatic	Start time: Infants Birth Duration: Infants 12 months Arm 1: 0.00% Description: Control, no DHA or AA Blinding: NR Arm 2: 0.32% Description: 0.32% DHA DHA: 17mg/100 kcal AA: 34 mg/100 kcal Arm 3: 0.64% DHA: 34mg/100 kcal AA: 34 mg/100 kcal Arm 4: 0.96% DHA: 51mg/100 kcal AA: 34 mg/100 kcal	Outcome domain: Cognitive development Outcome: Macarthur-Bates Communicative Development Inventory Follow-up time: 18 months Arm 1: Sample size 18; mean 71.0; SEM (20) Arm 2: Sample size 21; mean 55.0; SEM (15) Arm 3: Sample size 18; mean 97.0; SEM (20) Arm 4: Sample size 24; mean 73.0; SEM (15) Outcome: Weschler Primary Preschool Test of Intelligence: Full Scale IQ (Secondary) Follow-up time: 6 year 66; mean 96.2; SE (2) Arm 1: Sample size 18; mean 90.5; SE (3) Outcome domain: Neurological development Outcome: Bayley PDI (Secondary) Follow-up time: 18 months Arm 1: Sample size 18; mean 99.0; SEM (5) Arm 2: Sample size 21; mean 97.0; SEM (5) Arm 3: Sample size 18; mean 97.0; SEM (5) Arm 4: Sample size 24; mean 98.0; SEM (5)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		disease, type 1 or type 2 diabetes, alcoholism, or substance abuse)		
Courville et al., 2011[38] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Government	Study Population: Healthy pregnant women Pregnant enrolled 47 Pregnant withdrawals 0 Pregnant completers 47 Pregnant age: NR (NR) NR Race of Mother: White European (8.5) Black (10.6) Asian (4.3) Minority (Puerto Rican/Latino 66%; African - other 8.5%; Other or mixed ethnicity = 2%) Baseline Omega-3 intake: Dietary DHA intake (mg/d), not including the intervention food, from 24 h dietary recalls: DHA-FF 67+-7 (SD); Placebo 87+-10 (SD), P=0.059	Inclusion Criteria: Healthy pregnant women, mid-pregnancy (20–24 weeks) Exclusion Criteria: parity .5; history of chronic hypertension; hyperlipidemia; renal or liver disease; heart disease; thyroid disorder; multiple gestations; having been pregnant or lactating in the previous 2 years.	Start time: Pregnant 20-24 wk of gestation Duration: Pregnant until birth Arm 1: Placebo Description: placebo bars (Manufacturer: Nestec Limited (Vevey, Switzerland) Dose: 5 placebo bars per week Blinding: NR Arm 2: DHA-FF Description: DHA cereal-based bars Manufacturer: Nestec Limited (Vevey, Switzerland) Dose: 5DHA cereal-based bars per week DHA: 241 mg/d EPA: 30.1 mg/d	Outcome domain: Birth weight Outcome: birth weight (kg) (Unspecified) Follow-up time: birth Arm 1: Sample size 25; mean 3.19; SD (0.44) Arm 2: Sample size 22; mean 3.33; SD (0.46) Outcome domain: duration of gestation Outcome: gestational age (weeks) (Unspecified) Follow-up time: birth Arm 1: Sample size 25; mean 39.4; SD (1.2) Arm 2: Sample size 22; mean 39.9; SD (1.1)
Currie et al., 2015[115] Study name: Diamond	Study Population: Healthy infants	Inclusion Criteria: Healthy, singleton, term (37–42 weeks	Start time: Infants birth Duration: Infants 12 months	Outcome domain: growth Outcome: BMI (Secondary) Follow-up time: 2-6 years

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study dates: 2003-2011 Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Government, Manufacturer supplied product Study follow-up: 6 years Original, same study, or follow-up studies: Birch, 2010[121]; Drover, 2011[122]; Drover. 2012[123]; Colombo, 2013[124]	Infants enrolled 159 Infants completers 92 Mother age: 22.9 y (4.1 y) Race of Mother: White European (NR) Black (59-87%) Asian (NR) Hispanic (0-9%) Inuit Eskimo (NR) Other race/ethnicity (NR) Non-black (13-41%)	gestation), formula-fed infants were eligible for the study if they weighed between 2490 and 4550 g at birth. All were born between September 2003 and October 2005. Only one child per family could participate. Exclusion Criteria: Infants were excluded if they were older than 9 days, had received human breast milk within 24 h of randomization or if there were newborn health conditions known to interfere with normal growth and development or cognitive function (e.g., intrauterine growth restriction, congenital anomalies or established genetic disorders associated with intellectual disability). Infants were also excluded if they previously demonstrated any evidence of cows' milk	Arm 1: Placebo Manufacturer: Mead Johnson Nutrition Blinding: eight colored labeling scheme and provided to participants by courier Arm 2: DHA < ARA Description: 0.32% DHA 0.64% ARA Manufacturer: Mead Johnson Nutrition DHA: 0.32% AA: 0.64% Arm 3: DHA = ARA Description: 0.64% DHA 0.64% ARA Manufacturer: Mead Johnson Nutrition DHA: 0.64% AA: 0.64% Arm 4: DHA > ARA Description: 0.96% DHA 0.64% ARA Manufacturer: Mead Johnson Nutrition DHA: 0.96% AA: 0.64%	Arm 1: Sample size 15; mean 16.6; SE (0.4) Arm 2: Sample size 54; mean 16.9; SE (0.4) Outcome: BMI-for-age percentile (Secondary) Follow-up time: 2-6 years Arm 1: Sample size 15; mean 61.2; SE (4.8) Arm 2: Sample size 54; mean 67.8; SE (3.2) Outcome: Length-for-age percentile (Secondary) Follow-up time: 2-6 years Arm 1: Sample size 15; mean 46.5; SE (4.6) Arm 2: Sample size 54; mean 59.1; SE (3.5) Follow-up time: birth-18 months Arm 1: Sample size 15; mean 53.1; SE (3.7) Arm 2: Sample size 54; mean 61.8; SE (2.4) Outcome: Weight-for-age percentile (Secondary) Follow-up time: 2-6 years Arm 1: Sample size 15; mean 49.8; SE (12) Arm 2: Sample size 54; mean 68.0; SE (10.8) Follow-up time: birth-18 months Arm 1: Sample size 15; mean 50.0; SE (3.8) Arm 2: Sample size 54; mean 54.5; SE (2.6)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		formula intolerance or if born to mothers with physician-documented chronic illness (e.g., HIV, renal or hepatic disease, type 1 or 2 diabetes, alcoholism or other substance abuse).		
D'Vaz et al., 2012[142] Study name: IFOS Study dates: 2005-2009 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies, None, Manufacturer supplied product Original, same study, or follow-up studies: Meldrum, 2012[140]	Study Population: Pregnant women with allergies Infants enrolled 420 Infants completers 323 Pregnant age: Placebo: 33.2 Fish Oil: 32.5 (Placebo: 4.2 Fish Oil: 4.8) Infant age: Term (39.3 weeks gestation) Race of Mother: NR (100)	Inclusion Criteria: Maternal: Pregnant History of doctor diagnosed asthma or allergic rhinitis Skin prick positive to at least one allergen Exclusion Criteria: Maternal: Smoking Auto-immune disease Pre-existing medical conditions other than asthma High-risk pregnancy Seafood allergy Fish eaten more than three times per week Fish oil supplementation already taken (in excess of 1000 mg per day) Exclusion from data analysis criteria due to protocol deviations: Pre-term delivery (gestation <36	Start time: Infants Birth Duration: Infants 6 months Arm 1: Placebo Description: Olive oil Manufacturer: Ocean Nutrition, Ltd Dose: 650 mg olive oil Blinding: Randomization was completed by external staff via computer software using an unpredictable allocation sequence, stratified according to maternal and paternal atopic history and parity. Mothers and study personnel were unaware of the group allocation. Maternal conditions Maternal allergies 100 Arm 2: Fish oil group Manufacturer: Ocean Nutrition Ltd. Purity Data: fatty acid composition remained unchanged over the study period Dose: 1 capsule contents, to be administered orally, prior to feeding in the morning Maternal conditions DHA: 280 mg	Outcome domain: allergies Outcome: allergic disease (any of IgE mediated food allergy, eczema or asthma) (Primary) Follow-up time: 12 months Arm 1: 66/167 (39.52%) Arm 2: 59/156 (37.82%) Outcome: food allergy (Primary) Follow-up time: 12 months Arm 1: 25/167 (14.97%) Arm 2: 19/156 (12.18%) Outcome domain: atopic dermatitis Outcome: eczema (Primary) Follow-up time: 12 months Arm 1: 68/167 (40.72%) Arm 2: 61/156 (39.1%) Outcome domain: respiratory illness Outcome: asthma (Primary) Follow-up time: 12 months Arm 1: 0/167 (0.0%) Arm 2: 0/156 (0.0%) Outcome: persistent cough (Primary) Follow-up time: 12 months Arm 1: 38/167 (22.75%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		weeks) Infant with congenital abnormalities or significant disease not related to intervention	EPA: 110 mg Maternal allergies 100	Arm 2: 42/156 (26.92%) Follow-up time: 6 months Arm 1: 27/167 (16.17%) Arm 2: 19/156 (12.18%) Outcome: recurrent wheeze (Primary) Follow-up time: 12 months Arm 1: 16/167 (9.58%) Arm 2: 21/156 (13.46%) Follow-up time: 6 months Arm 1: 27/167 (16.17%) Arm 2: 23/156 (14.74%)
Doornbos et al., 2009[90] Study name: NR Study dates: Not reported Study design: Trial randomized parallel Location: Netherlands Funding source / conflict: Industry Study follow-up: 3 months/12 weeks postpartum	Study Population: Healthy pregnant women Pregnant enrolled 182 Pregnant withdrawals 63 Pregnant completers 119 Pregnant age: NR (NR) NR Race of Mother: NR (100) Baseline biomarker information: Placebo group: DHA- 4.44 (3.00–6.92); AA-12.91 (9.95–14.95) DHA group: DHA- 5.51 (3.98–8.20); AA-12.13 (9.63–15.22) DHA+AA group: DHA-5.57 (2.48–8.32); AA-	Inclusion Criteria: women with first or second, singleton pregnancies Exclusion Criteria: women with a vegetarian or vegan diet or gestational diabetes and preterm delivery (<37 weeks)	Start time: Pregnant 16.5 (14-20) week of pregnancy Duration: Pregnant till 3 months after delivery Arm 1: Control group Description: Placebo-soybean oil Arm 2: DHA group Brand name: NR Manufacturer: NR DHA: 220mg Arm 3: DHA + AA group Brand name: NR Manufacturer: NR DHA: 220 mg AA: 220mg	Outcome domain: Ante or postnatal depression Outcome: Edinburgh Postnatal Depression Scale (EPDS) (Secondary) Follow-up time: 36 weeks pregnant Arm 1: Sample size 34; median 4.0; IQR Arm 2: Sample size 40; median 4.0; IQR Arm 3: Sample size 37; median 6.0; IQR Follow-up time: 6 weeks post-partum Arm 1: Sample size 32; median 5.0; IQR Arm 2: Sample size 38; median 4.0; IQR Arm 3: Sample size 30; median 5.0; IQR

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	13.60 (11.17–15.52)			
Drover et al., 2011[122] Study name: Diamond Study dates: 2003-2006 Study design: Trial randomized parallel Location: US Funding source / conflict: Industry Study follow-up: 18 months Original, same study, or follow-up studies: Birch, 2010[121]; Drover. 2012[123]; Colombo, 2013[124]; Currie, 2015[115]	Study Population: Healthy infants Infants enrolled 181 Infants withdrawals 64 Infants completers 117 Infant age: 18.1 month (0.2) Race of Mother: White European (70%) Minority (30%)	Inclusion Criteria: Children who had enrolled in the initial phase of the DIAMOND study at the Dallas site, and had completed the 12-month feeding protocol and the 12-month primary outcome visit (141 children) Exclusion Criteria: Infants who had diseases or congenital abnormalities known to affect growth, development, visual or cognitive maturation, or who had poor formula intake did not participate in the study. Infants were also excluded if they had received human milk within 24 h of randomization, or if they were born to mothers with chronic illness such as HIV disease, renal or hepatic disease, type 1 or type 2 diabetes, alcoholism, or	Start time: Infants birth (1 9 days) Duration: Infants 1 year Arm 1: No DHA (Control) Description: Cow's milk-based infant formula without DHA or ARA Brand name: Enfamil® with iron Manufacturer: Mead Johnson & Co, Evansville, IN Blinding: After obtaining signed assent from a parent, the study coordinator opened the next sequentially-numbered opaque sealed envelope to determine the code of the study formula to be assigned to that infant. All recruiting personnel, parents or guardians, study monitors, researchers, and pediatricians were masked to the infant's assigned formula. Arm 2: 0.32% DHA Description: 0.32% fatty acids from DHA & 0.64% ARA Brand name: Enfamil LIPIL®) Manufacturer: Enfamil LIPIL® DHA: 17mg/100 kcal, 0.32% DHA with 0.32% fatty acids from DHA AA: 34mg/100 kcal, 0.64% ARA Arm 3: 0.64% DHA Description: 0.64% DHA & 0.64% ARA Brand name: Enfamil LIPIL Manufacturer: Mead Johnson Nutrition DHA: 34 mg/100 kcal AA: 34mg/100 kcal, 0.64% ARA	Outcome domain: Cognitive development Outcome: Bayley Scale of Infant Development II (Mental developmental index) (Secondary) Follow-up time: 18 months Arm 1: Sample size 28; mean 98.4; SD (13.1) Arm 2: Sample size 29; mean 105.2; SD (10.7) Arm 3: Sample size 32; mean 104.2; SD (9.8) Arm 4: Sample size 28; mean 102.6; SD (11.9)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		substance abuse	Arm 4: 0.96% DHA Description: 0.96% DHA & 0.64% ARA Brand name: Enfamil LIPIL Manufacturer: Mead Johnson Nutrition DHA: 54 mg/100 kcal; 0.96% DHA AA: 34 mg/100 kcal; 0.64% ARA	
Drover et al., 2012[123] Study name: Diamond Study dates: NR Study design: Trial randomized parallel Location: US Funding source / conflict: Industry Study follow-up: 3.5 years Original, same study, or follow-up studies: Birch, 2010[121]; Drover, 2011[122]; Colombo, 2013[124]; Currie, 2015[115]	Study Population: Healthy infants Infants enrolled 343 Infants completers 88 Pregnant age: 31 years (4 years) Infant age: <= 9 days 1 to 9 days Race of Mother: NR (100)	Inclusion Criteria: Healthy term singleton-birth infants born in any of 5 hospitals Exclusion Criteria: Infants who had diseases or congenital abnormalities known to affect growth, development, visual or cognitive maturation, Infants were also excluded if they had received human milk within 24 h of randomization, or if they were born to mothers with chronic illness such as HIV disease, renal or hepatic disease, type 1 or type 2 diabetes, alcoholism, or substance abuse	Start time: Infants <=9 days after birth Duration: Infants 12 months Arm 1: Control group Description: Standard infant formula Brand name: Enfamil with Iron Manufacturer: Mead-Johnson Nutrition, Evansville IN Arm 2: 0.32% DHA formula Brand name: Enfamil LIPIL® Manufacturer: Mead-Johnson; DHA and ARA from algal and fungal oils manufactured by Martek Biosciences DHA: 0.32% or 17mg/100kcal AA: 0.64% FA or 34mg/100kcal Arm 3: 0.64% DHA formula Brand name: NR Manufacturer: NR DHA: 34mg/100kg AA: 0.64% FA or 34mg/100kcal Arm 4: 0.96% DHA formula Brand name: NR Manufacturer: NR DHA: 51mg/100kg	Outcome domain: Cognitive development Outcome: School Readiness Composite (SRC) (Secondary) Follow-up time: 2.5 years Arm 1: Sample size 19; mean 9.79; SD (2.42) Arm 2: Sample size 23; mean 10.3; SD (1.92) Arm 3: Sample size 27; mean 10.63; SD (2.75) Arm 4: Sample size 24; mean 10.79; SD (2.62)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			AA: 0.64% FA or 34mg/100kcal	
Dunstan et al., 2003[50] Study name: Dunstan Study dates: 1999-2001 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government Study follow-up: 1 year Original, same study, or follow-up studies: Dunstan, 2008[44]; Meldrum, 2015[51]	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 98 Pregnant withdrawals 15 Pregnant completers 83 Pregnant age: NR (NR) NR Race of Mother: NR (100)	Inclusion Criteria: All women had a history of physician-diagnosed allergic rhinitis and/or asthma and 1 or more positive skin prick tests to common allergens (house dust mite; grass pollens; molds; and cat, dog, and cockroach extracts) Exclusion Criteria: Women were ineligible for the study if they smoked; if they had other medical problems, complicated pregnancies, or seafood allergy; or if their normal dietary intake exceeded 2 meals of fish per week.	Start time: Pregnant 20 weeks of gestation Duration: Pregnant till delivery Arm 1: Placebo group Description: 46 women allocated and received placebo-olive oil Manufacturer: Pan Laboratories, Moorebank, NSW, Australia Active ingredients: 66.6% n-9 oleic acid Dose: 4 (1-g) capsules of olive oil per day Blinding: Randomization and allocation of capsules occurred at a different center separate from the recruitment of participants. Capsules were administered to the participants by someone separate from those doing the allocation. The capsules in the 2 groups were image-matched. Total N-3: <1% n-3 PUFAs Arm 2: Fish oil group Description: 52 women were randomized to receive fish oil Manufacturer: Ocean Nutrition, Halifax, Nova Scotia, Canada Dose: 4 (1g) fish oil capsules per day _x001E__x0007__x0005__x0015__x0013__x0007_ _x001E__x0013__x000F_ DHA: 56.0% EPA: 27.7% Total N-3: 3.7 g	Outcome domain: allergies Outcome: food allergy (Secondary) Follow-up time: 1 year Arm 1: 5/43 (11.63%) Arm 2: 3/40 (7.5%) Outcome domain: atopic dermatitis Outcome: atopic dermatitis (Secondary) Follow-up time: 1 year Arm 1: 13/43 (30.23%) Arm 2: 18/40 (45.0%) Outcome domain: respiratory illness Outcome: asthma (Secondary) Follow-up time: 1 year Arm 1: 6/43 (13.95%) Arm 2: 2/40 (5.0%) Outcome: chronic cough (Secondary) Follow-up time: 1 year Arm 1: 11/43 (25.58%) Arm 2: 5/40 (12.5%) Outcome: recurrent wheeze (Secondary) Follow-up time: 1 year Arm 1: 12/43 (27.91%) Arm 2: 10/40 (25.0%)
Dunstan et al., 2008[44] Study name: Dunstan	Study Population: Healthy infants Pregnant women with	Inclusion Criteria: Healthy term infants of pregnant women	Start time: Pregnant 20 weeks gestation Duration: Pregnant to term	Outcome domain: Birth weight Outcome: birth weight (g) (Secondary) Follow-up time: birth

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study dates: 2000-2003 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Multiple foundations and Societies Original, same study, or follow-up studies: Dunstan, 2003[50]; Meldrum, 2015[51]	allergies Pregnant enrolled 98 Pregnant completers 83 Infants enrolled 83 Infants withdrawals 11 (7 FO, 4 control) Infants completers 72 Pregnant age: Fish oil: 30.9 Control: 32.6 (Fish oil: 3.7 Control: 3.6) Infant age: Term (mean gestational period 275 days) Race of Mother: NR (NR) Baseline biomarker information: Cord blood erythrocyte (as % total fatty acids) 20:4n-6 14.9 (1.4) 17.6 (1.0) ,0.001 20:5n-3 1.3 (0.5) 0.4 (0.3) ,0.001 22:3n-6 2.8 (0.5) 3.9 (0.5) ,0.001 22:4n-6 0.8 (0.2) 1.5 (0.3) ,0.001 22:5n-3 6.3 (0.8) 6.0 (0.5) 0.037 22:6n-3 10.3 (1.1) 7.4 (0.9) ,0.001 Total n-6 PUFAs* 25.0 (1.8) 29.6 (1.1) ,0.001 Total n-3	enrolled in RCT of gestational supplementation Exclusion Criteria: Women were ineligible for the study if they smoked, had medical problems, a complicated pregnancy, seafood allergy, or if their normal dietary intake exceeded two meals of fish per week. Children were excluded from the study if they were born before 36 weeks' gestation or with major disease (to avoid the confounding effects on immune response) or if cord blood was not collected	Arm 1: Control Description: olive oil placebo Blinding: capsules image matched Maternal conditions Current smoker 0% Maternal allergies 100% Arm 2: Fish oil Description: same Manufacturer: Ocean Nutrition, Halifax Nova Scotia Active ingredients: 3-4mg/g vitamin E Viability: none reported Dose: 4 1-gm capsules fish oil per day Maternal conditions DHA: 2.2 EPA: 1.1 Other dose 1: fish oil supplying 2,2g/d DHA and 1.1g/day EPA Current smoker 0% Maternal allergies 100%	Arm 1: Sample size 39; mean 3434.0; SD (377) Arm 2: Sample size 33; mean 3508.0; SD (353) Outcome domain: Cognitive development Outcome: Griffith Mental Development Scales: Eye and hand coordination (Secondary) Follow-up time: 2.5 years Arm 1: Sample size 39; mean 108.0; SD (11.3) Arm 2: Sample size 33; mean 114.0; SD (10.2) Outcome: Griffith Mental Development Scales: Performance (Secondary) Follow-up time: 2.5 years Arm 1: Sample size 39; mean 115.8; SD (13.7) Arm 2: Sample size 33; mean 120.9; SD (12.7) Outcome: Griffith Mental Development Scales: Practical reasoning (Secondary) Follow-up time: 2.5 years Arm 1: Sample size 39; mean 113.6; SD (15) Arm 2: Sample size 33; mean 114.3; SD (14.5) Outcome: Griffith Mental Development Scales: Speech and hearing (Secondary) Follow-up time: 2.5 years Arm 1: Sample size 39; mean 109.6; SD (14.9) Arm 2: Sample size 33; mean 112.0; SD (15) Outcome: Griffith Mental Development

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	PUFAs{ 17.9 (1.9) 13.7 (1.3) ,0.001 Total n-3 to n-6{ 0.8 (0.1) 0.5 (0.1) ,0.001			Scales: General quotient score (Secondary) Follow-up time: 2.5 years Arm 1: Sample size 39; mean 110.5; SD (10.6) Arm 2: Sample size 33; mean 114.2; SD (9.8) Outcome: Griffith Mental Development Scales: Personal social (Secondary) Follow-up time: 2.5 years Arm 1: Sample size 39; mean 109.4; SD (11.5) Arm 2: Sample size 33; mean 112.4; SD (11.9) Outcome: Griffith Mental Development Scales: Locomotor (Secondary) Follow-up time: 2.5 years Arm 1: Sample size 39; mean 107.9; SD (12.6) Arm 2: Sample size 33; mean 112.5; SD (12.2) Outcome domain: duration of gestation Outcome: gestational age (days) (Secondary) Follow-up time: birth Arm 1: Sample size 39; mean 274.5; SD (8) Arm 2: Sample size 33; mean 276.0; SD (8) Outcome domain: growth Outcome: head circumference (cm) (Secondary) Follow-up time: 30 months Arm 1: Sample size 36; mean 49.8; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(1.7) Arm 2: Sample size 28; mean 49.4; SD (1.6) Outcome: length (cm) (Secondary) Follow-up time: 30 months Arm 1: Sample size 36; mean 93.3; SD (4.6) Arm 2: Sample size 28; mean 93.8; SD (3.8) Outcome: weight (kg) (Secondary) Follow-up time: 30 months Arm 1: Sample size 36; mean 14.1; SD (2) Arm 2: Sample size 28; mean 14.5; SD (2)
Escamilla-Nunez et al., 2014[59] Study name: POSGRAD Study dates: 2005-2009 Study design: Trial randomized parallel Location: Mexico Funding source / conflict: Government Study follow-up: 18 months Original, same study, or follow-up studies: Ramakrishnan, 2010[32]; Stein, 2012[33]; Imhoff-	Study Population: Pregnant women with allergies Pregnant enrolled 1,040 Pregnant completers 973 Pregnant age: 26.3 (4.8) 18-35 Race of Mother: Hispanic (100% Mexican) Baseline Omega-3 intake: DHA median (25th, 75th percentile), mg/d: 55(37, 99)	Inclusion Criteria: Maternal age 18 - 35 years, recruited between 18 and 22 weeks of gestation. Willingness to breastfeed exclusively or predominantly during at least the first 3 months of life of the newborn and with the intention to live in their area of residence for at least 2 years after delivery Exclusion Criteria: High-risk pregnancies (pregnancy complications, including premature placental abruption,	Start time: Pregnant 18-22 weeks gestation Duration: Pregnant to term Arm 1: Placebo Description: olive oil capsule Dose: 2 capsules per day Arm 2: DHA Description: Algal DHA Manufacturer: Martek Biosciences Dose: 2 capsules of 200mg each DHA: 200 mg algal DHA/capsule	Outcome domain: respiratory illness Outcome: breathing difficulty (number of episodes) Follow-up time: 18 months Arm 1: 48/440 Arm 2: 47/429 Outcome: cough (number of episodes) Follow-up time: 18 months Arm 1: 1151/440 Arm 2: 1178/429 Outcome: phlegm with congestion and/or nasal discharge, fever with phlegm and congestion and/or nasal discharge, or wheezing with fever (Primary) Follow-up time: 18 months Arm 1: 49/440 (11.11%) Arm 2: 48/429 (11.11%) Outcome: wheezing (number of episodes) Follow-up time: 18 months Arm 1: 262/440 Arm 2: 252/429

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Kunsch, 2011[58]; Gonzalez-Casanova, 2015[60]; Ramakrishnan, 2015[61]		preeclampsia, pregnancy-induced hypertension, severe bleeding episode in pregnancy or lipid absorption disorders; Regular consumption of fish oil or DHA supplements; Chronic use of certain medications (e.g., drugs for epilepsy)		
Escolano-Margarit et al., 2011[130] Study name: NUHEAL Study dates: 2001-2008 Study design: Trial randomized parallel Location: Germany, Spain, Hungary Funding source / conflict: Manufacturer supplied product Study follow-up: 5.5 years Original, same study, or follow-up studies: Campoy, 2011[141].	Study Population: Healthy pregnant women Pregnant enrolled 315 Pregnant completers 157 Infants enrolled 315 Infants completers 148 Pregnant age: 31 (NR) 18 to 41 Race of Mother: NR (100) Baseline biomarker information: For newborns mean plasma DHA Placebo group _x0007_6.9 Fish oil group 7.8 5-MHTF (folic	Inclusion Criteria: singleton pregnancy, gestation 20 week at enrollment, and intention to deliver in one of the obstetrical centers Exclusion Criteria: serious chronic illness (e.g., diabetes, hepatitis, or chronic enteric disease), use of FO supplements since the beginning of pregnancy or folate or vitamin B-12 supplements after gestation week 16	Start time: Pregnant week 22 of pregnancy Infants NA Duration: Pregnant until birth Arm 1: placebo Description: milk-based supplement Brand name: Blemil Plus Manufacturer: Ordesa Laboratorios, Barcelona, Spain) Active ingredients: vitamins and minerals in amounts meeting the recommended intakes during the second half of pregnancy for European women Dose: one daily dose of 15 g Blinding: supplements were not distinguishable with respect to the appearance of the sachets or to their contents Arm 2: fish oil Description: fish oil in milk-based supplement Manufacturer: Pronova Biocare, Lysaker, Norway	Outcome domain: Neurological development Outcome: number considered normal on Hempel exam (Secondary) Follow-up time: 5.5 years Arm 1: 81/87 (93.0%) Arm 2: 74/80 (93.0%) Outcome: number considered normal on Towen exam (Secondary) Follow-up time: 5.5 years Arm 1: 48/69 (70.0%) Arm 2: 55/79 (70.0%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	acid) group 6.2 _x0007_Fish oil + 5-MHTF group _x0007_7.0 mean plasma AA Placebo group 17.6 Fish oil group 16.8 5-MHTF (folic acid) group 17.3 _x0007_Fish oil + 5-MHTF group 16.4		Active ingredients: vitamins and minerals in amounts meeting the recommended intakes during the second half of pregnancy for European women Dose: one daily dose of 15 g DHA: 500 mg EPA: 100 mg Arm 3: folic acid Description: 400 _x0001_g 5-MTHF Manufacturer: BASF, Ludwigshafen, Germany Active ingredients: vitamins and minerals in amounts meeting the recommended intakes during the second half of pregnancy for European women Dose: one dose of 15 g Arm 4: folic acid + fish oil Description: fish oil + 400 _x0001_g 5-MTHF Manufacturer: BASF, Ludwigshafen, Germany Active ingredients: vitamins and minerals in amounts meeting the recommended intakes during the second half of pregnancy for European women Dose: one dose of 15 g DHA: 500 mg EPA: 100 mg	
Fang et al., 2005[137] Study name: NR Study dates: NR Study design: Trial randomized parallel	Study Population: Preterm infants Infants enrolled 28 Infants withdrawals 1 Infants completers 27 Infant age: 1 week	Inclusion Criteria: (1) A gestational age at birth between 30 and 37 weeks; (2) Normal fundus oculi; (3) Recruitment prior to commencement of feeding	Start time: Infants 1 week after birth Duration: Infants 24 weeks Arm 1: placebo Description: infant formula based on the composition of human milk Brand name: Neoangelac	Outcome domain: Cognitive development Outcome: Bayley Mental Development Index (Primary) Follow-up time: 1 year Arm 1: Sample size 11; mean 90.5; SD (6.9) Arm 2: Sample size 16; mean 98.7; SD (8) Follow-up time: 6 months

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Location: Taiwan Funding source / conflict: Manufacturer supplied product	(mean gestation age 33 weeks) (0.5 week) NA Race of Mother: NR (100)	Exclusion Criteria: (1) Breast feeding; (2) A maternal history of infection, diabetes mellitus, gestational diabetes mellitus, cocaine or alcohol abuse, systemic diseases or if intrauterine growth retardation had been diagnosed during pregnancy; (3) Major congenital abnormality; (4) Severe intraventricular hemorrhage > grade 2; (5) Cystic periventricular leukomalacia; (6) Retinopathy of prematurity stage 2; (7) Bronchopulmonary dysplasia on radiographs or oxygen usage 28 days; (8) Body weight less than the third percentile; (9) Surgical intervention for necrotizing enterocolitis (10) Mechanical ventilation after achieving enteral intake > 110 kcal/kg per day; (11) A 5-min	Manufacturer: Multipower Enterprise Corporation Dose: Babies were given more than 110 kcal/kg per day during the first 4 months and more than 70 kcal/kg per day from 4 to 6 months N-6 N-3: 10:1 linoleic:linolenic Arm 2: Neoangelac Plus Description: Neoangelac supplemented with Omega 3 Brand name: Neoangelac Plus Manufacturer: Multipower Enterprise Corporation Dose: Babies were given more than 110 kcal/kg per day during the first 4 months and more than 70 kcal/kg per day from 4 to 6 months DHA: 0.05% AA: 0.10%	Arm 1: Sample size 11; mean 91.7; SD (10.4) Arm 2: Sample size 16; mean 96.1; SD (8.6) Outcome domain: Neurological development Outcome: Bayley psychomotor development index (Primary) Follow-up time: 12 months Arm 1: Sample size 11; mean 86.7; SD (11.1) Arm 2: Sample size 16; mean 98.0; SD (5.8) Follow-up time: 6 months Arm 1: Sample size 11; mean 95.4; SD (13.2) Arm 2: Sample size 16; mean 102.2; SD (10.5) Outcome domain: Visual function Outcome: Hiding Heidi Analysis <100% (Primary) Follow-up time: 4 months Arm 1: 2/11 (18.0%) Arm 2: 5/16 (31.0%) Follow-up time: 6 months Arm 1: 10/11 (91.0%) Arm 2: 16/16 (100.0%) Outcome: Lea grating acuity card 1 or 2 cycles per degree (Primary) Follow-up time: 4 months Arm 1: 8/11 (72.0%) Arm 2: 16/16 (100.0%) Outcome: Lea grating acuity card 2 or4 cycles per degree (Primary)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		Apgar score < 7; (12) Administration of blood transfusion, blood products, or parenteral lipids with DHA or AA.		Follow-up time: 6 months Arm 1: 8/11 (73.0%) Arm 2: 15/16 (94.0%) Outcome: Visual evoked potential (log minimum angle of resolution in minutes of arc) (Primary) Follow-up time: 4 months Arm 1: Sample size 10; mean 0.36; SD (0.34) Arm 2: Sample size 14; mean 0.19; SD (0.27) Follow-up time: 6 months Arm 1: Sample size 10; mean 0.13; SD (0.22) Arm 2: Sample size 13; mean 0.1; SD (0.17)
Field et al., 2008[112] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: Canada Funding source / conflict: Industry	Study Population: Healthy infants Infants enrolled 30 Infants completers 30 Infant age: 2 weeks 7 to 14 days Race of Mother: NR (100)	Inclusion Criteria: Inclusion criteria for all infants stipulated that by age 14 d infants were receiving 100 % of their intake by mouth from human milk or commercial infant formula and that infants were healthy with birth weight, length and head circumference between the 10th and 90th percentile for gestational age, according to the National Center for Health Statistics	Start time: Infants no later than 14 days Duration: NR Arm 1: Formula (unsuppl) Description: Placebo/control formula Brand name: S-26 Manufacturer: Wyeth Nutrition ALA: 2.3% by weight Arm 2: Formula + LCP Description: LCP supplemented formula Brand name: S-26 Gold Manufacturer: Wyeth Nutrition Active ingredients: arachidonic acid - see below ALA: 1.9% DHA: 0.20% AA: 0.34%	Outcome domain: growth Outcome: head circumference (cm) (Secondary) Follow-up time: 6 wk Arm 1: Sample size 14; mean 38.6; SD (1.1) Arm 2: Sample size 16; mean 38.4; SD (1.4) Arm 3: Sample size 16; mean 38.9; SD (1.2) Outcome: length (cm) (Secondary) Follow-up time: 6 wk Arm 1: Sample size 14; mean 56.0; SD (2) Arm 2: Sample size 16; mean 56.0; SD (2) Arm 3: Sample size 16; mean 58.0; SD (3) Outcome: weight (g) (Secondary) Follow-up time: 6 wk Arm 1: Sample size 14; mean 4901.0; SD (590)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		growth charts14. Exclusion Criteria: Infants with major congenital malformations, documented systemic or congenital infection, significant neonatal morbidity, diagnosed maternal autoimmune disorders, acute illness precluding oral feedings, or conditions requiring infant feedings other than standard formula or human milk were excluded from the study. None of the infants had received corticosteroids, erythrocyte or plasma transfusions, or intravenous lipid emulsions before entering the study	Arm 3: Breastfed comparison Description: Breastfed group, not randomized	Arm 2: Sample size 16; mean 5076.0; SD (646) Arm 3: Sample size 16; mean 5045.0; SD (516)
Fleddermann et al., 2014[113] Study name: BeMIM (Belgrade-Munch Infant Milk Trial) Study dates: Jan 2010	Study Population: Healthy infants Infants enrolled 207 Infants completers 164 Mother age: Control: 30.6 Intervention: 30.7	Inclusion Criteria: Eligible infants had to be born apparently healthy from singleton pregnancies after 37-41 weeks of gestation, with a birth weight between the 3rd and	Start time: Infants within 28 days Duration: Infants until 120 days Arm 1: Control Formula (CF) Description: Placebo/control formula Manufacturer: HiPP GmbH & Co. Vertrieb KG (Pfaffenhofen, Germany)	Outcome domain: growth Outcome: head circumference gain (g/day) (Secondary) Follow-up time: about 92 days Arm 1: Sample size 82; mean 0.05; SD (0.01) Arm 2: Sample size 82; mean 0.05; SD (0.01)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
to May 2011 Study design: Trial randomized parallel Location: Serbia Funding source / conflict: Industry	Breastfed: 30.1 (Control: 5.5 Intervention: 5.5 Breastfed: 4.7) Infant age: Gestation (weeks) Control: 39.2 Intervention: 39.2 Breastfed: 39.2 (Gestation (weeks) Control: 1.1 Intervention: 1.0 Breastfed: 1.1) until 28 days Race of Mother: NR (100%)	97th weight-for-age percentile according to the EURO-Growth charts. Exclusion Criteria: Infants with malformations, congenital heart defects, congenital vascular diseases, severe diseases of gastrointestinal tract, kidney, liver, central nervous system, or metabolic disease.	Blinding: 600g cartons and labeled by random numbers. The products were packed in identical white boxes and labeled with the same product name. ALA: 0.1g/100mL Arm 2: Intervention Formula (IF) Manufacturer: HiPP GmbH & Co. Vertrieb KG (Pfaffenhofen, Germany) ALA: 0.1g/100mL DHA: 7.2g/100mL AA: 7.2g/100mL Arm 3: Breastfed Description: Breastfeeding reference group	Outcome: length gain (g/day) (Secondary) Follow-up time: about 92 days Arm 1: Sample size 82; mean 0.1; SD (0.02) Arm 2: Sample size 82; mean 0.11; SD (0.02) Outcome: weight gain (g/day) (Primary) Follow-up time: about 92 days Arm 1: Sample size 82; mean 28.3; SD (6.5) Arm 2: Sample size 82; mean 30.2; SD (6.3)
Furuhjelm et al., 2009[173] Study name: NR Study dates: 2003-2006 Study design: Trial randomized parallel Location: Sweden Funding source / conflict: Industry, Multiple foundations and Societies Study follow-up: 1 year Original, same study, or	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 145 Pregnant withdrawals 28 Pregnant completers 117 Infants enrolled 145 Infants withdrawals 28 Infants completers 117 Mother age: Intervention: 31.1 years (at delivery) Placebo: 31.7 years (at delivery) (Intervention: 4.1 years (at delivery) Placebo:	Inclusion Criteria: a family history of past of current allergic symptoms in at least one parent or older child. Exclusion Criteria: Mothers with an allergy to soy or fish or undergoing treatment with anticoagulants or commercial w-3 fatty acid supplements	Start time: Pregnant 25 weeks of gestation Duration: Pregnant 15 weeks (i.e., until delivery) Arm 1: Placebo Description: 75 women received soy oil as placebo Manufacturer: Pharma Nord Active ingredients: w-6 PUFA LA (58%, 2.5 g / day), a small amount (6%, 0.28 g / day) of the w-3 PUFA LNA and 36 mg a-tocopherol Viability: alpha-tocopherol was given as an antioxidant, a necessary ingredient according to the standard procedure of the manufacturer to assure the durability of the oil. Dose: nine soy oil capsules a day N-6 N-3: 9	Outcome domain: allergies Outcome: Food Allergy (Primary) Follow-up time: 12 months Arm 1: 10/65 (15.38%) Arm 2: 1/52 (1.92%) Outcome domain: atopic dermatitis Outcome: IgE associated eczema (Primary) Follow-up time: 12 months Arm 1: 15/63 (23.81%) Arm 2: 4/52 (7.69%) Follow-up time: 6 months Arm 1: 13/65 (20.0%) Arm 2: 4/52 (7.69%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
follow-up studies: Furuhjelm, 2011[172]	3.9 years (at delivery)) NR Race of Mother: NR (100) Baseline biomarker information: Treatment - mean(sd) mol % EPA- 1.3 (0.8) DHA- 5.5 (1.1) AA- 9.2 (1.7) AA/EPA- 9.1 (4.3) Placebo - mean(sd) mol % EPA- 1.2 (0.6) DHA- 5.4 (1.2) AA- 8.6 (1.5) AA/EPA- 8.6 (4.0) Baseline Omega-3 intake: DHA - 0.2g/day EPA- 0.1g/day		Arm 2: w3 group Description: 70 women are randomized into this group Brand name: Bio Marin capsules Manufacturer: Pharma Nord, Vejle, Denmark Active ingredients: 23 mg alpha-tocopherol Viability: alpha-tocopherol was given as an antioxidant, a necessary ingredient according to the standard procedure of the manufacturer to assure the durability of the oil. Dose: nine 500-mg capsules, once daily DHA: 1.1g EPA: 1.6g N-6 N-3: <0.1	
Furuhjelm et al., 2011[172] Study name: NR Study dates: 2003-2007 Study design: Trial randomized parallel Location: Sweden Funding source / conflict: Industry, Multiple foundations and Societies	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 145 Pregnant withdrawals 28 Pregnant completers 117 Infants enrolled 145 Infants withdrawals 28 Infants completers 117 Pregnant age: NR (NR) NR	Inclusion Criteria: family history of current or previous allergic symptoms, i.e. bronchial asthma, eczema, allergic food reactions, itching and running eyes and nose at exposure to pollen, pets or other known allergens. Exclusion Criteria: Allergy to soya or fish, treatment with	Start time: Pregnant 25 weeks of gestation Duration: Pregnant 15 weeks (i.e., until delivery) Arm 1: Placebo Description: soya bean oil Manufacturer: Pharma Nord, Vejle, Denmark Active ingredients: 58% linoleic acid (LA), 2.5 g/day Viability: the antioxidant a-tocopherol (placebo: 36 mg/day) to assure the stability of the oil Dose: nine capsules a day Blinding: The mothers, as well as the staff handling clinical and laboratory follow-up, were	Outcome domain: allergies Outcome: any food reactions (Primary) Follow-up time: 2 years Arm 1: 16/65 (24.62%) Arm 2: 6/54 (11.11%) Outcome domain: atopic dermatitis Outcome: any eczema (Primary) Follow-up time: 2 years Arm 1: 21/65 (32.31%) Arm 2: 11/54 (20.37%) Outcome domain: respiratory illness Outcome: any asthma (Primary) Follow-up time: 2 years

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study follow-up: 2 years Original, same study, or follow-up studies: Furuhjelm, 2009[173]	Race of Mother: NR (100)	anticoagulants or omega-3 fatty acid supplements.	blinded to group allocation, and the mothers were identified by their study number only. ALA: 6%, 0.28 g/day Arm 2: w-3 group Description: w-3 fatty acids Viability: the antioxidant a-tocopherol (w-3 group: 28 mg/day) to assure the stability of the oil Dose: nine capsules a day DHA: 25% DHA, 1.1 g/day EPA: 35% EPA, 1.6 g/day	Arm 1: 8/65 (12.31%) Arm 2: 7/54 (12.96%) Outcome: any rhinoconjunctivitis (Primary) Follow-up time: 2 years Arm 1: 2/65 (3.08%) Arm 2: 2/54 (3.7%)
Gonzalez-Casanova et al., 2015[60] Study name: POSGRAD Study dates: 2005-2012 Study design: Trial randomized parallel Location: Mexico Funding source / conflict: Government, None Study follow-up: 60 months Original, same study, or follow-up studies: Ramakrishnan, 2010[32]; Stein, 2012[33]; Imhoff-	Study Population: Healthy infants Preterm infants Pregnant enrolled 1040 Pregnant completers 968 Infants enrolled 973 Infants completers 802 Pregnant age: 26.3 y (4.7 y) Infant age: 20.5 weeks gestation (2.0) Race of Mother: NR (100)	Inclusion Criteria: Pregnant women 18–35 y of age, in week 18–22 of gestation, and planned to deliver at the hospital, breastfeed for >3 mo, and reside in the area for >2 y after delivery Exclusion Criteria: NR	Start time: Pregnant 18-22 weeks gestation Duration: Pregnant 18-22 weeks gestation until delivery Arm 1: Placebo Description: Soy and corn placebo Dose: 2 200 mg capsules/day Blinding: Soy-corn placebo of similar taste and appearance Arm 2: DHA (algal) Dose: 2 200 mg capsules/day DHA: 400mg	Outcome domain: growth Outcome: bmi-for-age z score (Primary) Follow-up time: 5 years Arm 1: Sample size 399; mean 0.1; SD (1.1) Arm 2: Sample size 403; mean 0.1; SD (1.1) Outcome: height (cm) (Primary) Follow-up time: 5 years Arm 1: Sample size 399; mean 108.4; SD (4.5) Arm 2: Sample size 403; mean 108.3; SD (4.4) Outcome: height-for-age z-score (Primary) Follow-up time: 5 years Arm 1: Sample size 399; mean -0.4; SD (0.9) Arm 2: Sample size 403; mean -0.4; SD (0.9) Outcome: weight (kg) (Primary) Follow-up time: 5 years Arm 1: Sample size 399; mean 18.4; SD (3)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Kunsch, 2011[58]; Escamilla-Nunez, 2014[59]; Ramakrishnan, 2015[61]				Arm 2: Sample size 403; mean 18.3; SD (3) Outcome: weight-for-age z-score (Primary) Follow-up time: 5 years Arm 1: Sample size 399; mean -0.1; SD (1.1) Arm 2: Sample size 403; mean -0.2; SD (1.1)
Goor et al., 2011[66] Study name: Groningen LCPUFA study Study dates: 2004-2009 Study design: Trial randomized parallel Location: Netherlands Funding source / conflict: Industry Study follow-up: 18 months Original, same study, or follow-up studies: Bouwstra, 2003[62]; Bouwstra, 2005[63]; de Jong, 2010[64]; de Jong, 2012[65]; van Goor, 2010[36]	Study Population: Healthy infants Pregnant enrolled 119 Infants enrolled 119 Infants completers 114 Pregnant age: Placebo: 32.7 DHA: 32.5 DHA+AA: 32.9 (Placebo: 5.1 DHA: 4.4 DHA+AA: 4.8) Infant age: 18 months Race of Mother: NR (100)	Inclusion Criteria: women with a first or second low-risk singleton pregnancy, between the 14th and 20th weeks of pregnancy Exclusion Criteria: women with vegetarian or vegan diets; women with diabetes mellitus; birth complications	Start time: Pregnant 14th-20th week pregnancy Lactating 3 months after delivery Mothers 3 months after delivery Infants NR Duration: Pregnant NR Lactating 33-39 weeks Mothers 33-39 weeks Infants NR Arm 1: placebo Description: Soy bean oil Brand name: none Arm 2: DHA Description: DHA plus soy bean oil Brand name: Marinol D40 Manufacturer: Lipid Nutrition B.V., Wormerveer, The Netherlands; AA: Dose: 1 capsule DHA and 1 capsule soy bean oil once a day ALA: 32 mg/d DHA: 220 mg/d EPA: 34 mg/d Arm 3: DHA+AA Description: DHA plus AA Brand name: AA: no brand name Manufacturer: Wuhan Alking Bioengeneering	Outcome domain: Birth weight Outcome: birth weight (g) (Unspecified) Follow-up time: birth Arm 1: Sample size 34; mean 3576.0; SD (551) Arm 2: Sample size 41; mean 3592.0; SD (465) Arm 3: Sample size 39; mean 3652.0; SD (377) Outcome domain: Cognitive development Outcome: Bayley Scale of Infant Development (Mental developmental index) (Unspecified) Follow-up time: 18 months Arm 1: Sample size 34; mean 115.2; SD (11.6) Arm 2: Sample size 41; mean 113.7; SD (13) Outcome domain: Neurological development Outcome: Bayley psychomotor development index (Unspecified) Follow-up time: 18 months Arm 1: Sample size 34; mean 91.7; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			Co. Ltd., Wuhan, China Dose: 2 capsules once a day ALA: 7 mg/d DHA: 220 mg/d EPA: 36 mg/d AA: 220 mg per capsule	(8.3) Arm 2: Sample size 41; mean 95.8; SD (11.4) Arm 3: Sample size 39; mean 92.4; SD (8.8) Outcome: fluency score (Unspecified) Follow-up time: 18 months Arm 1: Sample size 34; median 10.0; range Arm 2: Sample size 41; median 9.0; range Arm 3: Sample size 39; median 10.0; range Outcome: neurological optimality score (Unspecified) Follow-up time: 18 months Arm 1: Sample size 34; median 47.5; range Arm 2: Sample size 41; median 46.0; range Arm 3: Sample size 39; median 48.0; range Outcome: prevalence of complex minor neurological dysfunction (Unspecified) Follow-up time: 18 months Arm 1: 5/34 (14.7%) Arm 2: 3/41 (7.3%) Arm 3: 5/39 (12.8%) Outcome: prevalence of normal neurological condition (Unspecified) Follow-up time: 18 months Arm 1: 20/34 (58.8%) Arm 2: 24/41 (58.5%) Arm 3: 28/39 (71.8%) Outcome: prevalence of simple minor neurological dysfunction (Unspecified) Follow-up time: 18 months

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 1: 9/34 (26.5%) Arm 2: 14/41 (34.1%) Arm 3: 6/39 (15.4%) Outcome domain: growth Outcome: head circumference (cm) (Unspecified) Follow-up time: 18 months Arm 1: Sample size 34; mean 47.8; SD (1.5) Arm 2: Sample size 41; mean 47.6; SD (1.1) Arm 3: Sample size 39; mean 47.5; SD (1.4) Outcome: length (cm) (Unspecified) Follow-up time: 18 months Arm 1: Sample size 34; mean 84.0; SD (3.8) Arm 2: Sample size 41; mean 82.8; SD (4.7) Arm 3: Sample size 39; mean 83.6; SD (2.9) Outcome: weight (kg) (Unspecified) Follow-up time: 18 months Arm 1: Sample size 34; mean 11.5; SD (1.1) Arm 2: Sample size 41; mean 11.3; SD (1.4) Arm 3: Sample size 39; mean 11.5; SD (1.3)
Groh-Wargo et al., 2005[106] Study name: NR	Study Population: Preterm infants Infants enrolled 60 Infants withdrawals 3	Inclusion Criteria: Preterm infants with birth weights from 750 to 1800 g and GA at birth <33 wk were	Start time: Infants first enteral formula feeding Duration: Infants 24 kcal/fl oz formula until 40 wk corrected age; 22 kcal/fl oz formula from 40 wk CA to 1 year CA	Outcome domain: growth Outcome: head circumference (cm) (Secondary) Follow-up time: 12 months (corrected age) Arm 1: Sample size 14; mean 46.2; SE

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study dates: Sept 1997 - Sept 1998 Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Government	Infants completers 57 Infant age: GA= 30 weeks (0.5) NR Race of Mother: NR	recruited between September 1997 and September 1998 from the neonatal intensive care unit. No restrictions on the type of feeding before study entry. Exclusion Criteria: Congenital abnormalities that could affect growth or development, major surgery, periventricular hemorrhage greater than grade II (Papile classification), asphyxia resulting in severe and permanent neurologic damage, treatment with extracorporeal membrane oxygenation, maternal incapacity (including substance abuse), or uncontrolled systemic infection at the time of enrollment.	Arm 1: Control Description: Control formula without DHA or ARA Brand name: Similac Special Care to 40 wk GA; and NeoSure until 1 year ALA: 2.4 g/100 g (to 40 wk GA); 2.4 g/100 g (to 1 year) DHA: 0 EPA: 0 AA: 0 Arm 2: DHA+ARA (FF) Description: DHA or ARA from fish/fungal oil Brand name: Similac Special Care to 40 wk GA; and NeoSure until 1 year ALA: 2.6 g/100 g (to 40 wk GA); 2.4 g/100 g (to 1 year) DHA: 0.27 g/100 g (to 40 wk GA); 0.16 g/100 g (to 1 yr) EPA: 0.08 g/100 g (to 40 wk GA); 0 (to 1 yr) AA: 0.43 g/100 g (to 40 wk GA); 0 (to 1 yr) Arm 3: DHA+ARA (EF) Description: DHA or ARA from egg-derived triglyceride and fish oil Brand name: Similac Special Care to 40 wk GA; and NeoSure until 1 year ALA: 2.5 g/100 g (to 40 wk GA); 2.4 g/100 g (to 1 year) DHA: 0.24 g/100 g (to 40 wk GA); 0.15 g/100 g (to 1 yr) EPA: 0 AA: 0.41 g/100 g	(0.4) Arm 2: Sample size 14; mean 46.0; SE (0.4) Arm 3: Sample size 13; mean 46.2; SE (0.4) Follow-up time: 35 weeks (corrected age) Arm 1: Sample size 18; mean 30.8; SE (0.2) Arm 2: Sample size 17; mean 30.6; SE (0.5) Arm 3: Sample size 18; mean 30.3; SE (0.4) Follow-up time: 4 months (corrected age) Arm 1: Sample size 14; mean 41.9; SE (0.4) Arm 2: Sample size 16; mean 41.1; SE (0.6) Arm 3: Sample size 14; mean 42.0; SE (0.3) Follow-up time: 40 weeks (corrected age) Arm 1: Sample size 18; mean 25.4; SE (0.3) Arm 2: Sample size 18; mean 34.5; SE (0.5) Arm 3: Sample size 17; mean 35.0; SE (0.3) Outcome: length (cm) (Secondary) Follow-up time: 12 months (corrected age) Arm 1: Sample size 14; mean 73.9; SE (0.9) Arm 2: Sample size 14; mean 75.2; SE (0.9) Arm 3: Sample size 13; mean 76.3; SE (0.8) Follow-up time: 35 weeks (corrected age) Arm 1: Sample size 18; mean 42.5; SE

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(0.5) Arm 2: Sample size 17; mean 42.7; SE (0.7) Arm 3: Sample size 18; mean 42.7; SE (0.5) Follow-up time: 4 months (corrected age) Arm 1: Sample size 14; mean 61.8; SE (0.7) Arm 2: Sample size 16; mean 60.9; SE (0.6) Arm 3: Sample size 14; mean 62.8; SE (0.7) Follow-up time: 40 weeks (corrected age) Arm 1: Sample size 18; mean 48.0; SE (0.7) Arm 2: Sample size 18; mean 48.2; SE (0.7) Arm 3: Sample size 17; mean 48.1; SE (0.5) Outcome: weight (g) (Secondary) Follow-up time: 12 months (corrected age) Arm 1: Sample size 14; mean 9343.0; SE (307) Arm 2: Sample size 14; mean 8977.0; SE (293) Arm 3: Sample size 13; mean 9505.0; SE (243) Follow-up time: 35 weeks (corrected age) Arm 1: Sample size 18; mean 1916.0; SE (73) Arm 2: Sample size 17; mean 1871.0; SE (118) Arm 3: Sample size 18; mean 1874.0; SE (85) Follow-up time: 4 months (corrected age) Arm 1: Sample size 14; mean 6524.0; SE

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(220) Arm 2: Sample size 16; mean 6454.0; SE (212) Arm 3: Sample size 14; mean 6432.0; SE (217) Follow-up time: 40 weeks (corrected age) Arm 1: Sample size 18; mean 3280.0; SE (135) Arm 2: Sample size 18; mean 3147.0; SE (149) Arm 3: Sample size 17; mean 3136.0; SE (105)
Gustafson et al., 2013[74] Study name: NR Study dates: May 2009 - July 2011 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 67 Pregnant withdrawals 12 Pregnant completers 52 Infants enrolled 44 Infants completers 41 Pregnant age: placebo 25.6+; DHA 25.5 (placebo 4.8; DHA 4.3) Race of Mother: White European (46.3) Black (37.3) Asian (3) Hispanic (13.4) Baseline biomarker information: plasma	Inclusion Criteria: between 16–35.9 years of age and carrying a singleton pregnancy between the 12th and 20th week of gestation Exclusion Criteria: any serious health condition likely to affect the growth and development of the fetus or health of the mother including cancer, lupus, hepatitis, diabetes mellitus (Type1, Type 2 or gestational) or HIV/AIDS at baseline or fetal cardiac structural or conduction defects.	Start time: Pregnant 12-20 week gestation Infants birth Duration: Pregnant till birth Arm 1: Placebo Description: g 50% soy and 50% corn oil Manufacturer: Martek Biosciences, now DSM Nutritional Products Dose: 3 capsule a day each 500 mg Blinding: Only members of the investigational pharmacy knew the subject allocation. Participants and all members of the investigational team were blinded to the intervention assignment. Participants were allocated to either group based on the simple randomization procedure using random numbers generated by SAS. All capsules were the same color, size, weight and the oils were orange-flavored to prevent investigator or subject bias. Arm 2: algal oil as a source of DHA (200 mg of	Outcome domain: Birth weight Outcome: birth weight (g) (Secondary) Follow-up time: birth Arm 1: Sample size 24; mean 3435.5; SD (404.8) Arm 2: Sample size 22; mean 3416.8; SD (552.9) Outcome domain: Cognitive development Outcome: Neonatal Behavior Assessment: state organization (Primary) Follow-up time: 1-14 days post-partum Arm 1: Sample size 12; mean 13.5; SD (13.89) Arm 2: Sample size 15; mean 15.13; SD (8.02) Outcome: Neonatal Behavior Assessment: autonomic (Primary) Follow-up time: 1-14 days post-partum Arm 1: Sample size 12; mean 14.83; SD (16.9) Arm 2: Sample size 15; mean 18.13; SD (14.48)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	DHA (wt% TFA) placebo group: 3.91 (3.15-4.21); DHA group: 3.94(3.39-4.72) RBC DHA (wt%TFA) placebo group 4.30(3.99-5.03); DHA group 4.50 (3.73-5.44)	Women who self-reported illicit drug use or alcohol use during pregnancy and those with hypertension or BMI Z40 were excluded. Women who were taking more than 200 mg/day DHA in prenatal vitamins or over the counter supplements were excluded from participation	DHA per capsule for a total of 600 mg DHA/day) Dose: 3 capsule of 200mg DHA total 600 mg DHA: 200 mg * 3	Outcome: Neonatal Behavior Assessment: motor (Primary) Follow-up time: 1-14 days post-partum Arm 1: Sample size 12; mean 23.08; SD (11.4) Arm 2: Sample size 15; mean 26.07; SD (18.13) Outcome: Neonatal Behavior Assessment: reflexes (Primary) Follow-up time: 1-14 days post-partum Arm 1: Sample size 12; mean 21.92; SD (14.45) Arm 2: Sample size 15; mean 22.6; SD (14.33) Outcome: Neonatal Behavior Assessment: state regulation (Primary) Follow-up time: 1-14 days post-partum Arm 1: Sample size 12; mean 16.42; SD (20.02) Arm 2: Sample size 15; mean 16.93; SD (20.06) Outcome: Neonatal Behavior Assessment: habituation (Primary) Follow-up time: 1-14 days post-partum Arm 1: Sample size 12; mean 9.92; SD (9.28) Arm 2: Sample size 15; mean 8.47; SD (9.26) Outcome: Neonatal Behavior Assessment: orienting (Primary) Follow-up time: 1-14 days post-partum Arm 1: Sample size 12; mean 19.75; SD (15.45) Arm 2: Sample size 15; mean 23.4; SD (18.32)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Harper et al., 2010[29] Study name: NR Study dates: 01. 2005 - 10. 2006 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product Original, same study, or follow-up studies: Klebanoff, 2011[49]	Study Population: At risk for preterm labor Pregnant enrolled 852 Pregnant withdrawals 0 Pregnant completers 852 Pregnant age: n3: 28 placebo 27 n3 23-32; placebo 24-32 Race of Mother: White European (n3: 56.5; placebo 57.7) Black (n3: 34.1; placebo 34.9) Asian (n3: 3, placebo 1.2) Hispanic (n3: 14.7; placebo 13.6) Other race/ethnicity (NR)	Inclusion Criteria: a documented history of at least one prior singleton preterm delivery between 20 0/7 and 36 6/7 weeks of gestation after spontaneous preterm labor or premature rupture of the membranes, and a current singleton pregnancy between 16 and 21 6/7 weeks of gestation Exclusion Criteria: evidence of a major fetal anomaly, intake of a fish oil supplement in excess of 500 mg per week at any time during the preceding month, allergy to fish, anticoagulation therapy, hypertension, White's classification D or higher diabetes, drug or alcohol abuse, seizure disorder, uncontrolled thyroid disease, clotting disorder, current or planned cerclage, or a	Start time: Pregnant 16-22 week gestation age Duration: Pregnant 36 weeks of gestation Arm 1: placebo Description: inert mineral oil Manufacturer: Eminent Services, Frederick, MD Active ingredients: 10 IU vitamin E per capsule, injections of 17_x0001_-hydroxyprogesterone caproate Dose: four capsules of matching oil containing a minute amount of inert mineral oil Blinding: Boxes containing a woman's entire supply of capsules in blister packs were sequentially numbered according to the predetermined randomization sequence, and on enrollment a woman was assigned the next number in sequence. Study group assignment was not known by study participants, their health care providers, or the research personnel Arm 2: Eminent Services, Frederick, MD Active ingredients: 10 IU vitamin E per capsule, injections of 17_x0001_-hydroxyprogesterone caproate Dose: in 4 capsules total 2000 mg of n3 DHA: 800 mg EPA: 1200 mg	Outcome domain: Birth weight Outcome: birth weight (g) (Secondary) Follow-up time: birth Arm 1: Sample size 418; median 2923.0; IQR Arm 2: Sample size 434; median 2990.0; IQR Outcome domain: Gestational hypertension preeclampsia eclampsia Outcome: preeclampsia or gestational hypertension (Secondary) Follow-up time: during pregnancy Arm 1: 20/418 (4.8%) Arm 2: 20/434 (4.6%) Outcome domain: Infants born small gestational age Outcome: SGA less than 10th percentile (Secondary) Follow-up time: birth Arm 1: 41/410 (10.0%) Arm 2: 35/427 (8.2%) Outcome domain: LBW Outcome: birthweight <1500g (Secondary) Follow-up time: birth Arm 1: 29/410 (7.1%) Arm 2: 26/427 (6.1%) Outcome: birthweight <2500g Follow-up time: birth Arm 1: 112/410 (27.3%) Arm 2: 94/427 (22.0%) Outcome domain: duration of gestation

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		plan to deliver either elsewhere or before 37 weeks of gestation		Outcome: gestational age (weeks) (Secondary) Follow-up time: birth Arm 1: Sample size 418; mean 37.4; range Arm 2: Sample size 434; mean 37.7; range Outcome: incidence of premature birth (Primary) Follow-up time: birth Arm 1: 174/418 (41.6%) Arm 2: 164/434 (37.8%)
Hauner et al., 2012[37] Study name: INFAT Study dates: July 14 2006 - may 22 2009 Study design: Trial randomized parallel Location: Germany Funding source / conflict: Industry, Government, Multiple foundations and Societies	Study Population: Healthy pregnant women Pregnant enrolled 208 Pregnant withdrawals 38 Pregnant completers 170 Infants enrolled 188 Infants withdrawals 18 Infants completers 170 Pregnant age: 31.9 (4.9) 18-43 Race of Mother: NR (NR) Baseline biomarker information: Maternal fatty acid profile in RBCs at 15th wk: EPA,	Inclusion Criteria: healthy pregnant women before the 15th wk of gestation, between 18 and 43 y of age, pre-pregnancy BMI (in kg/m2) between 18 and 30, willingness to implement the dietary recommendations, sufficient German language skills. Exclusion Criteria: high-risk pregnancy (multiple pregnancy, rhesus incompatibility, hepatitis B infection, or parity .4); hypertension; chronic diseases (e.g., diabetes) or	Start time: Pregnant 15th wk of gestation Duration: Pregnant to 4 mo postpartum Arm 1: Control Description: brief semi structured counseling on a healthy balanced diet according to the guidelines of the German Nutrition Society and were explicitly asked to refrain from taking fish oil or DHA supplements N-6 N-3: 2.80 +- 1.17 (SD) at 32nd wk of gestation AA: 10.15 +- 3.89 SD) at 32nd wk of gestation Arm 2: Intervention Description: Fish-oil supplement + nutritional counseling (to normalize the consumption of AA Brand name: Marinol D-40 Manufacturer: Lipid Nutrition DHA: 1020 mg EPA: 180 mg N-6 N-3: 1.54 +- 0.63 (SD) at 32nd wk of	Outcome domain: Birth weight Outcome: birth weight (g) (Secondary) Follow-up time: birth Arm 1: Sample size 96; mean 3357.0; SD (557) Arm 2: Sample size 92; mean 3534.0; SD (465) Outcome domain: Infants born small gestational age Outcome: incidence of premature birth (Secondary) Follow-up time: birth Arm 1: 4/96 (4.2%) Arm 2: 3/92 (3.3%) Outcome domain: duration of gestation Outcome: gestational age (days) (Secondary) Follow-up time: birth Arm 1: Sample size 96; mean 275.1; SD (11.4) Arm 2: Sample size 92; mean 279.9; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	DHA, AA, and n-6:n-3 LCUFA ratio (reported in Table 2 by intervention and control groups). No significant differences between groups. Baseline Omega-3 intake: 7-d dietary records completed by participants at the 15th (baseline) and 32nd wk of gestation but only dietary intake at 32nd we of gestation was reported (in Table 2). At week 32 of gestation, the dietary n-6:n-3 PUFA ratio was .5:1 in the intervention group compared with :1 in the control group, as originally intended.	gastrointestinal disorders accompanied by maldigestion, malabsorption, or elevated energy and nutritional requirements (e.g., gluten enteropathy); known metabolic defects (e.g., phenylketonuria); psychiatric diseases; hyperemesis gravidarum; supplementation with n–3 LCPUFAs before randomization; and alcohol abuse and smoking.	gestation AA: 8.82 +- 2.84 (SD) at 32nd wk of gestation Other dose 1: Vit E 9 mg	(8.5) Outcome domain: growth Outcome: bmi (kg/m2) (Secondary) Follow-up time: 12 months Arm 1: Sample size 83; mean 16.7; SD (1.4) Arm 2: Sample size 87; mean 16.9; SD (1.5) Follow-up time: 4 months Arm 1: Sample size 87; mean 16.2; SD (1.3) Arm 2: Sample size 87; mean 16.5; SD (1.4) Follow-up time: 6 weeks Arm 1: Sample size 91; mean 15.3; SD (1.2) Arm 2: Sample size 89; mean 15.2; SD (1.4) Outcome: head circumference (cm) (Secondary) Follow-up time: 12 months Arm 1: Sample size 83; mean 46.1; SD (1.5) Arm 2: Sample size 87; mean 46.5; SD (1.6) Follow-up time: 4 months Arm 1: Sample size 87; mean 41.0; SD (1.3) Arm 2: Sample size 87; mean 41.2; SD (1.3) Follow-up time: 6 weeks Arm 1: Sample size 90; mean 38.8; SD (1.2) Arm 2: Sample size 89; mean 38.4; SD (1.1)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Outcome: length (cm) (Secondary) Follow-up time: 12 months Arm 1: Sample size 83; mean 74.9; SD (2.8) Arm 2: Sample size 87; mean 75.5; SD (2.4) Follow-up time: 4 months Arm 1: Sample size 87; mean 62.4; SD (2.2) Arm 2: Sample size 88; mean 62.6; SD (2) Follow-up time: 6 weeks Arm 1: Sample size 91; mean 55.6; SD (2.6) Arm 2: Sample size 89; mean 56.0; SD (2) Outcome: weight (g) (Secondary) Follow-up time: 12 months Arm 1: Sample size 83; mean 9379.0; SD (1035) Arm 2: Sample size 87; mean 9650.0; SD (1025) Follow-up time: 4 months Arm 1: Sample size 87; mean 6303.0; SD (724) Arm 2: Sample size 87; mean 6476.0; SD (679) Follow-up time: 6 weeks Arm 1: Sample size 91; mean 4736.0; SD (625) Arm 2: Sample size 89; mean 4793.0; SD (606)
Helland et al., 2008[76] Study name: NR Study dates: 1994-2003	Study Population: Healthy infants Healthy pregnant women Breast-feeding women	Inclusion Criteria: Healthy nulliparous or primiparous women, aged 19-35 with single pregnancies	Start time: Pregnant week 18 of pregnancy Duration: NR Arm 1: Cod oil	Outcome domain: Birth weight Outcome: birth weight (g) (Primary) Follow-up time: birth Arm 1: Sample size 61; mean 3518.0; SD (560)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study design: Trial randomized parallel Location: Norway Funding source / conflict: Industry, Government, Multiple foundations and Societies Study follow-up: 7 years Original, same study, or follow-up studies: Helland, 2001[86] and Helland, 2003[87] and which are both included in the original report	Infants enrolled 262 Infants completers 143 Pregnant age: cod oil 28.6 n=175 corn oil 27.6 n=166 (cod oil 3.4; corn oil 3.2) Race of Mother: NR (100) Baseline biomarker information: from id 10331 cod(n148) corn (n137) n-3 cod: 73.7 (30.0) corn 52.0 (14.9)*** 20:5n-3 cod: 10.8 (7.6) corn: 2.5 (1.8)*** 22:5n-3 cod: 5.0 (2.6) corn: 2.9 (1.3)*** 22:6n-3 cod: 55.8 (20.6) corn: 45.3 (12.8)*** Baseline Omega-3 intake: from 10331 cod n147 corn n159 18:3 n-3: cod: 1.3 (0.5) corn: 1.2 (0.5) 20:5 n-3 cod: 0.2 (0.2) corn:0.2 (0.2) 22:5 n-3 cod: 0.05 (0.03) corn: 0.05 (0.03) 22:6 n-3 cod: 0.3 (0.3) corn: 0.3 (0.3)	Exclusion Criteria: Unhealthy neonates	Manufacturer: Peter Moller, Avd Orkla ASA, Oslo, Norway Active ingredients: Vit 1: 117 ug/mL, Vit D3: 1 ug/mL, vit E: 1.4 mg/mL Viability: frozen at _x0003_ 70 ° C under nitrogen. Before storage, the samples were sonicated and ethylenediaminetetraacetic acid and butylated hydroxytoluene were added to a final concentration of 1.85 mg/mL and 75 _x0003_ g/mL, respectively DHA: 1183mg/10 mL EPA: 803 mg/10mL Total N-3: 2494 mg/10mL Arm 2: corn oil Active ingredients: Vit 1: 117 ug/mL, Vit D3: 1 ug/mL, vit E: 1.4 mg/mL Viability: frozen at _x0003_ 70 ° C under nitrogen. Before storage, the samples were sonicated and ethylenediaminetetraacetic acid and butylated hydroxytoluene were added to a final concentration of 1.85 mg/mL and 75 _x0003_ g/mL, respectively ALA: 92 mg/10mL	Arm 2: Sample size 82; mean 3613.0; SD (458) Outcome domain: Cognitive development Outcome: Kaufman Assessment Battery for Children (K-ABC): mental processing composite (Secondary) Follow-up time: 4 years Arm 1: Sample size 28; mean 102.0 Arm 2: Sample size 30; mean 107.0 Follow-up time: 7 years Arm 1: Sample size 28; mean 108.0 Arm 2: Sample size 30; mean 110.0 Outcome: Kaufman Assessment Battery for Children (K-ABC): non-verbal abilities (Secondary) Follow-up time: 4 years Arm 1: Sample size 28; mean 102.0 Arm 2: Sample size 30; mean 107.0 Follow-up time: 7 years Arm 1: Sample size 28; mean 112.0 Arm 2: Sample size 30; mean 112.0 Outcome: Kaufman Assessment Battery for Children (K-ABC): sequential processing (Secondary) Follow-up time: 4 years Arm 1: Sample size 28; mean 107.0 Arm 2: Sample size 30; mean 109.0 Follow-up time: 7 years Arm 1: Sample size 28; mean 105.0 Arm 2: Sample size 30; mean 107.0 Outcome: Kaufman Assessment Battery for Children (K-ABC): simultaneous processing (Secondary) Follow-up time: 4 years Arm 1: Sample size 28; mean 98.0

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 2: Sample size 30; mean 102.0 Follow-up time: 7 years Arm 1: Sample size 28; mean 110.0 Arm 2: Sample size 30; mean 110.0 Outcome domain: growth Outcome: bmi (kg/m2) (Secondary) Follow-up time: 7 years Arm 1: Sample size 61; mean 16.3; SD (1.7) Arm 2: Sample size 82; mean 16.4; SD (1.7) Outcome: length (cm) (Secondary) Follow-up time: 7 years Arm 1: Sample size 61; mean 128.6; SD (5) Arm 2: Sample size 82; mean 127.5; SD (5.5) Outcome: weight (kg) (Secondary) Follow-up time: 7 years Arm 1: Sample size 61; mean 27.0; SD (4.1) Arm 2: Sample size 82; mean 26.8; SD (4.1)
Henriksen et al., 2008[107] Study name: Unnamed Trial D Study dates: 2003-2006 Study design: Trial randomized parallel Location: Norway	Study Population: Preterm infants Infants enrolled 141 Infants completers 129 Mother age: Median: Intervention: 31 years Control: 32 years 28-35 years	Inclusion Criteria: All VLBW infants (<1500g) born between December 2003 and November 2005 at Rikshospitalet-Radiumhospitalet Medical Center, Akershus University Hospital, Buskerud Hospital, and Vestfold	Start time: Infants (intervention began when the infant received most of his nutrients enterally: >100ml human milk/kg body weight/day Duration: Infants Until discharge or bottle of study oil was empty (average 63 days of age) Arm 1: Control Description: Study oil: soy oil and medium chain triglycerides Active ingredients: 127mg linolenic acid/100 ml	Outcome domain: Cognitive development Outcome: Ages and Stages: Communication Follow-up time: 6 months Arm 1: Sample size 55; mean 46.6; SD (9.1) Arm 2: Sample size 50; mean 45.4; SD (7.9) Outcome: Ages and Stages: Fine motor Follow-up time: 6 months Arm 1: Sample size 55; mean 45.8; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Funding source / conflict: Multiple foundations and Societies, Manufacturer supplied product Study follow-up: 6 months Original, same study, or follow-up studies: Ane, 2011[125]; Almaas, 2015[126]	Infant age: Median Gestational age: Control: 28.9 weeks Intervention: 28.4 weeks Gestational age: 26.6-30.9 weeks Race of Mother: White European (Intervention: 79%; Control 84%)	Hospital in Norway Exclusion Criteria: Major congenital abnormalities or cerebral hemorrhage (grade 3 or 4, as determined through ultrasonography)	milk(27.1% total fatty acids) Dose: 0.5 ml study oil/100 ml human milk Blinding: Study oils packed in numbered bottles in hospital pharmacy ALA: 16mg/100 ml milk; 3.4% total fatty acids Arm 2: Intervention Description: DHA and AA-containing oil Manufacturer: Martek Biosciences Active ingredients: 88mg/100 ml linoleic acid per 100 ml milk (18.8%) Dose: 0.5 ml study oil per 100 ml milk, ad lib Maternal conditions Infant conditions DHA: 32mg/100ml milk (6.9%) AA: 31 mg/100 ml milk (6.7% total fatty acids Current smoker 22% during pregnancy Low birth weight 100% (median 1090 g)	(14.3) Arm 2: Sample size 50; mean 45.2; SD (10.7) Outcome: Ages and Stages: Gross motor Follow-up time: 6 months Arm 1: Sample size 55; mean 30.9; SD (11.1) Arm 2: Sample size 50; mean 33.3; SD (11.5) Outcome: Ages and Stages: Personal-social Follow-up time: 6 months Arm 1: Sample size 55; mean 42.2; SD (12.3) Arm 2: Sample size 50; mean 43.2; SD (12.8) Outcome: Ages and Stages: Problem-solving Follow-up time: 6 months Arm 1: Sample size 55; mean 49.5; SD (9.5) Arm 2: Sample size 50; mean 53.4; SD (7) Outcome: Ages and Stages: Total Follow-up time: 6 months Arm 1: Sample size 55; mean 215.0; SD (39) Arm 2: Sample size 50; mean 221.0; SD (32) Outcome domain: growth Outcome: head circumference (mm/day) (Secondary) Follow-up time: day 65 Arm 1: Sample size 50; mean 1.0; SD (0.4) Arm 2: Sample size 50; mean 1.2; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(0.7)
Hoffman et al., 2008[114] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Manufacturer supplied product	Study Population: Healthy infants Infants enrolled 244 Infants withdrawals 3 Infants completers 241 Infant age: 14 days Race of Mother: NR	Inclusion Criteria: 12–16 days of age, had a minimum birth weight of 2,500 g, and solely received formula at least 24 h prior to randomization Exclusion Criteria: history of underlying disease or malformation that could interfere with growth and development; large-for-gestational-age infants whose mothers were diabetic; breastfeeding within 24 h prior to randomization; evidence of formula intolerance or poor intake at time of randomization; weight at randomization less than 98% of birth weight; enlarged liver or spleen; or plans to move outside of the study area within the study time frame (120 days)	Start time: Infants 14 day Duration: NR Arm 1: Control Description: soy formula without supplementation Brand name: Enfamil ProSobee1, Mead Johnson & Company, Evansville, IN Blinding: Aside from the addition of DHA and ARA, the formulas were identical in all other respects. Arm 2: DHA + ARA Description: soy formula supplemented with a minimum 17 mg DHA/100kcal from algal oil and 34 mg ARA/100kcal from fungal oil Brand name: Enfamil ProSobee1 LIPIL1, Mead Johnson & Company, Evansville, IN) DHA: 0.3% AA: 0.6%	Outcome domain: growth Outcome: head circumference (cm/day) (Secondary) Follow-up time: 14-120d Arm 1: Sample size 86; mean gain 0.05; SE (0.001) Arm 2: Sample size 93; mean gain 0.05; SE (0.001) Outcome: length (cm/day) (Secondary) Follow-up time: 14-120d Arm 1: Sample size 86; mean change 0.1; SE (0.002) Arm 2: Sample size 93; mean change 0.1; SE (0.002) Outcome: weight (g/day) (Secondary) Follow-up time: 14-120d Arm 1: Sample size 86; mean change 27.8; SE (0.8) Arm 2: Sample size 93; mean change 27.3; SE (0.7)
Imhoff-Kunsch et al.,	Study Population:	Inclusion Criteria:	Start time: Pregnant 18 to 22 weeks gestation	Outcome domain: respiratory illness

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
2011[58] Study name: POSGRAD Study dates: February 2005 - February 2007 Study design: Trial randomized parallel Location: Mexico Funding source / conflict: Government, March of Dimes Original, same study, or follow-up studies: Ramakrishnan, 2010[32]; Stein, 2012[33]; Escamilla-Nunez, 2014[59]; Gonzalez-Casanova, 2015[60]; Ramakrishnan, 2015[61]	Healthy pregnant women Pregnant enrolled 1094 Pregnant completers 851 Infants enrolled 851 Infants completers 834 Pregnant age: DHA: 26.3 Placebo:20.5 (DHA: 4.9 Placebo: 1.9) Race of Mother: NR (100%)	Women were considered for inclusion in the study if they were in gestation week 18 to 22, were aged 18 to 35 years, planned to deliver at the IMSS General Hospital in Cuernavaca, planned to predominantly breastfeed for at least 3 months, and planned to live in the area for 2 years after delivery Exclusion Criteria: Exclusion criteria included (1) high-risk pregnancy, (2) lipid metabolism/absorption disorders, (3) regular intake of fish oil or DHA supplements, or (4) chronic use of certain medications.	Duration: Pregnant until parturition Arm 1: Placebo Description: Placebo/control corn and soy oil capsule Dose: 2 capsules daily Blinding: The placebo capsules, which were similar in appearance and taste to the DHA capsules, contained a corn and soy oil blend with no added antioxidants....All participants and members of the study team were blinded to the treatment scheme throughout the intervention period of the study. Data were unblinded for the analytical study team after the last infant in the study was born and had reached the age of 6 months. Arm 2: DHA Description: DHA capsule Manufacturer: Martek Biosciences Corporation, Columbia, MD Dose: 2 capsules daily DHA: 200mg/ capsule	Outcome: cold (any of cough, phlegm, nasal congestion, nasal secretion) (Secondary) Follow-up time: 1 month (preceding 15 days) Arm 1: 190/427 (44.6%) Arm 2: 159/422 (37.6%) Follow-up time: 3 months Arm 1: 185/419 (44.1%) Arm 2: 157/415 (37.8%) Follow-up time: 6 months (preceding 15 days) Arm 1: 193/414 (46.6%) Arm 2: 194/420 (46.2%) Outcome: cough (Secondary) Follow-up time: 1 month (preceding 15 days) Arm 1: 47/427 (11.0%) Arm 2: 40/422 (9.5%) Follow-up time: 3 months Arm 1: 100/419 (23.9%) Arm 2: 80/415 (19.3%) Follow-up time: 6 months (preceding 15 days) Arm 1: 136/414 (32.9%) Arm 2: 139/420 (33.1%) Outcome: difficulty breathing (Secondary) Follow-up time: 1 month (preceding 15 days) Arm 1: 10/427 (2.3%) Arm 2: 10/422 (2.4%) Follow-up time: 3 months Arm 1: 10/419 (2.4%) Arm 2: 12/415 (2.9%) Follow-up time: 6 months (preceding 15 days)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 1: 7/414 (1.7%) Arm 2: 6/420 (1.4%) Outcome: nasal congestion (Secondary) Follow-up time: 1 month (preceding 15 days) Arm 1: 140/427 (32.8%) Arm 2: 119/422 (28.2%) Follow-up time: 3 months Arm 1: 119/419 (28.4%) Arm 2: 104/415 (25.1%) Follow-up time: 6 months (preceding 15 days) Arm 1: 116/414 (28.0%) Arm 2: 124/420 (29.6%) Outcome: nasal secretion (Secondary) Follow-up time: 1 month (preceding 15 days) Arm 1: 46/427 (10.8%) Arm 2: 30/422 (7.1%) Follow-up time: 3 months Arm 1: 72/419 (17.2%) Arm 2: 62/415 (14.9%) Follow-up time: 6 months (preceding 15 days) Arm 1: 122/414 (29.5%) Arm 2: 118/420 (28.2%) Outcome: phlegm (Secondary) Follow-up time: 1 month (preceding 15 days) Arm 1: 82/427 (19.2%) Arm 2: 71/422 (16.8%) Follow-up time: 3 months Arm 1: 78/419 (18.6%) Arm 2: 81/415 (19.5%) Follow-up time: 6 months (preceding 15 days)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 1: 100/414 (24.2%) Arm 2: 100/420 (23.9%) Outcome: wheezing (Secondary) Follow-up time: 1 month (preceding 15 days) Arm 1: 30/427 (7.0%) Arm 2: 35/422 (8.3%) Follow-up time: 3 months Arm 1: 34/419 (8.1%) Arm 2: 29/415 (7.0%) Follow-up time: 6 months (preceding 15 days) Arm 1: 45/414 (10.9%) Arm 2: 50/420 (11.9%)
Innis et al., 2008[145] Study name: NR Study dates: NR, <2008 Study design: Trial randomized parallel Location: Canada Funding source / conflict: Government, None, Manufacturer supplied product Study follow-up: 60 days	Study Population: Healthy pregnant women Pregnant enrolled NR Pregnant completers 135 Infants enrolled 135 Infants completers 134 Pregnant age: 33 years (0. 4 years) Infant age: 14 to 16 weeks gestation Race of Mother: White European (72%) Baseline biomarker	Inclusion Criteria: 14 – 16 wk gestation, not taking any lipid supplement, no complications likely to affect maternal or fetal metabolism or fetal development, expected to deliver one full-term infant Exclusion Criteria: NR	Start time: Pregnant 16 weeks gestation Infants 16 weeks gestation Duration: Pregnant to birth Infants to birth Arm 1: placebo Description: corn oil / soybean oil capsule Manufacturer: Martek Biosciences, Columbia, MD) Dose: 2 capsules Blinding: identical capsules, containing an orange flavor to assist in further blinding Maternal conditions ALA: 40 mg Other dose 1: LA 265 mg Current smoker 2/67 Arm 2: DHA supplement Description: capsule containing 200 mg DHA Manufacturer: Martek Biosciences, Columbia, MD)	Outcome domain: Visual function Outcome: Teller Acuity Card procedure (visual acuity) (cyc/deg) (Secondary) Follow-up time: 60 days Arm 1: Sample size 68; mean 2.42; SD (0.63) Arm 2: Sample size 67; mean 2.6; SD (0.5)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	information: 16 week gestation baseline values for both groups similar. Reported graphically, so approximations. 22:6n-3: 7 %wt of total FA 22:5n-3: 4 %wt of total FA 20:5n-3: 1 %wt of total FA 18:3n-3: 0.4 %wt of total FA Baseline Omega-3 intake: For mothers, at assignment: Linoleic acid (g) median 13.5 range 2.52–43 Alpha Linolenic acid (g) median 1.48 range 0.46–9.21 Arachidonic acid (mg) median 90 range 20–360 EPA (mg) median 70 range 10–280 DHA (mg) median 110 range 10–760		Dose: 2 capsules Maternal conditions DHA: 200 mg/g Current smoker 0/68	
Isaacs et al., 2011[99] Study name: Unnamed Trial A Study dates: Recruitment of infants from 1995 through 1997 with 10-year follow-up	Study Population: Preterm infants Infants enrolled 238 Infants completers 107 Infant age: birth (at < 35 weeks gestation) NA Race of Mother: NR	Inclusion Criteria: birth weight of < 2000 g, and gestational age of < 35 weeks Exclusion Criteria: congenital malformations	Start time: Infants at hospital discharge Duration: Infants 9 months Arm 1: control Description: control formula Active ingredients: protein, minerals, vitamins A, E, K, D DHA: 0 EPA: 0	Outcome domain: ADHD Outcome: Test of Everyday Attention for Children: Attention scaled score (Secondary) Follow-up time: 10 years Arm 1: Sample size 57; mean 8.3; SD (2.6) Arm 2: Sample size 50; mean 8.2; SD (2.5) Outcome: Test of Everyday Attention for

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study design: Trial randomized parallel Location: UK Funding source / conflict: Industry, Government, Some authors have received research funding from infant formula manufacturers Study follow-up: 10 years Original, same study, or follow-up studies: Fewtrell, 2002[158] is the original study; Llorente, 2003[98] reports post-partum depression	(NR)		AA: 0 Other dose 1: C18:2, n-6, linoleic acid 11.5 g / 100g fat Other dose 2: C18:3, n-3, alpha_x0004_-linolenic acid 1.6 g / 100g fat Arm 2: Omega 3 supplemented formula Description: LCPUFA-Supplemented Formula Active ingredients: protein, minerals, vitamins A, E, K, D Infant conditions DHA: 0.5 g / 100g fat EPA: 0.1 g/ 100g fat AA: 0.04 g / 100g fat Other dose 1: C18:2, n-6, linoleic acid 12.3 g / 100g fat Other dose 2: C18:3, n-6, gamma-linoleic acid 0.9 g / 100g fat Other dose 3: C18:3, n-3, _x0004_alpha-linolenic acid 1.5 g / 100g fat Pre-term birth 100% Low birth weight 100%	Children: Creature counting scale score (Secondary) Follow-up time: 10 years Arm 1: Sample size 57; mean 9.6; SD (2.1) Arm 2: Sample size 50; mean 10.0; SD (2.7) Outcome: Test of Everyday Attention for Children: Dual-task decrement scaled score (Secondary) Follow-up time: 10 years Arm 1: Sample size 57; mean 7.3; SD (2.8) Arm 2: Sample size 50; mean 7.6; SD (2.5) Outcome: Test of Everyday Attention for Children: Opposite Worlds different scaled score (Secondary) Follow-up time: 10 years Arm 1: Sample size 57; mean 8.4; SD (2.8) Arm 2: Sample size 50; mean 8.9; SD (3.5) Outcome: Test of Everyday Attention for Children: Score! Scale scored (Secondary) Follow-up time: 10 years Arm 1: Sample size 57; mean 7.8; SD (3.4) Arm 2: Sample size 50; mean 7.7; SD (3.4) Outcome domain: Cognitive development Outcome: Wechsler Abbreviated Scale of Intelligence: FSIQ (Secondary) Follow-up time: 10 years

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 1: Sample size 57; mean 92.7; SD (12.3) Arm 2: Sample size 50; mean 95.1; SD (13.2) Outcome: Wechsler Abbreviated Scale of Intelligence: Performance IQ (Secondary) Follow-up time: 10 years Arm 1: Sample size 57; mean 94.5; SD (14.1) Arm 2: Sample size 50; mean 94.2; SD (12.7) Outcome: Wechsler Abbreviated Scale of Intelligence: VIQ (Secondary) Follow-up time: 10 years Arm 1: Sample size 57; mean 92.6; SD (12.6) Arm 2: Sample size 50; mean 96.7; SD (13.2)
Jensen et al., 2005[136] Study name: Unnamed Trial B Study dates: <2004 Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Government Original, same study, or	Study Population: Breast-feeding women Lactating enrolled 227 Lactating completers 174 Infants enrolled 230 Infants completers 177 Lactating enrolled 227 Lactating completers 174 Lactating age: 31.5 years (5 years) 18-40	Inclusion Criteria: maternal age between 18 and 40 y, infant gestational age >=37 wk, infant birth weight between 2500 and 4200 g Exclusion Criteria: chronic maternal disorders, major congenital anomalies, obvious gastrointestinal or metabolic disorders of the infant	Start time: Lactating 5 days after delivery Infants 5 days after birth Duration: Lactating 4 months Infants 4 months Arm 1: placebo Description: capsule containing corn & soy oil Manufacturer: Martek Biosciences Purity Data: 15% saturated fatty acids, 23.5% monounsaturated fatty acids, 56.3% linoleic acid (18: 2n_x0001_6), and 3.9% _x0001_-linolenic acid (18:3n_x0001_3) Dose: 1 capsule Blinding: identical capsules ALA: 56.3% linoleic acid (18: 2n_x0001_6), 3.9% _x0001_-linolenic acid (18:3n_x0001_3) Total N-3: 57.2%	Outcome domain: Neurological development Outcome: Bayley Physical Developmental Index (Primary) Follow-up time: 30 months Arm 1: Sample size 65; mean 108.4; SD (13.8) Arm 2: Sample size 68; mean 116.8; SD (15.2) Outcome: Clinical Linguistic and Auditory Milestone Scale (CLAMS) (Secondary) Follow-up time: 30 months Arm 1: Sample size 72; mean 106.6; SD (14.9) Arm 2: Sample size 75; mean 106.8; SD (15.2) Follow-up time: 12 months

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
follow-up studies: Jensen, 2010[135]	Infant age: birth (NA) NA Race of Mother: NR		Arm 2: DHA algal triacylglycerol (DHASCO) Description: DHA capsule Brand name: DHASCO Manufacturer: Martek Biosciences Purity Data: 44%saturatedfattyacids, 13.6% monounsaturated fatty acids, 0.8% linoleic acid (18:2n _x0001_ 6), and 41.7% DHA (22:6n-3) by weight Dose: 1 capsule ALA: 0.8% (18:2n-6) DHA: 200 mg, 41.7% (22:6n-3) Total N-3: 42.5%	Arm 1: Sample size 76; mean 102.5; SD (13.2) Arm 2: Sample size 86; mean 100.6; SD (14.6) Outcome: Clinical adaptive test development quotient (CAT DQ) (Secondary) Follow-up time: 30 months Arm 1: Sample size 72; mean 98.3; SD (8.7) Arm 2: Sample size 75; mean 98.1; SD (9) Follow-up time: 12 months Arm 1: Sample size 76; mean 110.0; SD (10.8) Arm 2: Sample size 86; mean 109.0; SD (10) Outcome: Gesell Gross Motor development quotient (DQ) (Secondary) Follow-up time: 30 months Arm 1: Sample size 72; mean 102.4; SD (10.2) Arm 2: Sample size 75; mean 100.8; SD (11.4) Follow-up time: 12 months Arm 1: Sample size 76; mean 99.5; SD (13.3) Arm 2: Sample size 86; mean 101.8; SD (13.8) Outcome domain: Visual function Outcome: Sweep VEP (cyc/deg) (Secondary) Follow-up time: 4 months Arm 1: Sample size 79; mean 9.4; SD (0.21) Arm 2: Sample size 81; mean 9.4; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(0.23) Outcome: Teller Acuity Card procedure (cyc/deg) (Secondary) Follow-up time: 4 months Arm 1: Sample size 77; mean 5.3; SD (0.56) Arm 2: Sample size 70; mean 5.6; SD (0.71) Follow-up time: 8 months Arm 1: Sample size 73; mean 13.5; SD (0.57) Arm 2: Sample size 74; mean 12.3; SD (0.53) Outcome: Visual evoked potential amplitude (mV) (Secondary) Follow-up time: 4 months Arm 1: Sample size 82; mean 33.3; SD (12.4) Arm 2: Sample size 86; mean 28.9; SD (12.1) Follow-up time: 8 months Arm 1: Sample size 74; mean 27.9; SD (11) Arm 2: Sample size 79; mean 24.3; SD (8.9) Outcome: Visual evoked potential latency (ms) (Secondary) Follow-up time: 4 months Arm 1: Sample size 82; mean 123.9; SD (10.6) Arm 2: Sample size 86; mean 124.8; SD (11.7) Follow-up time: 8 months Arm 1: Sample size 74; mean 115.3; SD (10.5) Arm 2: Sample size 79; mean 115.1; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(8.1)
Jensen et al., 2010[135] Study name: Unnamed Trial B Study dates: NR (<2010) Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Government Study follow-up: 5 years Original, same study, or follow-up studies: Jensen, 2005[136]	Study Population: Breast-feeding women Lactating enrolled 227 Infants enrolled 230 Infants completers 119 Lactating enrolled 227 Lactating age: 31.5 years (5 years) 18 to 40 Infant age: birth (NA) NA Race of Mother: NR (NR)	Inclusion Criteria: maternal age between 18 and 40 y, infant gestational age >=37 wk, infant birth weight between 2500 and 4200 g Exclusion Criteria: chronic maternal disorders, major congenital anomalies, obvious gastrointestinal or metabolic disorders of the infant	Start time: Infants birth Duration: Infants 4 months Arm 1: placebo Description: capsule containing corn & soy oil Manufacturer: Martek Biosciences Purity Data: 50:50 mixture of soy and corn oils consisting, by weight, of 15% saturated fatty acids, 23.5% monounsaturated fatty acids, 56.3% linoleic acid (18:2 n-6) and 3.9% a-linolenic acid (18:3 n-3) Dose: 1 capsule Blinding: capsules were identical ALA: 3.9% Arm 2: omega 3 capsule Description: high-DHA algal triglyceride capsule Brand name: DHASCO Manufacturer: Martek Purity Data: by weight, 44% saturated fatty acids, 13.6% monounsaturated fatty acids, 0.8% linoleic acid (18:2n-6) and 41.7% DHA (22:6n-3) Dose: 1 capsule DHA: 200 mg	Outcome domain: Cognitive development Outcome: Wechsler Primary and Preschool Scale of Intelligence - Revised : Vocabulary Subset (Secondary) Follow-up time: 5 years Arm 1: Sample size 57; mean 12.9; SD (2.4) Arm 2: Sample size 60; mean 12.3; SD (2.8) Outcome: Wechsler Primary and Preschool Scale of Intelligence - Revised : Animal Pegs Subset (Secondary) Follow-up time: 5 years Arm 1: Sample size 57; mean 12.2; SD (1.8) Arm 2: Sample size 60; mean 12.1; SD (2.4) Outcome: Wechsler Primary and Preschool Scale of Intelligence - Revised : Block Design Subset (Secondary) Follow-up time: 5 years Arm 1: Sample size 57; mean 11.1; SD (2.2) Arm 2: Sample size 60; mean 11.3; SD (2.1) Outcome: Wechsler Primary and Preschool Scale of Intelligence - Revised : Information Subset (Secondary) Follow-up time: 5 years Arm 1: Sample size 57; mean 11.2; SD (2.6) Arm 2: Sample size 60; mean 10.8; SD (2.6)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Outcome domain: Neurological development Outcome: Development test of Visual-Motor Integration (Secondary) Follow-up time: 5 years Arm 1: Sample size 56; mean 11.8; SD (1.8) Arm 2: Sample size 57; mean 11.6; SD (1.9) Outcome: Kaufman Assessment Battery for Children: hand movement (Secondary) Follow-up time: 5 years Arm 1: Sample size 56; mean 9.02; SD (2.84) Arm 2: Sample size 59; mean 8.39; SD (2.55) Outcome: McCarthy (leg coordination) (Secondary) Follow-up time: 5 years Arm 1: Sample size 56; mean 10.7; SD (1.9) Arm 2: Sample size 59; mean 10.6; SD (1.5) Outcome: Purdue pegboard test (dominant hand) (Secondary) Follow-up time: 5 years Arm 1: Sample size 57; mean 9.8; SD (2.7) Arm 2: Sample size 59; mean 9.6; SD (1.7) Outcome: Purdue pegboard test (non-dominant hand) (Secondary) Follow-up time: 5 years Arm 1: Sample size 57; mean 8.9; SD (2.7) Arm 2: Sample size 59; mean 8.9; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(1.6) Outcome domain: Visual function Reason results are not reported: intervention first 4 months Outcome: VEP Latency (30' check sizes) (ms) (Secondary) Follow-up time: 5 years Arm 2: Sample size 60; mean 110.0; SD (8.1) Outcome domain: Visual function Reason results are not reported: intervention first 4 months; same trial as 3433 (later fu) Outcome: Bailey Lovie Acuity - left eye (number of letters correct) (Secondary) Follow-up time: 5 years Arm 1: Sample size 57; mean 52.1; SD (4.9) Arm 2: Sample size 60; mean 53.1; SD (4.7) Outcome: Bailey Lovie Acuity - right eye (number of letters correct) (Secondary) Follow-up time: 5 years Arm 1: Sample size 58; mean 51.6; SD (5.6) Arm 2: Sample size 60; mean 52.6; SD (4.6) Outcome: Sweep VEP acuity (cyc/deg) (Secondary) Follow-up time: 5 years Arm 1: Sample size 55; mean 11.8; SD (0.3) Arm 2: Sample size 56; mean 11.9; SD (0.3)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Outcome: VEP Amplitude (mV) (Secondary) Follow-up time: 5 years Arm 1: Sample size 56; mean 45.3; SD (18) Arm 2: Sample size 60; mean 39.6; SD (13.7) Outcome: VEP Latency (30' check sizes) (ms) (Secondary) Follow-up time: 5 years Arm 1: Sample size 56; mean 108.0; SD (6.5)
Judge et al., 2007[39] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: US Funding source / conflict: Industry, Government, None	Study Population: Healthy pregnant women Pregnant enrolled 29 Pregnant completers 29 Pregnant age: 23.75 years (.4 years) NR Race of Mother: NR (100%)	Inclusion Criteria: women aged 18 –35 y who were at 20 wk of gestation Exclusion Criteria: Women with a history of drug or alcohol addiction, hypertension, smoking, hyperlipidemia, renal disease, liver disease, diabetes, or psychiatric disorder	Start time: Pregnant 24 weeks gestation Duration: Pregnant until birth Arm 1: placebo Description: cereal based placebo bars Manufacturer: Nestec Active ingredients: 18 g carbohydrates, 1.3 grams protein, 92 calories, 1.7 g fat Viability: NR Dose: 5 bars per week Blinding: NR Arm 2: DHA supplemented cereal bars Manufacturer: Nestec Active ingredients: 18 g carbohydrates, 1.3 grams protein, 92 calories, 1.7 g fat Viability: NR Dose: 5 bars per week. DHA-containing cereal based bars [1.7 g total fat, 300 mg DHA as low-eicosapentaenoic oil (EPA) fish oil; EPA:DHA 1:8 per bar DHA: mg/d	Outcome domain: Birth weight Outcome: birth weight (g) (Secondary) Follow-up time: birth Arm 1: Sample size 15; mean 3222.0; SD (363) Arm 2: Sample size 14; mean 3465.0; SD (406) Outcome domain: duration of gestation Outcome: gestational age (weeks) (Secondary) Follow-up time: birth Arm 1: Sample size 15; mean 39.0; SD (1) Arm 2: Sample size 14; mean 39.9; SD (0.8)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			EPA: .75 mg (calculated based on EPA:DHA ratio) EPA-DHA: 1:8	
Judge et al., 2012[40] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: US Funding source / conflict: Multiple foundations and Societies	Study Population: Healthy pregnant women Pregnant enrolled 48 Pregnant age: Treatment group: 23.93 Placebo: 23.86 (Treatment group: 4.32 Placebo: 4.53) Race of Mother: White European (Treatment: 11.1%, Placebo: 0%) Black (Treatment: 18.5%, Placebo: 4.8%) Asian (Treatment: 3.7%, Placebo: 0%) Hispanic (Treatment: 59.3%, Placebo: 80.9%) NR (Treatment: 7.4%, 3 (14.3%)) Baseline biomarker information: Maternal plasma phospholipid (PL) fatty acids (FA): 2.85 +/- .87 % in treatment group and 2.95 +/- .91% in placebo group. Infant RBC PL	Inclusion Criteria: The women were either primiparous or had not been pregnant for the past 2 years. Exclusion Criteria: parity greater than 5, history of chronic hypertension, hyperlipidemia, renal, liver or heart disease, thyroid disorder, multiple gestations or pregnancy induced complications including hypertension, preeclampsia or preterm labor, smoking and psychiatric disorders. Women who were treated during labor with analgesics such as Stadol (butorphanol tartrate), that may cause infant respiratory distress were also excluded. In addition, infants born preterm and infants	Start time: Pregnant 24 weeks gestation Duration: Pregnant until delivery Arm 1: Placebo Description: Control group Manufacturer: Nestec, S.A., Switzerland Blinding: The total macronutrient content was the same in both the DHA and placebo bars with respect to carbohydrate, protein and fat, how- ever, the DHA bars contained fish oil (300 mg DHA) and the placebo bars contained corn oil. Arm 2: DHA Description: Intervention group Manufacturer: Nestec, S.A., Switzerland Dose: average of 5 bars weekly DHA: 300 mg EPA-DHA: 8:1 ratio of DHA to EPA	Outcome domain: Birth weight Outcome: birth weight (g) (Secondary) Follow-up time: birth Arm 1: Sample size 21; mean 3224.62; SD (431.25) Arm 2: Sample size 27; mean 3394.7; SD (430) Outcome domain: Neurological development Outcome: Infant sleep: Active Sleep (AS, %) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 51.81; SD (10.43) Arm 2: Sample size 27; mean 49.39; SD (10.32) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 51.7; SD (11.13) Arm 2: Sample size 24; mean 51.57; SD (14.54) Outcome: Infant sleep: Active–Quiet Sleep Transition (AQST, %) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 0.53; SD (0.23) Arm 2: Sample size 27; mean 0.59; SD (0.37) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 0.41; SD (0.27)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	FA: 7.55 +/- 1.61% in treatment group and 7.07 +/- 1.25% in placebo group.	with less than 4 h of crib time in the first and second days postpartum were excluded from the analyses.		Arm 2: Sample size 24; mean 0.47; SD (0.3) Outcome: Infant sleep: Arousals in AS (Ar/AS) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 20.41; SD (4.39) Arm 2: Sample size 27; mean 17.41; SD (4.71) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 24.67; SD (6.82) Arm 2: Sample size 24; mean 24.04; SD (7.04) Outcome: Infant sleep: Arousals in QS (Ar/QS) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 5.89; SD (6.01) Arm 2: Sample size 27; mean 2.7; SD (2.65) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 5.44; SD (4.07) Arm 2: Sample size 24; mean 3.55; SD (3.98) Outcome: Infant sleep: Mean Sleep Period (LSP, min) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 185.95; SD (79.75) Arm 2: Sample size 27; mean 228.19; SD (104.89) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 202.6; SD (123.18)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 2: Sample size 24; mean 190.75; SD (102.75) Outcome: Infant sleep: Mean Sleep Period (MSP, min) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 46.09; SD (17.6) Arm 2: Sample size 27; mean 48.03; SD (17.55) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 48.85; SD (29.99) Arm 2: Sample size 24; mean 48.67; SD (21.18) Outcome: Infant sleep: Wakefulness (W, %) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 27.59; SD (11.54) Arm 2: Sample size 27; mean 29.57; SD (13.56) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 28.95; SD (12.14) Arm 2: Sample size 24; mean 30.71; SD (18.92) Outcome: Infant sleep: quiet sleep (QS,%) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 15.14; SD (4.26) Arm 2: Sample size 27; mean 15.88; SD (5.1) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 13.7; SD (4.76)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 2: Sample size 24; mean 12.7; SD (5.85) Outcome: Infant sleep: Active sleep bout length (ASBL, min) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 28.93; SD (9.67) Arm 2: Sample size 27; mean 29.0; SD (7.07) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 29.81; SD (12.5) Arm 2: Sample size 24; mean 30.48; SD (9.14) Outcome: Infant sleep: Active/Quiet Sleep Ratio(AS:QS) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 3.83; SD (2.15) Arm 2: Sample size 27; mean 3.38; SD (1.1) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 4.56; SD (3.13) Arm 2: Sample size 24; mean 4.46; SD (2.14) Outcome: Infant sleep: Quiet sleep bout length (QSBL, min) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 21.81; SD (4.93) Arm 2: Sample size 27; mean 22.74; SD (5.73) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 20.59; SD (4.98)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 2: Sample size 24; mean 18.75; SD (6.86) Outcome: Infant sleep: Sleep–Wake Transition (T, %) (Secondary) Follow-up time: 1 day after birth Arm 1: Sample size 19; mean 4.92; SD (1.48) Arm 2: Sample size 27; mean 4.57; SD (1.33) Follow-up time: 2 days after birth Arm 1: Sample size 15; mean 5.23; SD (1.88) Arm 2: Sample size 24; mean 4.5; SD (1.39) Outcome domain: duration of gestation Outcome: gestational age (weeks) (Secondary) Follow-up time: birth Arm 1: Sample size 21; mean 39.19; SD (1.17) Arm 2: Sample size 27; mean 39.72; SD (1.2)
Judge et al., 2014[91] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: US Funding source /	Study Population: Healthy pregnant women Pregnant enrolled 73 Pregnant completers 42 Pregnant age: 18-35 Race of Mother: NR (100)	Inclusion Criteria: No other births in the previous two years; 20 weeks pregnant; and 18-35 years of age. Exclusion Criteria: with a self-reported significant medical history (i.e., currently being treated for depression/psychiatric	Start time: Pregnant 24 weeks gestation Duration: Pregnant 24 weeks gestation until delivery Arm 1: Placebo Description: corn oil capsule Dose: 1 capsule, 5 days/week Blinding: Identical package and only ID information Arm 2: DHA group	Outcome domain: Ante or postnatal depression Outcome: Postpartum Depression Screening Scale (PDSS) total score (Primary) Follow-up time: 2 weeks Arm 1: Sample size 22; mean 53.86; SD (15.25) Arm 2: Sample size 20; mean 47.65; SD (12.96) Follow-up time: 3 months Arm 1: Sample size 22; mean 42.63; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
conflict: Multiple foundations and Societies, None Original, same study, or follow-up studies: none		illness, addiction problems, hyperlipidemia, hypertension, renal disease, liver disease, or diabetes).	Description: 300mg DHA fish oil capsule Dose: 1 capsule, 5 days/week DHA: 300mg	(9.52) Arm 2: Sample size 20; mean 45.28; SD (12.25) Follow-up time: 6 months Arm 1: Sample size 22; mean 48.42; SD (17.18) Arm 2: Sample size 20; mean 45.55; SD (13.5) Follow-up time: 6 weeks Arm 1: Sample size 22; mean 47.4; SD (12.42) Arm 2: Sample size 20; mean 47.61; SD (14.31)
Knudsen et al., 2006[45] Study name: Danish National Birth Cohort-Pregnant Women Study dates: 2001- Study design: Trial randomized parallel Location: Denmark Funding source / conflict: Multiple foundations and Societies	Study Population: Healthy pregnant women Pregnant enrolled 3098 Pregnant withdrawals 1033 Pregnant completers 2065 Pregnant age: Group 01: 28.4 years Group 03: 28.7 years Group 07: 28.4 years Group 14: 28.9 years Group 28: 28.8 years Group C18: 28.8 years Group CG: 28.5 years Race of Mother: NR Baseline biomarker information: Level of	Inclusion Criteria: Low dietary intake of fish (lowest 20% of fish consumption), no use of fish oil capsules in pregnancy, gestational age 17-27 weeks. Exclusion Criteria: NR	Start time: Pregnant 17-27 weeks gestation Duration: Pregnant until delivery Arm 1: CG Description: control group (flax oi) Blinding: The women in the control group were allocated to any treatment and were not contacted at all. ALA: 2.2 g/d Arm 2: 01 Description: Treatment Group 1 Brand name: Futura Fish Oil Manufacturer: Dansk Droge A/S, Ishoej, Denmark Active ingredients: 13.4 mg D-alpha-tocopherol per gram Dose: 1 0.5 g three times per week DHA: 22% EPA: 32% Total N-3: 0.1 g per day	Outcome domain: duration of gestation Outcome: gestational age (days) (Primary) Follow-up time: birth Arm 1: Sample size 748; mean 280.6; SD (11.7) Arm 2: Sample size 229; mean 281.5; SD (12.6) Arm 3: Sample size 224; mean 279.7; SD (12) Arm 4: Sample size 222; mean 280.5; SD (12.6) Arm 5: Sample size 212; mean 280.6; SD (12.6) Arm 6: Sample size 187; mean 279.6; SD (14.8) Arm 7: Sample size 176; mean 280.7; SD (12.8)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	EPA, DHA, and AA in erythrocyte phospholipids assessed in a subsample of women in the 6 treatment groups Baseline Omega-3 intake: EPA, DHA, EPA+DHA, ALA, AA		Arm 3: 03 Description: Treatment group 2 Brand name: Futura Fish Oil Manufacturer: Dansk Droge A/S, Ishoej, Denmark Active ingredients: 13.4 mg D- alpha-tocopherol per gram Dose: 1 0.5 g capsule per day Total N-3: 0.3 g per day Arm 4: 07 Description: Treatment group 3 Brand name: Futura Fish Oil Manufacturer: Dansk Droge A/S, Ishoej, Denmark Active ingredients: 13.4 mg D- alpha-tocopherol per gram Dose: 1 1 g capsule per day DHA: 22% EPA: 32% Total N-3: 0.7 g per day Arm 5: 14 Description: Treatment group 4 Brand name: Futura Fish Oil Manufacturer: Dansk Droge A/S, Ishoej, Denmark Active ingredients: 13.4 mg D- alpha-tocopherol per gram Dose: 2 1g capsules per day DHA: 22% EPA: 32% Total N-3: 1.4 g per day Arm 6: 28	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			Description: Treatment group 5 Brand name: Futura Fish Oil Manufacturer: Dansk Droge A/S, Ishoej, Denmark Active ingredients: 13.4 mg Dalpha-tocopherol per gram Dose: 4 g per day DHA: 22% EPA: 32% Total N-3: 2.8g per day Arm 7: c18 Description: Treatment group 6 - flax oil Brand name: Prima FlaxTM Manufacturer: Bioriginal Food & Science Corp., Saskatoon, Canada Dose: 4 1-g capsules of flax oil ALA: 2.2g per day	
Lagemaat et al., 2011[109] Study name: NR Study dates: 2003 - 2006 Study design: Trial randomized parallel Location: Netherlands Funding source / conflict: Industry	Study Population: Preterm infants Low birth weight infants Infants enrolled 152 Infants completers 139 Infant age: Gestational age (week) PDF: 30.5 TF: 30.5 HM: 30.0 (PDF: 1.4 TF: 1.4 HM: 1.6) Race of Mother: NR (100) Baseline biomarker	Inclusion Criteria: infants born at gestational ages of 32 weeks or less and/or with birth weights of 1500 g or less Exclusion Criteria: NR	Start time: Infants at term Duration: Infants 6 months Arm 1: Term Formula (TF) Description: Placebo/control formula Brand name: Friso 1 normal Manufacturer: FrieslandCampina, Leeuwarden, The Netherlands Blinding: NR ALA: 63mg / 100ml DHA: 7mg / 100ml AA: 7mg/ 100ml Arm 2: PDF Description: Post-discharge formula (LCPUFA enriched)	Outcome domain: growth Outcome: head circumference (cm) (Unspecified) Follow-up time: term age Arm 1: Sample size 41; mean 35.8; SD (1.5) Arm 2: Sample size 52; mean 35.9; SD (1.2) Arm 3: Sample size 46; mean 35.6; SD (1.5) Outcome: length (cm) (Unspecified) Follow-up time: term age Arm 1: Sample size 41; mean 48.7; SD (2.1) Arm 2: Sample size 52; mean 48.7; SD (2.3) Arm 3: Sample size 46; mean 48.2; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	information: Baseline (at term) Mean(SD) AA PDF: 13.74 (0.89) TF: 13.86 (0.93) HM: 14.06 (1.17) DHA PDF: 4.71 (0.70) TF: 4.59 (0.76) HM: 4.08 (0.55) EPA PDF: 0.34 (0.05) TF: 0.32 (0.06) HM: 0.33 (0.13) DHA/AA ratio PDF: 0.34 (0.05) TF: 0.33 (0.06) HM: 0.29 (0.04)		Brand name: Friso 1 premature Manufacturer: Friesland Foods ALA: 59mg/ 100ml DHA: 14mg/ 100ml EPA: 3.9mg/ 100ml AA: 14mg/ 100ml Arm 3: HM Description: Human milk	(2.5) Outcome: weight (g) (Unspecified) Follow-up time: term age Arm 1: Sample size 41; mean 3193.0; SD (489) Arm 2: Sample size 52; mean 3137.0; SD (511) Arm 3: Sample size 46; mean 3138.0; SD (513)
Lauritzen et al., 2004[127] Study name: Danish National Birth Cohort-Lactating Women Study dates: December 1998 to November 1999 Study design: Trial randomized parallel Location: Denmark Funding source / conflict: Industry, Government Study follow-up: 2 and 4 months Original, same study, or	Study Population: Breast-feeding mothers with lower than average fish intake Infants enrolled 175 Infants completers 149 Pregnant age: Olive oil 30.2 Fish oil 29.6 High fish 31.9 (Olive oil ± 4.1 Fish oil ± 4.3 High fish ± 4.1) Infant age: 40.1 weeks gestation (birth) (1.2 weeks) Race of Mother: NR (100) Baseline Omega-3	Inclusion Criteria: pregnant Danish women living in the greater Copenhagen area who had a fish intake below the 50th percentile of the DNBC population; an uncomplicated pregnancy, pre-pregnancy body mass index (BMI) < 30 kg/m2 , and an absence of metabolic disorders; intention to breast-feed for at least 4 mon at the time of recruiting; newborns had to be healthy (no admission to a neonatal department), term (37–43 wks of	Start time: NR Duration: NR Arm 1: Placebo Blinding: Intervention fish oil was deodorized Arm 2: FO Intervention Description: Fish oil powder baked into cookies Other dose 1: 17 g/d of deodorized microencapsulated FO powder, containing 4.5 g of FO and 1.5 g of n-3 LCPUF	Outcome domain: Visual function Outcome: swept visual evoked potential (SWEEP-VEP) (Primary) Follow-up time: 2 months Arm 1: Sample size 46; mean 0.84; SD (0.08) Arm 2: Sample size 42; mean 0.84; SD (0.09) Follow-up time: 4 months Arm 1: Sample size 45; mean 0.64; SD (0.09) Arm 2: Sample size 52; mean 0.62; SD (0.08)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
follow-up studies: Lauritzen, 2005[102]; Lauritzen, 2005[128]; Cheatham, 2011[129];	intake: Habitual n-3 LCPUFA intake (g/d) Olive oil: 0.3 ± 0.3 Fish oil: 0.3 ± 0.3 High fish: 1.1 ± 0.6	gestation), singleton infants with normal weight for gestation (20) and an Apgar score >7 at 5 min after delivery. Willingness to start on the supplements within 2 wks after birth; no use of other types of oil supplements Exclusion Criteria: BMI >= 30 kg/m2...		
Lauritzen et al., 2005[102] Study name: Danish National Birth Cohort-Lactating Women Study dates: Recruitment: April 1999-February 2000 Follow-up 2.5 years Study design: Trial randomized parallel Location: Denmark Funding source / conflict: Industry, Government Study follow-up: 2.5	Study Population: Breast-feeding women Infants enrolled 100 Infants completers 72 Mother age: High fish: 31.9 Fish oil: 29.6 Olive oil: 30.2 (High fish: 4.1 Fish oil: 4.3 Olive oil: 4.1) Race of Mother: NR (100%)	Inclusion Criteria: Pregnant women who were recruited for the Danish National Birth Cohort (DNBC) (16), all from the greater Copenhagen area, who were in their eighth month of gestation and had a fish intake below the median (0.40 g/d n-3LCPUFA) ... (554 women with a fish intake in the upper quartile (0.82 g/d n-3LCPUFA) were invited to participate in the study as a high fish intake reference group); uncomplicated	Start time: Lactating within 2 weeks of delivery Duration: Lactating 4 months Arm 1: Olive oil Description: Control group receiving olive oil supplement Dose: 2 muesli bars daily; or 4 1000-mg capsules Blinding: Investigators and families were blinded to the randomization throughout the first year of life of the infants. Fish oil as well as olive oil supplements were given as microencapsulated oils concealed in two muesli bars (produced by Halo Foods Ltd., Tywyn Gwynedd, Wales, UK) daily for the first 4 mo of lactation. Arm 2: Fish oil Description: Intervention group receiving fish oil supplement	Outcome domain: growth Outcome: bmi (kg/m2) (Secondary) Follow-up time: 2 months Arm 1: Sample size 51; mean 15.93; SD (1.37) Arm 2: Sample size 52; mean 15.74; SD (1.24) Arm 3: Sample size 50; mean 15.63; SD (1.36) Follow-up time: 2.5 years Arm 1: Sample size 28; mean 15.86; SD (1.21) Arm 2: Sample size 42; mean 16.51; SD (1.08) Arm 3: Sample size 29; mean 16.11; SD (1.08) Follow-up time: 4 months Arm 1: Sample size 46; mean 17.04; SD (1.7) Arm 2: Sample size 52; mean 16.93; SD (1.23)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
years Original, same study, or follow-up studies: Lauritzen, 2004[127]; Lauritzen, 2005[128]; Cheatham, 2011[129];		pregnancy; body mass index (BMI) <30 kg/m2; no metabolic disorders; intention to breastfeed for at least 4 mo.; willingness to begin supplement within 2 weeks of birth. Newborns had to be healthy (no admission to a neonatal department), term (37– 43 wk of gestation), singleton infants with normal weight for gestation (17) and an Apgar score 7 at 5 min after delivery. Exclusion Criteria: NR	Manufacturer: BASF Health and Nutrition A/S, Ballerup, Denmark Dose: 2 muesli bars providing 0.62g EPA and 0.79g DHA; or fish oil capsules providing 0.36g EPA and 0.99g DHA DHA: 0.79g/d EPA: 0.62g/d Total N-3: 1.5g/d Arm 3: High fish Description: Group with high fish intake as reference group	Arm 3: Sample size 49; mean 16.57; SD (1.66) Follow-up time: 9 months Arm 1: Sample size 47; mean 17.64; SD (1.52) Arm 2: Sample size 53; mean 17.91; SD (1.24) Arm 3: Sample size 48; mean 17.27; SD (1.39) Outcome: head circumference (cm) (Secondary) Follow-up time: 1 week Arm 1: Sample size 56; mean 35.72; SD (1.53) Arm 2: Sample size 54; mean 36.11; SD (1.25) Arm 3: Sample size 51; mean 36.18; SD (1.59) Follow-up time: 2 months Arm 1: Sample size 50; mean 39.28; SD (1.16) Arm 2: Sample size 50; mean 39.7; SD (1.22) Arm 3: Sample size 47; mean 39.68; SD (1.27) Follow-up time: 2.5 years Arm 1: Sample size 30; mean 49.74; SD (1.34) Arm 2: Sample size 41; mean 50.42; SD (1.2) Arm 3: Sample size 29; mean 50.62; SD (1.23) Follow-up time: 4 months Arm 1: Sample size 46; mean 41.84; SD (1.12) Arm 2: Sample size 45; mean 42.17; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(1.16) Arm 3: Sample size 45; mean 42.4; SD (1.38) Follow-up time: 9 months Arm 1: Sample size 45; mean 45.29; SD (1.4) Arm 2: Sample size 52; mean 45.85; SD (1.53) Arm 3: Sample size 42; mean 45.81; SD (1.36) Outcome: length (cm) (Secondary) Follow-up time: 2 months Arm 1: Sample size 51; median 58.7; 10th, 90th percentile Arm 2: Sample size 52; median 58.8; 10th, 90th percentile Arm 3: Sample size 50; median 59.1; 10th, 90th percentile Follow-up time: 2.5 years Arm 1: Sample size 28; mean 92.65; SD (3.04) Arm 2: Sample size 42; mean 92.58; SD (3.14) Arm 3: Sample size 29; mean 93.74; SD (2.93) Follow-up time: 4 months Arm 1: Sample size 46; mean 64.02; SD (2.16) Arm 2: Sample size 52; mean 64.21; SD (2.08) Arm 3: Sample size 50; mean 64.7; SD (1.71) Follow-up time: 9 months Arm 1: Sample size 47; mean 72.15; SD (2.04) Arm 2: Sample size 53; mean 72.66; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(2.35) Arm 3: Sample size 48; mean 72.75; SD (2.01) Outcome: weight (kg) (Secondary) Follow-up time: 2 months Arm 1: Sample size 51; mean 5.4; 10th, 90th percentile Arm 2: Sample size 53; median 5.5; 10th, 90th percentile Arm 3: Sample size 50; median 5.3; 10th, 90th percentile Follow-up time: 2.5 years Arm 1: Sample size 30; mean 13.71; SD (1.26) Arm 2: Sample size 42; mean 14.16; SD (1.26) Arm 3: Sample size 29; mean 14.18; SD (1.43) Follow-up time: 4 months Arm 1: Sample size 47; mean 7.0; SD (0.85) Arm 2: Sample size 53; mean 7.0; SD (0.73) Arm 3: Sample size 49; mean 6.93; SD (0.67) Follow-up time: 9 months Arm 1: Sample size 47; mean 9.19; SD (0.94) Arm 2: Sample size 53; mean 9.47; SD (0.94) Arm 3: Sample size 48; mean 9.15; SD (0.9)
Lauritzen et al., 2005[128] Study name: Danish	Study Population: Healthy infants Breast-feeding women	Inclusion Criteria: pregnant women with a fish intake below the	Start time: Lactating 9 days after birth Infants 9 days after birth	Outcome domain: Cognitive development Outcome: Infant Planning Test (problem solving) (Secondary)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
National Birth Cohort-Lactating Women Study dates: Enrolled in 1999 Study design: Trial randomized parallel Location: Denmark Funding source / conflict: Industry, Government Study follow-up: 9 months, 1 year, 2 years Original, same study, or follow-up studies: Lauritzen, 2004[127]; Lauritzen, 2005[102]; Cheatham, 2011[129];	Lactating enrolled 122 Lactating completers 89 Infants enrolled 122 Infants completers 89 Lactating enrolled 122 Lactating completers 89 Pregnant age: NR (NR) NR Infant age: 9 days (3 days) NA Race of Mother: NR (100%) Baseline Omega-3 intake: < 0.4 g n-3 LCPUFA/d	population median (< 0.4 g n-3 LCPUFA·d–1), uncomplicated pregnancy, a normal pre-pregnancy body mass index (< 30 kg·m–2), no metabolic disorders, an intention to breastfeed for at least four months. Newborns had to be healthy, singleton, term infants with normal weight for gestation [33] and an Apgar score > 7 five minutes after delivery. Exclusion Criteria: NR	Duration: Lactating 4 months Infants 4 months Arm 1: placebo group Description: olive oil in muesli bars, cookies, or capsules Manufacturer: BASF Dose: one bar/cookie/capsule containing 4.5 g olive oil Blinding: identical bars/cookies/capsules Arm 2: fish oil Description: fish oil in muesli bars, cookies, or capsules Manufacturer: BASF Dose: one bar/cookie/capsule containing 4.5 g fish oil DHA: 0.9 g Total N-3: Other FA (not DHA): 0.6 g Arm 3: high n-3 reference group Description: top quartile fish intake at baseline Dose: no supplementation, high fish intake Total N-3: > 0.8 n-3 LCPUFA/d	Follow-up time: 9 months Arm 1: Sample size 38; mean 4.3; SD (3.6) Arm 2: Sample size 48; mean 4.5; SD (3.1) Arm 3: Sample size 42; mean 4.5; SD (3.3) Outcome: MacArthur Communicative Development Inventory Linguistic Development: late gestures (Secondary) Follow-up time: 1 year Arm 1: Sample size 37; mean 15.0; SD (7) Arm 2: Sample size 52; mean 14.0; SD (6) Arm 3: Sample size 42; mean 16.0; SD (7) Outcome: MacArthur Communicative Development Inventory Linguistic Development: number of irregular words (Secondary) Follow-up time: 2 years Arm 1: Sample size 31; median 3.0; IQR Arm 2: Sample size 40; median 3.0; IQR Arm 3: Sample size 40; median 4.0; IQR Outcome: MacArthur Communicative Development Inventory Linguistic Development: number of over regularized words (Secondary) Follow-up time: 2 years Arm 1: Sample size 31; median 1.0; IQR Arm 2: Sample size 40; median 1.0; IQR Arm 3: Sample size 40; median 1.0; IQR Outcome: MacArthur Communicative Development Inventory Linguistic Development: early gestures (Secondary) Follow-up time: 1 year Arm 1: Sample size 37; median 11.0; IQR Arm 2: Sample size 52; median 11.0; IQR

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 3: Sample size 42; median 12.0; IQR Outcome: MacArthur Communicative Development Inventory Linguistic Development: percent starting to talk (Secondary) Follow-up time: 1 year Arm 1: 6/37 (16.0%) Arm 2: 6/52 (12.0%) Arm 3: 7/42 (17.0%) Outcome: MacArthur Communicative Development Inventory Linguistic Development: phrases understood (Secondary) Follow-up time: 1 year Arm 1: Sample size 37; mean 11.0; SD (6) Arm 2: Sample size 52; mean 11.0; SD (5) Arm 3: Sample size 42; mean 11.0; SD (5) Outcome: MacArthur Communicative Development Inventory Linguistic Development: talk about abstract (Secondary) Follow-up time: 2 years Arm 1: 29/31 (94.0%) Arm 2: 30/40 (75.0%) Arm 3: 38/40 (95.0%) Outcome: MacArthur Communicative Development Inventory Linguistic Development: use grammar (Secondary) Follow-up time: 2 years Arm 1: 10/31 (32.0%) Arm 2: 10/40 (25.0%) Arm 3: 16/40 (40.0%) Outcome: MacArthur Communicative Development Inventory Linguistic Development: vocabulary comprehension (Secondary)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Follow-up time: 1 year Arm 1: Sample size 37; mean 71.0; SD (45) Arm 2: Sample size 52; mean 54.0; SD (37) Arm 3: Sample size 42; mean 65.0; SD (40) Outcome: MacArthur Communicative Development Inventory Linguistic Development: vocabulary production (Secondary) Follow-up time: 1 year Arm 1: Sample size 37; median 5.0; IQR Arm 2: Sample size 52; median 3.0; IQR Arm 3: Sample size 42; median 5.0; IQR Follow-up time: 2 years Arm 1: Sample size 31; mean 297.0; SD (147) Arm 2: Sample size 40; mean 242.0; SD (170) Arm 3: Sample size 40; mean 312.0; SD (146)
Linnamaa et al., 2010[79] Study name: NR Study dates: 2004-2008 Study design: Trial randomized parallel Location: Finland Funding source / conflict: Government,	Study Population: Healthy infants Healthy pregnant women Infants enrolled 314 Infants withdrawals 137 Infants completers 177 Mother age: NR (NR) NR Race of Mother: NR (NR)	Inclusion Criteria: All pregnant mothers <16 weeks of gestation Exclusion Criteria: Sick children and those born prematurely who required more intensive care (n=8)	Start time: Pregnant 8th to 16th weeks of pregnancy and then continued Infants when exclusive breastfeeding ended Duration: Pregnant until the end of the exclusive breastfeeding period Infants until 2 years of age Arm 1: Controls Description: Olive oil Manufacturer: Santagata Luigi s.r.l., Genova, Italia Dose: 3 g/day for mothers, 1 mL/day for infants	Outcome domain: Birth weight Outcome: birth weight (g) (Secondary) Follow-up time: birth Arm 1: Sample size 129; mean 3599.0; SD (468) Arm 2: Sample size 112; mean 3595.0; SD (461) Outcome domain: allergies Outcome: positive egg skin test (Secondary) Follow-up time: 12 months Arm 1: 18/104 (17.31%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Multiple foundations and Societies			Blinding: NR "double-blind" ALA: 0 DHA: 0 EPA: 0 EPA-DHA: 0 AA: 0 Total N-3: 0 Other dose 1: LA (18:2n-6): 9 weight% of total Arm 2: Intervention Description: Blackcurrant seed oil Manufacturer: Aromtech Ltd, Tornio, Finland Dose: 3 g/day for mothers, 1 mL/day for infants ALA: 14 weight% of total DHA: 0 EPA: 0 EPA-DHA: 0 AA: 0 Total N-3: 17 weight% of total Other dose 1: SDA: 3 weight% of total	Arm 2: 14/98 (14.29%) Follow-up time: 24 months Arm 1: 7/87 (8.05%) Arm 2: 4/79 (5.06%) Follow-up time: 3 months Arm 1: 1/126 (0.79%) Arm 2: 1/112 (0.89%) Outcome domain: atopic dermatitis Outcome: atopic dermatitis (Primary) Follow-up time: 12 months Arm 1: 52/110 (47.27%) Arm 2: 33/100 (33.0%) Follow-up time: 24 months Arm 1: 10/92 (11.11%) Arm 2: 9/85 (11.11%) Follow-up time: 3 months Arm 1: 14/129 (11.11%) Arm 2: 12/112 (11.11%)
Llorente et al., 2003[98] Study name: Unnamed Trial A Study dates: <2002 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied	Study Population: Breast-feeding women Lactating enrolled 138 Lactating completers 101 Lactating enrolled 138 Lactating completers 101 Lactating age: 31.5 years (4.5 years) 18 - 42 Race of Mother: White	Inclusion Criteria: pregnant women who were 18 to 42 years old and planned to breast feed for at least 4 months Exclusion Criteria: those with chronic medical conditions, or taking dietary supplements other than vitamins, or smokers, or who had been pregnant >5	Start time: Lactating birth Duration: Lactating 4 months Arm 1: placebo Description: placebo capsule Manufacturer: Martek Biosciences Corporation, Columbia, MD Dose: 1 capsule Blinding: capsules were identical in appearance Arm 2: omega 3 capsule Description: algae-derived triglyceride capsule Brand name: DHASCO	Outcome domain: Ante or postnatal depression Outcome: Beck Depression Inventory (BDI) (Unspecified) Follow-up time: 2 months Arm 1: Sample size 45; mean 4.4; SD (4.2) Arm 2: Sample size 44; mean 5.5; SD (4.3) Follow-up time: 3 weeks Arm 1: Sample size 45; mean 6.3; SD (4.7) Arm 2: Sample size 44; mean 7.1; SD (5.7) Follow-up time: 4 months

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
product Study follow-up: 18 months Original, same study, or follow-up studies: Isaacs, 2011[99]	European (82%) Black (14%) Hispanic (2.3%) Other race/ethnicity (1.6%) Baseline biomarker information: Placebo group Total saturated 49.7 ± 2.3 Total monounsaturated 12.2 ± 1.9 Total __6 33.7 ± 2.2 Total __3 4.37 ± 0.91 Intervention group Total saturated 49.3 ± 2.7 Total monounsaturated 12.3 ± 1.3 Total __6 34.2 ± 2.0 Total __3 4.14 ± 0.89	times	Manufacturer: Martek Biosciences Corporation, Columbia, MD Dose: 1 capsule DHA: 200 mg	Arm 1: Sample size 45; mean 4.8; SD (5.9) Arm 2: Sample size 44; mean 5.8; SD (5.2) Outcome: Edinburgh Postnatal Depression Scale (EPDS) (Unspecified) Follow-up time: 18 months Arm 1: Sample size 32; mean 6.3; SD (4.1) Arm 2: Sample size 31; mean 6.3; SD (5.2) Outcome: responder: BDI<10 (Unspecified) Follow-up time: at either 2, 4 or 18 months Arm 1: 36/45 (79.0%) Arm 2: 33/44 (76.0%) Outcome: responder: BDI<20 (Unspecified) Follow-up time: at either 2, 4 or 18 months Arm 1: 43/45 (95.5%) Arm 2: 40/44 (91.1%)
Lucia Bergmann et al., 2007[41] Study name: NR Study dates: 2000-2002 Study design: Trial randomized parallel Location: Germany Funding source / conflict: NR	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 144 Pregnant withdrawals 51 Pregnant completers 69 Pregnant age: 31 (DHA 4.69; control 4.89) Infant age: DHA 39.1; control 39.5 weeks	Inclusion Criteria: at least 18 years of age and willing to breastfeed for at least three months were enrolled at 21 weeks' gestation during the period October 2000 to August 2002 Exclusion Criteria: increased risk of premature delivery or multiple pregnancy,	Start time: Pregnant 21th week Duration: Pregnant 37th week Arm 1: Vitamins and minerals Manufacturer: Nestle´ (Vevey, Switzerland) Arm 2: Prebiotic Description: basic supplement plus the prebiotic, fructooligosaccharide (FOS) (4.5 g) Manufacturer: Nestle´ (Vevey, Switzerland) Active ingredients: fructooligosaccharide (FOS) (4.5 g)	Outcome domain: Birth weight Outcome: birth weight (g) (Unspecified) Follow-up time: birth Arm 1: Sample size 74; mean 3548.0; SD (469.3) Arm 3: Sample size 43; mean 3427.0; SD (493.6) Outcome domain: duration of gestation Outcome: gestational age (weeks) (Unspecified) Follow-up time: birth Arm 1: Sample size 74; mean 39.5; SD (1.38)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Original, same study, or follow-up studies: Lucia, 2007[52]	(DHA 1.64; control 1.38) Race of Mother: White European (100) Baseline biomarker information: DHA % of all identified fatty acid in RBC: Vitamin: 5.76 +-2.45 (47); DHA: Prebiotic:5.94+-2.37(48) DHA: DHA: 5.69+-2.40(47) ARA Vitamin: 14.01+-4.04(47) ARA Prebiotic 14.82+-3.60(48) ARA DHA: 14.18+-4.32(47) EPA Vitamin: 0.72+-0.32(47) EPA Prebiotic: 0.78+-0.38(48) EPA DHA: 0.79+-0.41(47)	allergy to cow milk protein, lactose intolerance, diabetes, smoking, consumption of alcohol ()20 g/week), or participation in another study. Infants excluded if they were premature at birth (<37 week gestation, or had any major malformations or hospitalized for more than one week.	Arm 3: DHA Description: basic supplement with FOS and DHA (200 mg) Manufacturer: Nestle´ (Vevey, Switzerland) Dose: 200 mg DHA prepared from fish oil (assuming that some EPA but dose was not reported) DHA: 200 mg EPA: NR	Arm 3: Sample size 43; mean 39.1; SD (1.64) Outcome domain: growth Outcome: bmi (kg/m2) (Unspecified) Follow-up time: 1 month Arm 1: Sample size 74; mean 14.2; SE (0.37) Arm 3: Sample size 43; mean 14.06; SE (0.4) Follow-up time: 21 months Arm 1: Sample size 74; mean 15.46; SE (0.32) Arm 3: Sample size 43; mean 14.7; SE (0.36) Follow-up time: 3 months Arm 1: Sample size 74; mean 15.58; SE (0.38) Arm 3: Sample size 43; mean 16.14; SE (0.44) Outcome: head circumference (cm) (Unspecified) Follow-up time: 1 month Arm 1: Sample size 74; mean 37.4; SE (0.41) Arm 3: Sample size 43; mean 37.1; SE (0.44) Follow-up time: 21 months Arm 1: Sample size 74; mean 47.7; SE (0.36) Arm 3: Sample size 43; mean 48.4; SE (0.4) Follow-up time: 3 months Arm 1: Sample size 74; mean 40.6; SE (0.43) Arm 3: Sample size 43; mean 40.6; SE

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(0.5) Outcome: length (cm) (Unspecified) Follow-up time: 1 month Arm 1: Sample size 74; mean 55.6; SE (0.64) Arm 3: Sample size 43; mean 56.3; SE (0.69) Follow-up time: 21 months Arm 1: Sample size 74; mean 85.4; SE (0.56) Arm 3: Sample size 43; mean 85.5; SE (0.62) Follow-up time: 3 months Arm 1: Sample size 74; mean 61.9; SE (0.65) Arm 3: Sample size 43; mean 61.7; SE (0.76) Outcome: weight (kg) (Unspecified) Follow-up time: 1 month Arm 1: Sample size 74; mean 4.45; SE (0.226) Arm 3: Sample size 43; mean 4.52; SE (0.244) Follow-up time: 21 months Arm 1: Sample size 74; mean 11.35; SE (0.197) Arm 3: Sample size 43; mean 10.75; SE (0.22) Follow-up time: 3 months Arm 1: Sample size 74; mean 6.03; SE (0.23) Arm 3: Sample size 43; mean 6.19; SE (0.269)
Makrides et al., 2009[116]	Study Population: Preterm infants Breast-	Inclusion Criteria: infants born at < 33 wk	Start time: Infants 4 days after birth	Outcome domain: Cognitive development Outcome: Bayley Scale of Infant

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study name: DINO Study dates: Enrollment April 2001 to October 2005 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies, Manufacturer supplied product, Some authors serve on scientific advisory boards for corporations, Some authors have received research funding from infant formula manufacturers Study follow-up: 18 months Original, same study, or follow-up studies: Smithers, 2008[104]; Smithers, 2010[117]; Manley, 2011[118]; Collins, 2011[105]; Atwell, 2013[119]; Collins, 2015[120]	feeding women Pregnant enrolled 545 Infants enrolled 657 Infants completers 614 Lactating age: 30 years (5.5 years) NR Infant age: 4 days after birth (29 weeks gestation) 2 to 6 days after birth Race of Mother: White European (90%)	of gestation Exclusion Criteria: Infants born with major congenital or chromosomal abnormalities, lactating women for whom tuna oil was contraindicated(wome n with bleeding disorders or taking anticoagulants)	Duration: Infants until infants reached their "expected" date of delivery Arm 1: Placebo Description: Soy oil capsules or regular preterm formula Manufacturer: Clover Corporation Dose: six 500-mg soy oil capsules Blinding: all capsules were similar in size, shape, and color Maternal conditions Infant conditions Current smoker 25.1% during pregnancy Pre-term birth 100% Low birth weight 44.5% Other conditions 1 SGA 18.6% Arm 2: tuna oil capsules Description: DHA-rich tuna oil capsules or high-DHA formula Manufacturer: Clover Corporation Dose: 6 500 mg capsules Maternal conditions Infant conditions DHA: Capsules: Intended to achieve breast milk concentration of 1.0%.Formula: 1.0% AA: Capsules: not intended to alter AA levels. Formula: 0.6% Current smoker 25.6% during pregnancy Pre-term birth 100% Low birth weight 45.7% Other conditions 1 SGA 18.9%	Development (Mental developmental index) (Primary) Follow-up time: 18 months Arm 1: Sample size 335; mean 93.0; SD (17.3) Arm 2: Sample size 322; mean 94.9; SD (14.5) Outcome domain: Neurological development Outcome: Bayley psychomotor development index (Secondary) Follow-up time: 18 months Arm 1: Sample size 335; mean 92.1; SD (16.3) Arm 2: Sample size 322; mean 93.1; SD (16.1)
Makrides et al., 2010[35]	Study Population:	Inclusion Criteria: with	Start time: Pregnant < 21 week's gestation	Outcome domain: Ante or postnatal

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study name: DOMInO Study dates: 2005-2008 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Manufacturer supplied product Original, same study, or follow-up studies: Smithers, 2011[53]; Palmer, 2012[54]; Zhou, 2012[55]; Palmer, 2013[56]; Makrides, 2014 [57]	Healthy pregnant women Pregnant enrolled 2399 Pregnant withdrawals 1 Infants enrolled 605 Infants withdrawals 32 Infants completers 726 Pregnant age: 28.9 (DHA5.7___ control5.6) Race of Mother: NR (NR)	singleton pregnancies at less than 21 weeks' gestation were approached by study research assistants while attending routine antenatal appointments Exclusion Criteria: already taking a prenatal supplement with DHA, their fetus had a known major abnormality, they had a bleeding disorder in which tuna oil was contraindicated, were taking anticoagulant therapy, had a documented history of drug or alcohol abuse, were participating in another fatty acid trial, were unable to give written informed consent, or if English was not the main language spoken at home	Duration: NR Arm 1: vegetable oil capsules Description: a blend of 3 non-genetically modified oils (rapeseed, sunflower, and palm) in equal proportions Manufacturer: Efamol, Surrey, England. Dose: 3* 500mg capsule / day Blinding: All capsules were similar in size, shape, and color Arm 2: DHA Description: DHA-rich fish oil concentrate Manufacturer: ; Incromega 500 TG, Croda Chemicals, East Yorkshire, England Dose: 500mg capsule *3/day DHA: 800mg EPA: 100mg	depression Outcome: % with Edinburgh Postnatal Depression Scale (EPDS) > 12 (Primary) Follow-up time: 6 months Arm 1: 138/1202 (11.5%) Arm 2: 117/1197 (9.74%) Follow-up time: 6 weeks Arm 1: 131/1202 (10.88%) Arm 2: 115/1197 (9.61%) Outcome domain: Birth weight Reason results are not reported: duplicate data of id 4404 Outcome: (Secondary) Outcome domain: Cognitive development Outcome: Bayley Scale of Infant Development III (Cognitive Component) (Primary) Follow-up time: 18 months Arm 1: Sample size 375; weighted mean 101.75; SD (12.56) Arm 2: Sample size 351; weighted mean 101.81; SD (11.05) Outcome domain: LBW Reason results are not reported: duplicate data of id 4404 Outcome domain: duration of gestation Outcome: gestational age (days) (Secondary) Follow-up time: birth Arm 1: Sample size 1202; median 281.0; IQR Arm 2: Sample size 1197; median 282.0;

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				IQR Outcome: incidence of premature birth (Secondary) Follow-up time: birth Arm 1: 88/1202 (7.34%) Arm 2: 67/1197 (5.6%)
Makrides et al., 2014[57] Study name: DOMInO Study dates: October 31, 2005 to September 25, 2012 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Manufacturer supplied product, Some authors have received research funding from infant formula manufacturers Original, same study, or follow-up studies: Makrides, 2010 [35] Smithers, 2011[53]; Palmer, 2012[54]; Zhou, 2012[55]; Palmer, 2013[56]	Study Population: Healthy pregnant women Infants enrolled 726 Infants completers 646 Race of Mother: NR (100)	Inclusion Criteria: Women with singleton pregnancies at less than 21 weeks' gestation Exclusion Criteria: Already taking a prenatal supplement with DHA, fetus had a known major abnormality, had a bleeding disorder in which tuna oil was contraindicated, were taking anticoagulant therapy, had a documented history of drug or alcohol abuse, were participating in another fatty acid trial, were unable to give written informed consent, or if English was not the main language spoken at home	Start time: Pregnant <21 weeks gestation Duration: Pregnant <21 weeks gestation until birth Arm 1: Placebo Description: rapeseed, sunflower, and palm oil capsules Manufacturer: Enfamol Dose: 3 500mg capsules/day Blinding: similar in size, shape, and color Arm 2: DHA supplement Description: DHA-rich fish oil capsules Manufacturer: Enfamol Dose: 3 500mg capsules/day DHA: 800 mg/d EPA: 100 mg/day	Outcome domain: ADHD Outcome: hyperactivity disorder Follow-up time: 4 years Arm 1: 0/333 (0.0%) Arm 2: 0/313 (0.0%) Outcome domain: Autism Outcome: diagnosis of autism Follow-up time: 4 years Arm 1: 4/333 (1.2%) Arm 2: 2/313 (0.64%) Outcome domain: Cognitive development Outcome: Behavior Rating Inventory of Executive Function-Preschool: Emergent Meta-Cognition Index (Secondary) Follow-up time: 4 years Arm 1: Sample size 333 Arm 2: Sample size 313 Outcome: Behavior Rating Inventory of Executive Function-Preschool: Emotional Control Scale (Secondary) Follow-up time: 4 years Arm 1: Sample size 333 Arm 2: Sample size 313 Outcome: Behavior Rating Inventory of Executive Function-Preschool: Flexibility Index (Secondary) Follow-up time: 4 years

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 1: Sample size 333 Arm 2: Sample size 313 Outcome: Behavior Rating Inventory of Executive Function-Preschool: Global Executive Composite score (Secondary) Follow-up time: 4 years Arm 1: Sample size 333 Arm 2: Sample size 313 Outcome: Behavior Rating Inventory of Executive Function-Preschool: Inhibition Scale (Secondary) Follow-up time: 4 years Arm 1: Sample size 333 Arm 2: Sample size 313 Outcome: Behavior Rating Inventory of Executive Function-Preschool: Inhibitory Self-Control Index (Secondary) Follow-up time: 4 years Arm 1: Sample size 333 Arm 2: Sample size 313 Outcome: Behavior Rating Inventory of Executive Function-Preschool: Plan/Organize Scale (Secondary) Follow-up time: 4 years Arm 1: Sample size 333 Arm 2: Sample size 313 Outcome: Behavior Rating Inventory of Executive Function-Preschool: Shift Scale (Secondary) Follow-up time: 4 years Arm 1: Sample size 333 Arm 2: Sample size 313 Outcome: Behavior Rating Inventory of Executive Function-Preschool: Working Memory Scale (Secondary) Follow-up time: 4 years

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 1: Sample size 333 Arm 2: Sample size 313 Outcome: CELF-P2 Core Language Score (Secondary) Follow-up time: 4 years Arm 1: Sample size 333 Arm 2: Sample size 313 Outcome: Day-night stroop (measure of efficiency) (Secondary) Follow-up time: 4 years Arm 1: Sample size 333 Arm 2: Sample size 313 Outcome: Differential Ability Scales, second edition (DAS II) score: General Conceptual Ability Score (Secondary) Follow-up time: 4 years Arm 1: Sample size 333 Arm 2: Sample size 313
Malcolm et al., 2003[100] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: NR Funding source / conflict: NR	Study Population: NR Pregnant enrolled 100 Pregnant withdrawals 37 Pregnant completers 63 Infants enrolled 60 Infants withdrawals 5 Infants completers 55 Infant age: 279.6 (8.5) Race of Mother: NR (NR) Baseline biomarker	Inclusion Criteria: d women who were expected to deliver their infants at term and planned to feed them on breast and/or formula milk Exclusion Criteria: diabetes, twin pregnancies, pre-eclampsic toxaemia, a past history of abruption or postpartum hemorrhage, allergy to fish products, a	Start time: Pregnant week 15 Infants birth Duration: Pregnant birth Arm 1: Placebo Description: contained 323 mg sunflower oil with high levels of oleic acid and was free of any significant amounts of LCPUFAs or their precursors Manufacturer: R P Scherer Limited (Swindon, Wiltshire, UK) Dose: 323 mg per capsule * 2 Blinding: e identical in appearance and could not be identified on the basis of scent or taste Total N-3: 0 Arm 2: DHA	Outcome domain: Visual function Outcome: Peak latencies of major components of the transient flash visual evoked potential waveform: N1 (Primary) Follow-up time: 50 weeks (corrected age) Arm 1: Sample size 18; mean 58.1; SD (21.4) Arm 2: Sample size 19; mean 54.7; SD (16.2) Follow-up time: 66 weeks (corrected age) Arm 1: Sample size 24; mean 57.3; SD (10.7) Arm 2: Sample size 23; mean 61.5; SD (5.4) Follow-up time: birth Arm 1: Sample size 4; mean 74.8; SD (16.8)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	information: Only reported: "The fish oil and placebo groups did not differ in maternal RBC and plasma fatty acid composition at enrollment"	thrombophilic tendency, or who were receiving drugs that affect thrombocyte function (non-steroidal anti-inflammatories)	Description: f a blended fish oil, Marinol D40, and contained 100 mg DHA in 323 mg oil per capsule Manufacturer: R P Scherer Limited (Swindon, Wiltshire, UK) Dose: 323 mg capsule * 2 DHA: 200 mg EPA: .64 mg (estimated based on the FA composition)	Arm 2: Sample size 5; mean 62.2; SD (3.8) Outcome: Peak latencies of major components of the transient flash visual evoked potential waveform: N2 (Primary) Follow-up time: 50 weeks (corrected age) Arm 1: Sample size 28; mean 112.8; SD (46.5) Arm 2: Sample size 24; mean 128.9; SD (47.9) Follow-up time: 66 weeks (corrected age) Arm 1: Sample size 26; mean 122.1; SD (33.7) Arm 2: Sample size 25; mean 128.5; SD (30.3) Follow-up time: birth Arm 1: Sample size 22; mean 149.9; SD (28) Arm 2: Sample size 27; mean 153.5; SD (28.9) Outcome: Peak latencies of major components of the transient flash visual evoked potential waveform: N3 (Primary) Follow-up time: 50 weeks (corrected age) Arm 1: Sample size 20; mean 277.3; SD (49.4) Arm 2: Sample size 14; mean 241.8; SD (49.8) Follow-up time: 66 weeks (corrected age) Arm 1: Sample size 15; mean 209.2; SD (38.2) Arm 2: Sample size 11; mean 228.9; SD (55.9) Follow-up time: birth Arm 1: Sample size 27; mean 298.4; SD (52.8)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 2: Sample size 26; mean 292.2; SD (58.2) Outcome: Peak latencies of major components of the transient flash visual evoked potential waveform: P1 (Primary) Follow-up time: 50 weeks (corrected age) Arm 1: Sample size 22; mean 84.2; SD (22.5) Arm 2: Sample size 23; mean 80.3; SD (21.1) Follow-up time: 66 weeks (corrected age) Arm 1: Sample size 26; mean 76.5; SD (19.5) Arm 2: Sample size 25; mean 80.1; SD (15.8) Follow-up time: birth Arm 1: Sample size 5; mean 107.8; SD (11.8) Arm 2: Sample size 9; mean 101.0; SD (13.6) Outcome: Peak latencies of major components of the transient flash visual evoked potential waveform: P2 (Primary) Follow-up time: 50 weeks (corrected age) Arm 1: Sample size 26; mean 162.5; SD (26.5) Arm 2: Sample size 21; mean 164.2; SD (29.9) Follow-up time: 66 weeks (corrected age) Arm 1: Sample size 19; mean 152.5; SD (43.6) Arm 2: Sample size 12; mean 150.6; SD (33) Follow-up time: birth Arm 1: Sample size 27; mean 201.8; SD (33.3)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 2: Sample size 28; mean 201.9; SD (28.4) Outcome domain: growth Outcome: head circumference (cm) (Secondary) Follow-up time: 50 weeks PCA (postconceptional age) Arm 1: Sample size 27; mean 40.1; SD (2.3) Arm 2: Sample size 28; mean 39.9; SD (1.5) Follow-up time: 66 weeks (post conceptional age) Arm 1: Sample size 27; mean 44.1; SD (1.7) Arm 2: Sample size 28; mean 43.8; SD (2.4) Outcome: length (cm) (Secondary) Follow-up time: 50 weeks PCA (postconceptional age) Arm 1: Sample size 27; mean 60.5; SD (2.9) Arm 2: Sample size 28; mean 60.0; SD (2.6) Follow-up time: 66 weeks (post conceptional age) Arm 1: Sample size 27; mean 69.1; SD (3.2) Arm 2: Sample size 28; mean 68.5; SD (2.6) Outcome: weight (g) (Secondary) Follow-up time: 50 weeks PCA (postconceptional age) Arm 1: Sample size 27; mean 5995.7; SD (827.9)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 2: Sample size 28; mean 5894.4; SD (662.3) Follow-up time: 66 weeks (post conceptional age) Arm 1: Sample size 27; mean 8626.7; SD (208.2) Arm 2: Sample size 28; mean 8263.7; SD (999.4)
Manley et al., 2011[118] Study name: DINO Study dates: 2001-2007 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies, Manufacturer supplied product, Some authors serve on scientific advisory boards for corporations Study follow-up: 18 months Original, same study, or follow-up studies: Smithers, 2008[104]; Makrides, 2009[116];	Study Population: Preterm infants Breast-feeding women Infants enrolled 657 Infants completers 614 Lactating age: Intervention: 29.9 (5.8) Placebo: 30.2 (5.4) Infant age: 4 days (median) Race of Mother: NR (100%)	Inclusion Criteria: Infants born before 33 weeks' gestation, within 5 days of the infant commencing any enteral feedings. Exclusion Criteria: major congenital or chromosomal abnormalities, from a multiple birth in which not all live-born infants were eligible, enrolled in other trials of fatty acid supplementation, or mother with contraindication to fish oil	Start time: Infants Within 5 days (or less) of starting enteral feeding Duration: Infants NR Arm 1: Standard DHA diet Description: Soy bean oil Manufacturer: Clover Corporation Dose: 6 capsules per day Maternal conditions Infant conditions Current smoker 25% during pregnancy Other maternal conditions 1arm_1_maternal_conditions_other1 Other maternal conditions 10 Birth by C-section: 69% Pre-term birth 100% Low birth weight 18.6% Arm 2: High DHA Description: Tuna fish oil Manufacturer: Clover Corporation Dose: 6 500-mg DHA-rich tuna oil capsules per day Maternal conditions Infant conditions DHA: DHA to achieve a breast milk	Outcome domain: allergies Outcome: hay fever (Secondary) Follow-up time: 12 months Arm 1: 13/249 (5.22%) Arm 2: 5/232 (2.16%) Follow-up time: 12 or 18 months Arm 1: 21/244 (8.61%) Arm 2: 8/231 (3.46%) Follow-up time: 18 months Arm 1: 10/311 (3.22%) Arm 2: 7/292 (2.4%) Outcome domain: atopic dermatitis Outcome: eczema (Secondary) Follow-up time: 12 months Arm 1: 40/249 (16.06%) Arm 2: 29/232 (12.5%) Follow-up time: 12 or 18 months Arm 1: 67/248 (27.02%) Arm 2: 61/236 (25.85%) Follow-up time: 18 months Arm 1: 51/311 (16.4%) Arm 2: 48/292 (16.44%) Outcome domain: respiratory illness Outcome: asthma (Secondary) Follow-up time: 12 months

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Smithers, 2010[117]; Collins, 2011[105]; Atwell, 2013[119]; Collins, 2015[120]			concentration that was 1% of total fatty acids Other dose 1: If supplementary formula was required, infants were given a high- DHA preterm formula (approximately 1.0%DHAand 0.6% AA). Current smoker 25% during pregnancy Other maternal conditions 1arm_2_maternal_conditions_other1 Other maternal conditions 10 Birth by C-section: 68.3% Pre-term birth 100% Low birth weight 18.9%	Arm 1: 25/249 (10.04%) Arm 2: 18/232 (7.76%) Follow-up time: 12 or 18 months Arm 1: 53/252 (21.03%) Arm 2: 47/237 (19.83%) Follow-up time: 18 months Arm 1: 46/311 (14.79%) Arm 2: 41/292 (14.04%)
Marks et al., 2006[168] Study name: CAPS Study dates: 1997-2004 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies Study follow-up: 5 years Original, same study, or follow-up studies: Mihrshahi, 2003[166]; Mihrshahi, 2004[167]; Brew, 2015[165]; Toelle,	Study Population: Pregnant women with allergies Pregnant enrolled 616 Pregnant withdrawals 100 Pregnant completers 516 Infants completers 516 Race of Mother: NR	Inclusion Criteria: pregnant women whose unborn children were at increased risk of developing asthma because 1 or more parents or siblings had asthma or wheezing Exclusion Criteria: with a pet cat at home, strict vegetarians, women with a non-singleton pregnancy, and infants born earlier than 36 weeks of gestation. Infants had birth weights less than 2.5 kg, significant congenital malformations, or other significant neonatal disease.	Start time: Infants from the time the child started bottle-feeding, or to solid foods from age 6 months Duration: NR Arm 1: Diet control Description: polyunsaturated oils and spreads, containing 40% w6 FA, and sunola oil capsules Manufacturer: Crisco-Meadow Lea Foods Inc., Sydney, Australia Blinding: The approach to blinding participants and research staff is described in this article's Online Repository at www.jacionline.org. Arm 2: Active Description: canola-based oils and spreads, which are low in n-6 fatty acids, and tuna oil capsules, which contain n-3 fatty acids.	Outcome domain: allergies Outcome: any atopy (from skin prick test) (Secondary) Follow-up time: 5 years Arm 1: 108/249 (43.37%) Arm 2: 109/267 (40.82%) Outcome: rhinitis (Secondary) Follow-up time: 5 years Arm 1: 102/249 (40.96%) Arm 2: 111/267 (41.57%) Outcome domain: atopic dermatitis Outcome: current eczema (Secondary) Follow-up time: 5 years Arm 1: 59/249 (23.69%) Arm 2: 54/267 (20.22%) Outcome domain: respiratory illness Outcome: cough without cold (Secondary) Follow-up time: 5 years Arm 1: 36/249 (14.46%) Arm 2: 55/267 (20.6%) Outcome: frequent wheeze (Secondary)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
2010[169]				Follow-up time: 5 years Arm 1: 4/249 (1.61%) Arm 2: 5/267 (1.87%) Outcome: probable current asthma (Primary) Follow-up time: 5 years Arm 1: 51/249 (20.48%) Arm 2: 62/267 (23.22%)
Meldrum et al., 2012[140] Study name: Infant FishOil Supplementation Study (IFOS) Study dates: Recruitment from June 2005 through October 2008 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, None, Manufacturer supplied product Original, same study, or follow-up studies: D'Vaz, 2012[142]	Study Population: Pregnant women with allergies Pregnant enrolled 420 Infants enrolled 420 Infants completers 287 Mother age: NR (NR) NR Infant age: Birth (NA) NA Race of Mother: NR Baseline biomarker information: Cord blood data Fish oil group LA, linoleic acid 3.71 ALA, a-linolenic acid 0·496 EPA 0·334 DHA 7·36 DPA 0·700 AA, arachidonic acid 15·76 Olive oil group LA, linoleic acid 3.81 ALA,	Inclusion Criteria: allergic pregnant women were recruited as their infants are at a higher risk of developing allergic disease. Maternal atopy was defined by at least one positive skin prick test to at least one of a defined panel of allergens. Exclusion Criteria: maternal smoking, a pre-existing medical condition or high-risk pregnancy, more than three fish meals consumed per week or fish oil intake during pregnancy in excess of 1000 mg/d, preterm delivery, and infants with significant congenital abnormalities or	Start time: Infants birth Duration: Infants 6 months Arm 1: placebo Description: olive oil capsule Manufacturer: Ocean Nutrition, Canada Active ingredients: 66·6 % n-9 oleic acid Viability: he composition was regularly tested by an independent laboratory during the trial Dose: one 650 mg capsule Blinding: image and scent matched Arm 2: fish oil capsules Manufacturer: Ocean Nutrition, Canada Viability: he composition was regularly tested by an independent laboratory during the trial. Dose: one 650 mg capsule DHA: 280 mg EPA: 110 mg	Outcome domain: Cognitive development Outcome: Bayley Scales of Infant and Toddler Development (BSID-III) Composite Scores Cognitive (Primary) Follow-up time: 18 months Arm 1: Sample size 149; mean 105.28; SD (19.9) Arm 2: Sample size 138; mean 107.65; SD (11.6) Outcome: Bayley Scales of Infant and Toddler Development (BSID-III) Standard Scores Cognitive (Primary) Follow-up time: 18 months Arm 1: Sample size 149; mean 11.43; SD (2.3) Arm 2: Sample size 138; mean 11.55; SD (2.2) Outcome: Macarthur-Bates Communicative Development Inventory raw score: early gestures (Primary) Follow-up time: 12 months Arm 1: Sample size 66; mean 9.56; SD (3.14) Arm 2: Sample size 62; mean 10.29; SD (3.5) Follow-up time: 18 months Arm 1: Sample size 84; mean 13.62; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	a-linolenic acid 0·513 EPA 0·308 DHA 7·44 DPA 0·673 AA, arachidonic acid 15·54 Baseline Omega-3 intake: From maternal food questionnaire, while pregnant Fish oil group LA, linoleic acid 10·59 ALA, a-linolenic acid 0·87 EPA 0·07 DHA 0·09 AA, arachidonic acid 0·87 Olive oil group LA, linoleic acid 9·90 ALA, a-linolenic acid 0·89 EPA 0.06 DHA 0·08 AA, arachidonic acid 0·84	medical conditions.		(7.7) Arm 2: Sample size 77; mean 14.09; SD (2.3) Outcome: Macarthur-Bates Communicative Development Inventory raw score: later gestures (Primary) Follow-up time: 12 months Arm 1: Sample size 66; mean 11.26; SD (7.5) Arm 2: Sample size 62; mean 15.16; SD (8.3) Follow-up time: 18 months Arm 1: Sample size 84; mean 28.08; SD (7.7) Arm 2: Sample size 77; mean 30.81; SD (7.6) Outcome: Macarthur-Bates Communicative Development Inventory raw score: phrases understood (Primary) Follow-up time: 12 months Arm 1: Sample size 66; mean 13.6; SD (5.8) Arm 2: Sample size 62; mean 13.34; SD (6.7) Follow-up time: 18 months Arm 1: Sample size 84; mean 23.5; SD (5.1) Arm 2: Sample size 77; mean 24.06; SD (4.7) Outcome: Macarthur-Bates Communicative Development Inventory raw score: total gestures (Primary) Follow-up time: 12 months Arm 1: Sample size 66; mean 20.76; SD (10.1) Arm 2: Sample size 62; mean 25.47; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(10.9) Follow-up time: 18 months Arm 1: Sample size 84; mean 41.48; SD (9.3) Arm 2: Sample size 77; mean 44.75; SD (9) Outcome: Macarthur-Bates Communicative Development Inventory raw score: words spoken (Primary) Follow-up time: 12 months Arm 1: Sample size 66; mean 5.52; SD (8.7) Arm 2: Sample size 62; mean 6.11; SD (7.5) Follow-up time: 18 months Arm 1: Sample size 84; mean 58.5; SD (63.5) Arm 2: Sample size 77; mean 49.16; SD (55.8) Outcome: Macarthur-Bates Communicative Development Inventory raw score: words understood (Primary) Follow-up time: 12 months Arm 1: Sample size 66; mean 61.42; SD (52.2) Arm 2: Sample size 62; mean 68.3; SD (47.6) Follow-up time: 18 months Arm 1: Sample size 84; mean 190.43; SD (94.5) Arm 2: Sample size 77; mean 199.09; SD (83.7) Outcome domain: Neurological development Outcome: Categorical Child Behavior

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Checklist: Sleep problems - number with t-score>59 (Primary) Follow-up time: 18 months Arm 1: 56/144 (39.0%) Arm 2: 54/125 (43.5%)
Meldrum et al., 2015[51] Study name: Dunstan Study dates: 10/2012-12/2013 for 12-year follow-up Study design: Trial randomized parallel Location: Australia Funding source / conflict: Multiple foundations and Societies, None Study follow-up: 12 years Original, same study, or follow-up studies: Dunstan, 2003[50]; Dunstan, 2008[44];	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 98 Pregnant completers 82 Infants enrolled 82 Infants completers 50 Pregnant age: Fish oil 30.9 Control 32.6 (Fish oil: 3.7 Control: 3.6) Infant age: NR (NR) Race of Mother: NR (100)	Inclusion Criteria: Pregnant women with allergies Exclusion Criteria: Women were ineligible for the study if they smoked, had medical problems, a complicated pregnancy, seafood allergy, or if their normal dietary intake exceeded two meals of fish per week. Children were excluded from the study if they were born before 36 weeks' gestation or with major disease (to avoid the confounding effects on immune response) or if cord blood was not collected	Start time: Pregnant 20 weeks gestation Duration: Pregnant to birth Arm 1: Placebo Description: Olive oil capsules Manufacturer: Pan Laboratories Dose: 4 1g capsules per day Blinding: Randomisation and allocation of capsules was carried out in a blinded manner, and capsules in the two groups were image matched Arm 2: Fish oil Manufacturer: Ocean Nutrition Active ingredients: 3–4 mg/g oil a-tocopherol (vitamin E) Dose: 4 1g capsules per day DHA: 2.2g EPA: 1.1g	Outcome domain: Cognitive development Outcome: Wechsler Intelligence Scale for Children IV (Secondary) Follow-up time: 12 years Arm 1: Sample size 25; mean 107.6; SD (9.9) Arm 2: Sample size 25; mean 108.6; SD (12.2) Outcome domain: Neurological development Outcome: Beery-Buktenica Development Test of Visual-Motor Integration (TVMI) (Secondary) Follow-up time: 12 years Arm 1: Sample size 23; mean 103.2; SD (9.9) Arm 2: Sample size 24; mean 104.4; SD (9)
Mihrshahi et al., 2003[166] Study name: CAPS Study dates: 1997-2002	Study Population: Pregnant women with allergies Pregnant enrolled 616	Inclusion Criteria: At least one parent or sibling with symptoms of asthma as assessed by screening	Start time: Infants initiation of bottle feeding or 6 months of age Duration: Infants NR	Outcome domain: allergies Outcome: any atopy Follow-up time: 18 months Arm 1: 58/275 (21.1%) Arm 2: 51/279 (18.2%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies, Manufacturer supplied product Study follow-up: 18 months Original, same study, or follow-up studies: Mihrshahi, 2004[167]; Mihrshahi, 2006[168]; Brew, 2015[165] Toelle, 2010[169]	(all 4 arms) Pregnant withdrawals 62 Pregnant completers 554 Pregnant age: 28.5 (5.3) Race of Mother: NR (96.9%) Other race/ethnicity (Aboriginal 3.1%)	questionnaire, Reasonable fluency in English, Telephone at home, Reside within 30 km from center of recruitment Exclusion Criteria: Pet cat at home, Families on strict vegetarian diet, Multiple births, Babies born earlier than 36 weeks gestation, with congenital malformations or other serious disease, or requiring major surgery or hospitalization for greater than 1 week	Arm 1: Diet Control/HDM control or intervention Brand name: Sunola oil Manufacturer: Clover Corporation Arm 2: Dietary intervention/HDM control or intervention Description: 500mg n-3 rich tuna fish oil supplement Manufacturer: Clover Corporation DHA: 76-128 mg EPA: 18-30 mg Other dose 1: based on age and fluid intake	Outcome domain: atopic dermatitis Outcome: eczema or dermatitis (Primary) Follow-up time: 18 months Arm 1: 77/275 (28.1%) Arm 2: 85/279 (30.5%) Outcome domain: respiratory illness Outcome: asthma (Primary) Follow-up time: 18 months Arm 1: 34/275 (12.5%) Arm 2: 41/279 (14.7%) Outcome: wheeze ever (Primary) Follow-up time: 18 months Arm 1: 145/275 (52.6%) Arm 2: 119/279 (42.8%)
Miles et al., 2011[78] Study name: SiPS Study dates: NR Study design: Trial randomized parallel Location: UK Funding source / conflict: Government, Some authors employed	Study Population: Healthy pregnant women Pregnant enrolled 123 Pregnant completers 101 Pregnant age: Salmon: 29.5 Control: 28.4 (Salmon 0.5 Control: 0.6) Race of Mother: NR	Inclusion Criteria: age 18–40 y; ,19 wk gestation; healthy, uncomplicated singleton pregnancy; infant at risk of atopy (one or more first-degree relatives of the baby affected by atopy, asthma, or allergy by self-report); consuming <2 portions of oily fish/mo (excluding canned	Start time: Pregnant Week 20 Duration: Pregnant Week 20 until Term (delivery) Arm 1: Control Description: No added fish DHA: 16 mg/d in diet EPA: 10 mg/d in diet EPA-DHA: 24 mg/d in diet Arm 2: Salmon Description: 2 portions salmon per week DHA: 326 mg/d	Outcome domain: Birth weight Outcome: birth weight (g) (Secondary) Follow-up time: birth Arm 1: Sample size 54; mean 3425.0; SE (82) Arm 2: Sample size 53; mean 3449.0; SE (72)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
by industry (companies that make the supplements) Original, same study, or follow-up studies: Noakes, 2012[88]	(100%)	tuna); not using fish-oil supplements currently or in the previous 3 mo Exclusion Criteria: age <18 or >40 y; .19 wk gestation; no first-degree relatives of the infant affected by atopy, asthma, or allergy; consuming >2 portions of oily fish/mo (excluding canned tuna); use of fish-oil supplements within previous 3 mo; participation in another research study; known diabetic; or presence of any autoimmune disease, learning disability, terminal illness, or mental health problems	EPA: 162 mg/d EPA-DHA: 491 mg/d	
Min et al., 2014[43] Study name: NR Study dates: Jan 2008 - Dec 2011 Study design: Trial randomized parallel Location: UK	Study Population: Healthy pregnant women, Pregnant women with type 2 diabetes Pregnant enrolled 85 Pregnant completers 59 Pregnant age: 29 18-44	Inclusion Criteria: Pregnant women of 17–45 years old with singleton pregnancies with either pre-existing Type 2 diabetes or without any known medical condition (uncomplicated pregnancy group)	Start time: Pregnant average: 9.9-12.1 weeks gestation (range: 4.3-15.9 weeks gestation) Duration: Pregnant until delivery; average: 26.5 weeks for placebo arm; 28.4 weeks for the fish oil arm Arm 1: Placebo, healthy women Description: high oleic acid sunflower oil Manufacturer: Equazen/Vifor Pharma Ltd. Active ingredients: oleic acid, 82.6%; vitamin E	Outcome domain: LBW Outcome: birthweight <1500g (Secondary) Follow-up time: birth Arm 1: 0/27 (0.0%) Arm 2: 1/32 (3.1%) Outcome: birthweight <2500g (Secondary) Follow-up time: birth Arm 1: 3/27 (11.1%) Arm 2: 4/32 (12.5%) Outcome domain: duration of gestation

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Funding source / conflict: Industry, Government, Multiple foundations and Societies, Manufacturer supplied product Original, same study, or follow-up studies: none	Infant age: 11.0-12.1 weeks gestation 6.0-15.9 weeks gestation Race of Mother: White European (22.3%) Black (28.2%) Asian (40.0%) Other race/ethnicity (9.4%)	Exclusion Criteria: Women planning to receive tocolytic or corticosteroid therapy. Note that pregnant women with pre-existing Type 2 diabetes were excluded from this systematic review.	(d- a tocopherol) NR% Dose: 2x 750 mg capsules/day Blinding: identical oblong soft gelatin capsule Maternal conditions Current smoker 0% Arm 2: Fish oil, healthy women Description: HA-enriched fish oil Brand name: Mumomega Manufacturer: Equazen/Vifor Pharma Ltd. Active ingredients: vitamin E (d- a tocopherol) NR% Dose: 2 750 mg capsules/day Maternal conditions DHA: 43.7% (600 mg/d) EPA: 7.5% (estimated to be 103 mg/d) Current smoker 13.3% Arm 3: Placebo, diabetic women Description: igh oleic acid sunflower oil Manufacturer: Equazen/Vifor Pharma Ltd. Active ingredients: oleic acid, 82.6%; vitamin E (d- a tocopherol) NR% Dose: 2 750 mg capsules/day Maternal conditions Current smoker 0% Other maternal conditions 1arm_3_maternal_conditions_other1 Other maternal conditions 10 Type 2 diabetes: 100% Arm 4: Fish oil, diabetic women Description: HA-enriched fish oil Brand name: Mumomega Manufacturer: Equazen/Vifor Pharma Ltd. Active ingredients: vitamin E (d- a tocopherol)	Outcome: gestational age birth (weeks) (Secondary) Follow-up time: birth Arm 1: Sample size 27; median 39.3; range Arm 2: Sample size 32; median 39.3; range Outcome: preterm birth (Secondary) Follow-up time: birth Arm 1: 3/27 (11.1%) Arm 2: 3/32 (9.4%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			NR% Dose: 2 750 mg capsules/day Blinding: identical oblong soft gelatin capsule Maternal conditions DHA: 43.7% EPA: 7.5% Current smoker 4.9% Other maternal conditions 1arm_4_maternal_conditions_other1 Other maternal conditions 10 Type 2 diabetes: 100%	
Mozurkewich et al., 2013[42] Study name: NR Study dates: Oct 2008 - May 2011 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product	Study Population: Healthy pregnant women Pregnant enrolled 126 Pregnant withdrawals 8 Pregnant completers 118 Pregnant age: EPA 29.9; DHA 30.6; placebo 30.4 (EPA 5.0; DHA 4.5; placebo 5.9) Race of Mother: White European (85%; 76%; 83%) Black (10%; 11%; 5%) Asian (3%; 3%; 2%) Hispanic (0%; 11%; 7%) Inuit Eskimo (0%; 0%; 2%) Pacific Islander (NR) Baseline biomarker	Inclusion Criteria: past history of depression, an EPDS score 9-19 (at risk for depression or mildly depressed), singleton gestation, a maternal age of 18 years or older, and a gestational age of 12-20 weeks Exclusion Criteria: had a history of a bleeding disorder, thrombophilia requiring anticoagulation, multiple gestation, bipolar disorder, current major depressive disorder, current substance abuse, lifetime substance dependence, or	Start time: Pregnant 12-20 week gestation Duration: Pregnant assuming till birth Arm 1: Control/Placebo Description: 98% soy oil and 1% each of lemon and fish oil Manufacturer: Nordic Naturals Corporation in Watsonville, CA Viability: centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose: 2 large and 4 small placebo capsules Blinding: The placebos were formulated to be identical in appearance to both the EPA- and DHA-rich supplements Arm 2: EPA-rich fish oil Description: an approximate 4:1 ratio of EPA to DHA (1060 mg EPA plus 274 mg DHA) Brand name: ProEPAXtra, Nordic Naturals Viability: centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose: 2 large EPA capsule and 4 small placebo	Outcome domain: Ante or postnatal depression Outcome: Beck Depression Inventory (BDI) (Primary) Follow-up time: 26-28 weeks Arm 1: Sample size 41; mean 6.3; SD (3.9) Arm 2: Sample size 39; mean 8.7; SD (4.2) Arm 3: Sample size 38; mean 7.0; SD (4.6) Follow-up time: 34-36 weeks Arm 1: Sample size 41; mean 7.4; SD (5.5) Arm 2: Sample size 39; mean 8.2; SD (5.7) Arm 3: Sample size 38; mean 6.9; SD (6.3) Follow-up time: 6-8 weeks post-partum Arm 1: Sample size 41; mean 5.9; SD (6.1) Arm 2: Sample size 39; mean 6.6; SD (5.2) Arm 3: Sample size 38; mean 5.7; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	information: EPA group: EPA 0.29+-0.18; DHA 4.24+-2.30; total n3 FA: 22.10+-3.72 DHA group: EPA 0.31+-0.24; DHA 4.66+-2.29; total n3 FA 36.41+-9.71 placebo: EPA .34+-0.22; DHA 3.85+-1.77; omega3 fa 322.86+-5.02	schizophrenia. Women were also ineligible if they were currently taking omega-3 fatty acid supplements or antidepressant medications or eating more than 2 fish meals per week.	DHA: 274 mg EPA: 1060 mg Arm 3: DHA-rich fish oil Description: DHA and EPA in an approximate 4:1 ratio o (900 mg DHA plus 180 mg EPA) Brand name: ProDHA, Nordic Naturals Viability: centrifuged before separation into the 6 aliquots and were stored at 70 degrees C. Dose: 2 large placebo oil and 4 small DHA rich DHA: 900 mg EPA: 180 mg	(4.8) Outcome domain: Birth weight Outcome: birth weight (g) (Secondary) Follow-up time: birth Arm 1: Sample size 40; mean 3309.0; SD (555) Arm 2: Sample size 40; mean 3402.0; SD (550) Arm 3: Sample size 38; mean 3774.0; SD (438) Outcome domain: Gestational hypertension preeclampsia eclampsia Outcome: gestational hypertension or preeclampsia (Secondary) Follow-up time: during pregnancy Arm 1: 5/41 (12.0%) Arm 2: 8/39 (21.0%) Arm 3: 2/38 (5.0%) Outcome domain: duration of gestation Outcome: gestational age (weeks) (Secondary) Follow-up time: birth Arm 1: Sample size 41; mean 39.1; SD (1.5) Arm 2: Sample size 39; mean 39.1; SD (1.5) Arm 3: Sample size 38; mean 40.4; SD (0.9)
Mulder et al., 2014[75] Study name: NR	Study Population: Healthy pregnant women	Inclusion Criteria: at least 16 wk gestation, not taking any lipid or fatty acid supplement,	Start time: Pregnant 16 weeks gestation Duration: Pregnant Until birth	Outcome domain: Birth weight Outcome: birth weight (g) (Unspecified) Follow-up time: birth Arm 1: Sample size 111; mean 3497.0;

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study dates: 2004 to 2008 Study design: Trial randomized parallel Location: Canada Funding source / conflict: Government Study follow-up: 18 months	Pregnant enrolled 271 Pregnant completers 200 Pregnant age: 33 years (4 years) NR Race of Mother: White European (73%) Other race/ethnicity (27%) Baseline biomarker information: maternal RBC Phusphatidylethanolamine DHA: placebo group 6.25 (1.60) g/ 100g DHA group 6.36 (1.62) g/ 100g Baseline Omega-3 intake: median (2.5 to 97.5th percentile range) intake: placebo group 80.0 (0.00-334) mg/day, DHA group 90.0 (6.00-472) mg/d	and were expected to deliver one infant at full-term gestation, with no maternal or fetal complications Exclusion Criteria: NR	Arm 1: placebo Description: corn and soybean oil supplement Manufacturer: Martek Biosciences Blinding: supplements were identical in appearance, contained an orange flavour mask Arm 2: DHA supplement Description: algal oil DHA supplement Manufacturer: Martek Biosciences DHA: 400 mg	SD (479) Arm 2: Sample size 104; mean 3494.0; SD (400) Outcome domain: Cognitive development Outcome: Number in highest quartile of Bayley Scales of Infant Development III: cognitive (Unspecified) Follow-up time: 18 months Arm 1: 18/80 (23.1%) Arm 2: 15/74 (20.0%) Outcome: Number in highest quartile of Bayley Scales of Infant Development III: expressive language (Unspecified) Follow-up time: 18 months Arm 1: 19/80 (24.1%) Arm 2: 28/74 (37.5%) Outcome: Number in highest quartile of Bayley Scales of Infant Development III: receptive language (Unspecified) Follow-up time: 18 months Arm 1: 16/80 (20.5%) Arm 2: 27/74 (36.5%) Outcome: Number in highest quartile of Infant MacArthur Communicative Development Inventory: words produced (Unspecified) Follow-up time: 14 months Arm 1: 13/81 (16.0%) Arm 2: 26/78 (33.3%) Follow-up time: 18 months Arm 1: 12/61 (19.1%) Arm 2: 27/73 (37.3%) Outcome: Number in highest quartile of Infant MacArthur Communicative Development Inventory: words understood

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(Unspecified) Follow-up time: 14 months Arm 1: 12/81 (14.8%) Arm 2: 28/78 (35.9%) Follow-up time: 18 months Arm 1: 11/61 (18.8%) Arm 2: 27/73 (37.3%) Outcome: Number in highest quartile of Toddler MacArthur Communicative Development Inventory: words produced (Unspecified) Follow-up time: 18 months Arm 1: 10/61 (17.1%) Arm 2: 26/73 (35.0%) Outcome domain: Neurological development Outcome: Number in highest quartile of Bayley Scales of Infant Development III: fine motor (Unspecified) Follow-up time: 18 months Arm 1: 20/80 (25.6%) Arm 2: 22/74 (30.1%) Outcome: Number in highest quartile of Bayley Scales of Infant Development III: gross motor (Unspecified) Follow-up time: 18 months Arm 1: 21/80 (26.6%) Arm 2: 22/74 (29.7%) Outcome domain: Visual function Outcome: number with visual acuity>==13 cycles/degree (Unspecified) Follow-up time: 12 months Arm 1: 20/95 (21.1%) Arm 2: 20/81 (24.7%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Outcome: number with visual acuity>==3.3 cycles/degree (Unspecified) Follow-up time: 2 months Arm 1: 8/94 (8.51%) Arm 2: 17/90 (18.9%) Outcome domain: growth Outcome: length-for-age z score (Unspecified) Follow-up time: 12 months Arm 1: Sample size 94; mean 0.44; SD (1.11) Arm 2: Sample size 84; mean 0.11; SD (1.06) Follow-up time: 18 months Arm 1: Sample size 82; mean 0.41; SD (1.14) Arm 2: Sample size 76; mean 0.16; SD (1.11) Follow-up time: 2 months Arm 1: Sample size 102; mean 0.29; SD (1.08) Arm 2: Sample size 92; mean 0.17; SD (1.04) Follow-up time: 6 months Arm 1: Sample size 101; mean 0.25; SD (1.06) Arm 2: Sample size 95; mean 0.17; SD (1.04) Follow-up time: 9 months Arm 1: Sample size 95; mean 0.22; SD (1.08) Arm 2: Sample size 88; mean -0.06; SD (1.05) Outcome: weight-for-age z score (Unspecified)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Follow-up time: 12 months Arm 1: Sample size 94; mean 0.15; SD (1.02) Arm 2: Sample size 81; mean 0.12; SD (1.05) Follow-up time: 18 months Arm 1: Sample size 70; mean 0.27; SD (0.99) Arm 2: Sample size 74; mean 0.21; SD (1.04) Follow-up time: 2 months Arm 1: Sample size 101; mean 0.06; SD (1.08) Arm 2: Sample size 90; mean -0.19; SD (1.08) Follow-up time: 6 months Arm 1: Sample size 101; mean 0.1; SD (1.01) Arm 2: Sample size 95; mean -0.06; SD (1.11) Follow-up time: 9 months Arm 1: Sample size 94; mean 0.03; SD (0.99) Arm 2: Sample size 87; mean 0.04; SD (1.11) Outcome: weight-for-length z score (Unspecified) Follow-up time: 12 months Arm 1: Sample size 93; mean -0.04; SD (0.99) Arm 2: Sample size 81; mean 0.14; SD (1.09) Follow-up time: 18 months Arm 1: Sample size 70; mean 0.14; SD (1.05) Arm 2: Sample size 74; mean 0.14; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(1.05) Follow-up time: 2 months Arm 1: Sample size 101; mean -0.16; SD (1.08) Arm 2: Sample size 90; mean -0.42; SD (1.2) Follow-up time: 6 months Arm 1: Sample size 101; mean 0.04; SD (1.04) Arm 2: Sample size 95; mean -0.11; SD (1.02) Follow-up time: 9 months Arm 1: Sample size 94; mean -0.04; SD (0.99) Arm 2: Sample size 87; mean 0.17; SD (1.05)
Noakes et al., 2012[88] Study name: SiPS Study dates: Not reported Study design: Trial randomized parallel Location: UK Funding source / conflict: Government, None Original, same study, or follow-up studies: Miles, 2011[78]	Study Population: Healthy pregnant women Pregnant enrolled 123 Pregnant withdrawals 37 Pregnant completers 86 Pregnant age: Mean(SEM)(n):Control group -28.4 (0.6)(61); Salmon group- 29.5(0.5) (62) (NR) 18-40 years Race of Mother: NR (100)	Inclusion Criteria: age 18–40 y; >19 wk gestation; healthy uncomplicated singleton pregnancy; infant at risk of atopy (one or more first-degree relatives of the infant affected by atopy, asthma or allergy by self-report); consumption of < 2 portions oily fish per month, excluding tinned tuna; and no use of fish-oil supplements currently or in the previous 3 months.	Start time: Pregnant 20 weeks of gestation Duration: Pregnant until birth Arm 1: Control group Description: Women in the control group (n = 61) were asked to continue their habitual diet Blinding: Researchers responsible for assessing outcome measures (both laboratory and clinical) remained blinded to the groups Arm 2: Salmon group Description: Women in the salmon group (n = 62) were asked to incorporate 2 portions of farmed salmon (150 g/portion) into their diet per week Active ingredients: 30.5 g protein, 16.4 g fat,4.1 mg alpha-tocopherol, 1.6 mg gamma-tocopherol, 6 micro-g vitamin A, 14 micro-g	Outcome domain: atopic dermatitis Outcome: atopic dermatitis (Primary) Follow-up time: 6 months Arm 1: 12/48 (25.0%) Arm 2: 7/38 (18.42%) Outcome domain: respiratory illness Outcome: chest infection (Secondary) Follow-up time: 6 months Arm 1: 1/46 (2.17%) Arm 2: 3/37 (8.11%) Outcome: pneumonia/bronchiolitis (Secondary) Follow-up time: 6 months Arm 1: 1/46 (2.17%) Arm 2: 1/37 (2.7%) Outcome: wheeze (Secondary) Follow-up time: 6 months Arm 1: 11/46 (23.91%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		Exclusion Criteria: age <18 or >40 y; <19 wk gestation; no first-degree relatives of the infant affected by atopy, asthma, or allergy; consumption of >2 portions oily fish per month, excluding tinned tuna; use of fish-oil supplements within the previous 3 mo; participation in another research study; known diabetes; presence of any autoimmune disease; learning disability; terminal illness; and mental health problems.	vitamin D3, and 43 micro-g Selenium Dose: two 150-g portions per week DHA: 1.16 g per portion EPA: 0.57g per portion EPA-DHA: 1.73 per portion Total N-3: 3.56g per portion Other dose 1: Docosapentaenoic acid-0.35g	Arm 2: 7/37 (18.92%)
Olsen et al., 2008[187] Study name: NR Study dates: 1989-2006 Study design: Trial randomized parallel Location: Denmark Funding source / conflict: Multiple	Study Population: Healthy pregnant women Pregnant enrolled 533 Infants enrolled 531 Infants completers 522 Pregnant age: Fish oil: 29.4 Olive oil: 29.7 No oil: 29.1 (Fish oil: (4.4) Olive oil: (4.3) No oil:	Inclusion Criteria: Women seen in the main midwife clinic in Aarhus Denmark at week 30 gestation Exclusion Criteria: History of placental abruption in a previous pregnancy or a serious bleeding episode in the current pregnancy; multiple pregnancies;	Start time: Pregnant 30 weeks gestation Duration: Pregnant to term Arm 1: Control Description: Olive oil Active ingredients: 72% oleic acid Dose: 4 one gram capsules Blinding: Gelatin capsules were coloured, and the capsules and their boxes looked identical. ALA: 12% Arm 2: Fish oil	Outcome domain: respiratory illness Outcome: asthma (all types) (Secondary) Follow-up time: 16 years Arm 1: 11/136 (8.09%) Arm 2: 8/263 (3.04%) Arm 3: 3/129 (2.33%) Outcome: asthma (allergic) (Secondary) Follow-up time: 16 years Arm 1: 8/136 (5.88%) Arm 2: 2/263 (0.76%) Arm 3: 0/129 (0.0%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
foundations and Societies Study follow-up: 16 years	(4.1)) NR Race of Mother: NR (100)	allergy to fish; regular use of fish oil prostaglandin inhibitors	Brand name: Pikasol Fish Oil Manufacturer: Lube Limited Active ingredients: 2mg tocopherol/ml Dose: 4 1-gm capsules EPA: 32% EPA-DHA: 23% Total N-3: 2.7g marine n-3PUFA/day Arm 3: No oil Description: no intervention at all	
Palmer et al., 2012[54] Study name: DOMInO Study dates: 2006-2009 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Industry, Government, Manufacturer supplied product Original, same study, or follow-up studies: Makrides, 2010[35]; Smithers, 2011[53]; Zhou, 2012[55]; Palmer, 2013[56]; Makrides, 2014 [57]	Study Population: Pregnant women with allergies Pregnant enrolled 706 Pregnant withdrawals 25 Pregnant completers 681 Infants enrolled 706 Infants withdrawals 25 Infants completers 681 Pregnant age: Treatment: 29.6 Placebo: 29.5 (Treatment: 5.7 Placebo: 5.6) NR Race of Mother: NR (100)	Inclusion Criteria: Included if the unborn baby had a mother, father, or sibling with a history of any medically diagnosed allergic disease (asthma, allergic rhinitis, eczema) and they were enrolled from the Women's and Children's Hospital or Flinders Medical Centre in Adelaide. Exclusion Criteria: NR	Start time: Pregnant 21 weeks of gestation Infants 21 weeks of gestation Duration: Pregnant until delivery Infants till delivery Arm 1: Placebo Description: 338 women assigned to control supplements-vegetable oil capsules Dose: three 500 mg vegetable oil capsules daily Blinding: All capsules were similar in size, shape, and colour. Neither the women nor the research staff was aware of the treatment allocated. Arm 2: n-3 LCPUFA group Description: 368 women assigned to fish oil concentrate Brand name: Incromega 500 TG Manufacturer: Croda Chemicals, East Yorkshire, UK Dose: e three 500 mg capsules daily DHA: 800mg EPA: 100mg	Outcome domain: allergies Outcome: food allergy with sensitization (Primary) Follow-up time: 1 year Arm 1: 11/338 (3.25%) Arm 2: 11/368 (2.99%) Outcome domain: atopic dermatitis Outcome: eczema with sensitization (Primary) Follow-up time: 1 year Arm 1: 39/338 (11.54%) Arm 2: 26/368 (7.07%) Outcome domain: respiratory illness Outcome: respiratory tract infection (Secondary) Follow-up time: 1 year Arm 1: 66/338 (19.53%) Arm 2: 65/368 (17.66%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Palmer et al., 2013[56] Study name: DOMInO Study dates: 2006-2011 (allergy follow-up to Domino study) Study design: Trial randomized parallel Location: Australia Funding source / conflict: Industry, Government, Some authors serve on scientific advisory boards for corporations Study follow-up: 3 years Original, same study, or follow-up studies: Makrides, 2010[35]; Smithers, 2011[53]; Palmer, 2012[54]; Zhou, 2012[55]	Study Population: Children with family history of allergy Pregnant enrolled 706 Pregnant completers 638 Infants enrolled 706 Infants completers 638 Pregnant age: DHA: 28.9 Control: 28.9 (DHA: 5.7) Control: 5.6) Infant age: Birth Race of Mother: NR (100)	Inclusion Criteria: Women whose infants had a parent or sibling with a history of any medically diagnosed allergic disease (asthma, allergic rhinitis, eczema) Exclusion Criteria: Already taking a prenatal supplement with DHA Fetus had a known major abnormality, Bleeding disorder in which tuna oil was contraindicated, Taking anticoagulant therapy A documented history of drug or alcohol abuse, Participating in another fatty acid trial, Unable to give written informed consent, or English was not the main language spoken at home	Start time: Pregnant <21 weeks gestation Duration: Pregnant to term Arm 1: Control Description: vegetable oil Dose: 3 500-mg vegetable oil capsules per day Blinding: This was a double-blinded study; all capsules were similar in size, shape and colour Arm 2: Fish oil Brand name: Incromega 500 TG, Manufacturer: Croda Chemicals, East Yorkshire, England Dose: 3 500-mg capsules per day DHA: 800 mg per day EPA: 100 mg per day	Outcome domain: allergies Outcome: allergic rhinitis (Primary) Follow-up time: 3 years Arm 1: 20/338 (5.92%) Arm 2: 18/368 (4.89%) Outcome: food allergy (Primary) Follow-up time: 3 years Arm 1: 14/338 (4.14%) Arm 2: 18/368 (4.89%) Outcome domain: atopic dermatitis Outcome: eczema (Primary) Follow-up time: 3 years Arm 1: 64/338 (18.93%) Arm 2: 15/368 (4.08%) Outcome domain: respiratory illness Outcome: asthma (Primary) Follow-up time: 3 years Arm 1: 5/338 (1.48%) Arm 2: 6/368 (1.63%)
Peat et al., 2004[167] Study name: CAPS Study dates: 2000-2003	Study Population: Pregnant women whose unborn children were at high risk of developing asthma	Inclusion Criteria: at least 1 parent or sibling with current asthma or frequent wheeze as assessed by screening	Start time: Infants 6 months of age Duration: Infants NR Arm 1: Placebo group Description: The control group received	Outcome domain: atopic dermatitis Outcome: any eczema (Secondary) Follow-up time: 3 years Arm 1: 81/259 (31.3%) Arm 2: 74/267 (27.7%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study design: Trial randomized factorial design Location: Australia Funding source / conflict: Industry, Government Study follow-up: 3 years Original, same study, or follow-up studies: Mihrshahi, 2003[166]; Mihrshahi, 2006[168]; Brew, 2015[165] Toelle, 2010[169]	Pregnant enrolled 616 Pregnant withdrawals 90 Pregnant completers 526 Pregnant age: Placebo: 29.1 Diet: 28.6 (Placebo: 5.0 Diet: 5.3) NR Race of Mother: NR (100)	questionnaire, fluency in English, a telephone at home, and residence within 30 km of the recruitment center. Exclusion Criteria: a pet cat at home, a vegetarian diet, multiple births, and less than 36 weeks gestation.	placebo supplement capsules of Sunola oil containing 83% monounsaturated oils (Clover Corp) and were provided with widely used soybean-based polyunsaturated oils and margarines high in omega-6 fatty acids for use in all food preparation Manufacturer: Clover Corp; Goodman Fielder Blinding: The research team responsible for recruitment was blind to the methods of randomization until recruitment was complete. The research nurses and research assistants who undertook the outcome assessments, laboratory analyses, and statistical analyses were blind to the group allocation of the participants. Arm 2: Active intervention group Description: tuna fish oil capsules Manufacturer: Clover Corp; Goodman Fielder Dose: 500 mg tuna fish oil capsules daily Total N-3: 184 mg	Outcome domain: respiratory illness Outcome: any asthma (Primary) Follow-up time: 3 years Arm 1: 108/259 (41.7%) Arm 2: 107/267 (40.07%) Outcome: any cough (Primary) Follow-up time: 3 years Arm 1: 157/259 (60.62%) Arm 2: 132/267 (49.44%) Outcome: any wheeze (Secondary) Follow-up time: 3 years Arm 1: 108/259 (41.7%) Arm 2: 107/267 (40.07%)
Pietrantoni et al., 2014[30] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: Italy Funding source / conflict: Government	Study Population: Healthy pregnant women Pregnant enrolled 300 Pregnant completers 255 Pregnant age: DHA 30.86 +-4.18/placebo group 29.92+-4.8 Race of Mother: NR (NR)	Inclusion Criteria: Caucasians 22 to 35 yrs, 8 week gestational age, single pregnancy, BMI between 18.5 and 25.0kg/m2, habitual fish consumption (twice a week at least), high school or university degree, average socioeconomic status, absence of uterine abnormalities (fibroids,	Start time: Pregnant 8th weeks Duration: Pregnant 8th week to delivery Arm 1: Placebo Description: Olive oil Arm 2: DHA group Description: DHA capsule Dose: 2* 100mg capsule DHA: 100mg * 2 capsule	Outcome domain: duration of gestation Outcome: preterm-premature rupture of membranes (Unspecified) Follow-up time: birth Arm 1: 4/126 (3.2%) Arm 2: 1/129 (0.8%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
		cervical incompetence, uterine malformations etc.) Exclusion Criteria: smoking, substance abuse including alcohol, allergy to fish or derivates, diabetes, hypertension, metabolic, cardiovascular, renal, psychiatric, neurologic, throbophilic, thyroid or autoimmune diseases, previous pregnancy complications (miscarriage, preterm or operative delivery), previous uterine surgery, recurrent genito-urinary infections		
Ramakrishnan et al., 2010[32] Study name: POSGRAD Study dates: Feb 2005 - Feb 2007 Study design: Trial randomized parallel Location: Mexico	Study Population: Healthy pregnant women Pregnant enrolled 1,094 Pregnant withdrawals 67 Pregnant completers 973 (for birthweight) Pregnant age: 26.2 (controls) 26.3 (DHA) (4.6 (controls) 4.8	Inclusion Criteria: 18-35 yrs. of age, in gestation weeks 18-22, planned to deliver at the IMSS General Hospital in Cuernavaca, exclusively or predominantly breastfeed for at least 3 months, liver in the area for at least 2	Start time: Pregnant at study entry Duration: Pregnant mid pregnancy (18-22 weeks gestation) until delivery Arm 1: Controls Description: Placebo containing olive oil Manufacturer: Martek Biosciences Dose: 1 capsule, twice a day Blinding: Identical tablets Arm 2: DHA	Outcome domain: Birth weight Outcome: birth weight (g) (Primary) Follow-up time: birth Arm 1: Sample size 486; mean 3202.0; SD (472) Arm 2: Sample size 487; mean 3207.2; SD (449.4) Outcome domain: LBW Outcome: birthweight <2500g (Secondary) Follow-up time: birth Arm 1: 27/486 (5.6%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Funding source / conflict: Government, March of Dimes Original, same study, or follow-up studies: Stein, 2012[33]; Imhoff-Kunsch, 2011[58]; Escamilla-Nunez, 2014[59]; Gonzalez-Casanova, 2015[60]; Ramakrishnan, 2015[61]; Stein, 2011[34]	(DHA)) Race of Mother: Hispanic (NR) Baseline Omega-3 intake: mg/day for all: LA: 17,846 in controls, 17,645 in DHA AA: 137 in controls, 140 in DHA ALA: 1,488 in controls, 1,477 in DHA EPA: 18 in controls, 18 in DHA DHA: 54 in controls, 56 in DHA	years after delivery. Exclusion Criteria: high-risk pregnancy; lipid metabolism or absorption disorders, regular intake of fish oil or DHA supplements; chronic use of certain medications (e.g., medications for epilepsy).	Description: Intervention Manufacturer: Martek Biosciences Dose: 1 capsule twice a day DHA: 400 mg/d, 200 mg/dl derived from algal source	Arm 2: 27/487 (5.5%) Outcome domain: duration of gestation Outcome: gestational age (weeks) (Primary) Follow-up time: birth Arm 1: Sample size 486; mean 39.1; SD (1.7) Arm 2: Sample size 487; mean 39.0; SD (1.9) Outcome: incidence of premature birth (Secondary) Follow-up time: birth Arm 1: 40/486 (8.3%) Arm 2: 49/487 (10.1%)
Ramakrishnan et al., 2015[61] Study name: POSGRAD Study dates: 2005-2009 Study design: Trial randomized parallel Location: Mexico Funding source / conflict: Government, None, March of Dimes Study follow-up: 18 months Original, same study, or	Study Population: Healthy pregnant women Pregnant enrolled 1094 Pregnant completers 968 Infants enrolled 973 Infants completers 730 Pregnant age: Placebo: 26.3 Intervention: 26.5 (Placebo: 4.6 Intervention: 4.9) Infant age: Placebo: 20.5 weeks gestation Intervention: 20.6 weeks gestation (Placebo: 2.1	Inclusion Criteria: Women who were in gestation week 18–22, age 18–35 years, planned to deliver at the IMSS General Hospital and to remain in the area for the next 2 years, and planned predominant breastfeeding for at least 3 months Exclusion Criteria: High risk pregnancy, had any lipid metabolism/absorption conditions, regularly took DHA or fish oil supplements, or used	Start time: Pregnant 18-22 weeks gestation Duration: Pregnant 18-22 weeks gestation until delivery Arm 1: Control Description: Corn and soy oils with no added antioxidants Dose: 2 capsules/day Blinding: Similar in appearance and taste to the DHA capsules Arm 2: Intervention Description: Algal-sourced DHA capsule Manufacturer: Martek Biosciences Dose: 2 capsules/day DHA: 200 mg * 2 = 400 mg/d	Outcome domain: Cognitive development Outcome: Bayley Mental Development Index (Primary) Follow-up time: 18 months Arm 1: Sample size 365; mean 95.2; SD (9.3) Arm 2: Sample size 365; mean 94.3; SD (10.7) Outcome domain: Infants born small gestational age Outcome: IUGR (Secondary) Follow-up time: birth Arm 1: 36/365 (9.9%) Arm 2: 39/365 (10.7%) Outcome domain: Neurological development Outcome: Bayley PDI (Primary) Follow-up time: 18 months

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
follow-up studies: Ramakrishnan, 2010[32]; Stein, 2012[33]; Imhoff-Kunsch, 2011[58]; Escamilla-Nunez, 2014[59]; Gonzalez-Casanova, 2015[60]; Ramakrishnan, 2015[61]	weeks Intervention: 2.0 weeks) Race of Mother: NR (NR) Baseline Omega-3 intake: From original study ref 3364 mg/day for all: LA: 17,846 in controls, 17,645 in DHA AA: 137 in controls, 140 in DHA ALA: 1,488 in controls, 1,477 in DHA EPA: 18 in controls, 18 in DHA DHA: 54 in controls, 56 in DHA	certain chronic medications (such as antiepileptic drugs)		Arm 1: Sample size 365; mean 93.3; SD (9.8) Arm 2: Sample size 365; mean 93.0; SD (8.9)
Sala-Vila et al., 2004[110] Study name: NR Study dates: NR Study design: Trial randomized parallel Location: Spain Funding source / conflict: Multiple foundations and Societies, Manufacturer supplied product	Study Population: Healthy infants Infants enrolled 35 Infants completers 35 Pregnant age: 28.3 Infant age: NR Race of Mother: NR (100)	Inclusion Criteria: full-term infants (37–42 wk gestation), of appropriate weight-for-gestation-age Exclusion Criteria: NR	Start time: Infants birth Duration: Infants 3 mo Arm 1: Human Milk (HM) Description: breast milk with composition of protein carbohydrate fat ash Arm 2: E-PL formula Description: E-PL formula provided 10% of its fat from egg PLs Brand name: Ovotin 120, Lucas Meyer DHA: 1.25% AA: 1.9% Arm 3: S-TG formula Description: single-cell (SC)-TG formula provided _x0004_0.3 and 0.5% of its fat from	Outcome domain: growth Outcome: head circumference (cm) (Unspecified) Follow-up time: 3 months Arm 1: Sample size 11; mean 41.86; SE (1.78) Arm 2: Sample size 12; mean 42.01; SE (1.46) Arm 3: Sample size 12; mean 43.98; SE (1.38) Outcome: length (cm) (Unspecified) Follow-up time: 3 months Arm 1: Sample size 11; mean 60.5; SE (6.31) Arm 2: Sample size 12; mean 61.08; SE (5.31) Arm 3: Sample size 12; mean 60.98; SE (3.98)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			TGs synthesized by single cells of algal and fungal microorganisms Manufacturer: Martek Biosciences DHA: 0.1g/100g; 0.3% of 40-45% DHASCO AA: 0.4g/100g, 0.5% of 38-44% ARASCO	Outcome: weight (g) (Unspecified) Follow-up time: 3 months Arm 1: Sample size 11; mean 6460.1; SE (630.6) Arm 2: Sample size 12; mean 6640.8; SE (741) Arm 3: Sample size 12; mean 6491.9; SE (906.1)
Smithers et al., 2008[104] Study name: DINO Study dates: 2001-2004 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Manufacturer supplied product Study follow-up: 2 months, 4 months Original, same study, or follow-up studies: Makrides, 2009[116]; Smithers, 2010[117]; Manley, 2011[118]; Collins, 2011[105]; Atwell, 2013[119]; Collins, 2015[120]	Study Population: Preterm infants Lactating enrolled unclear Infants enrolled 143 Infants completers 125 Lactating enrolled unclear Mother age: Control: 31 Treatment: 29 (Control: 6 Treatment: 6) Infant age: 5 days (control) (mean gestational age at birth 29.4 weeks) 6 days (Treatment) (3) Race of Mother: NR (NR) Baseline Omega-3 intake: Intervention	Inclusion Criteria: infants born_x0001_33 wk gestation at the Women's and Children's Hospital of the Child, Youth, and Women's Health Service, Adelaide, Australia, between April 2001 and September 2003 Exclusion Criteria: Infants with major congenital or chromosomal abnormalities, lactating mothers for whom tuna oil was contraindicated (women with blood-thinning disorders or currently taking anticoagulants)	Start time: Lactating approximately 5 days after birth Infants approximately 5 days after birth Duration: Lactating to estimated due date Infants to estimated due date Arm 1: Control group Description: Placebo capsules and/or formula Active ingredients: Linoleic acid 53.4% of fatty acids Dose: 6 500-mg capsules per day to mothers Blinding: The soy and tuna oil capsules were identical in size, color, and shape ALA: 5.9% of total fatty acids Arm 2: Treatment Description: DHA supplemented breastfeeding mothers and/or formula Active ingredients: Linoleic acid 2.7% of fatty acids Dose: 6 capsules or formula ad lib ALA: 0.4% total FA DHA: 29.5% total FA EPA: 6.5% total FA AA: 1.8% total FA	Outcome domain: Visual function Outcome: Visual evoked potential acuity (cyc/deg) (Primary) Follow-up time: 2 months (corrected age) Arm 1: Sample size 61; mean 5.6; SD (2.4) Arm 2: Sample size 54; mean 5.6; SD (2.4) Follow-up time: 4 months (corrected age) Arm 1: Sample size 51; mean 8.2; SD (1.8) Arm 2: Sample size 44; mean 9.6; SD (3.7) Outcome: Visual evoked potential latency: 48 min of arc (ms) (Secondary) Follow-up time: 4 months (corrected age) Arm 1: Sample size 67; mean 138.0; SD (23) Arm 2: Sample size 58; mean 135.0; SD (23) Outcome: Visual evoked potential latency: 69 min of arc (ms) (Secondary) Follow-up time: 2 months (corrected age) Arm 1: Sample size 66; mean 200.0; SD (29) Arm 2: Sample size 58; mean 193.0; SD (27)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
	begun at birth: see below			Follow-up time: 4 months (corrected age) Arm 1: Sample size 67; mean 131.0; SD (21) Arm 2: Sample size 58; mean 129.0; SD (20) Outcome: Visual evoked potential latency: 96 min of arc (ms) (Secondary) Follow-up time: 2 months (corrected age) Arm 1: Sample size 66; mean 188.0; SD (27) Arm 2: Sample size 58; mean 182.0; SD (24) Outcome domain: growth Reason results are not reported: duplicate data of id 8885 Outcome: (Secondary)
Smithers et al., 2010[117] Study name: DINO Study dates: April 2001 through September 2003 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies, Manufacturer supplied product, Some	Study Population: Preterm infants Lactating enrolled 545 Infants enrolled 657 Infants completers 614 Lactating enrolled 545 Lactating age: 30 years (5.5 years) NR Infant age: 4 days after birth (29 weeks gestation) 2 to 6 days after birth	Inclusion Criteria: infants born at < 33 wk of gestation Exclusion Criteria: Infants born with major congenital or chromosomal abnormalities or born to lactating women for whom tuna oil was contraindicated (women with bleeding disorders or taking anticoagulants)	Start time: Lactating 4 days after birth Infants 4 days after birth Duration: Lactating until infants reached their "expected" date of delivery. Infants until infants reached their "expected" date of delivery Arm 1: Placebo Description: Soy oil capsules or standard preterm formula if not breastfeeding Manufacturer: Clover Corporation Dose: six 500-mg soy oil capsules Blinding: all capsules were similar in size, shape, and color DHA: Formula: 0.35% AA: Formula: 0.6% Total N-3: Capsules: did not change FA content of breastmilk	Outcome domain: Cognitive development Outcome: MacArthur Communicative Development Inventory (MCDI) vocabulary production score (Secondary) Follow-up time: 26 months CA Arm 1: Sample size 67; mean 316.0; SD (192) Arm 2: Sample size 60; mean 308.0; SD (179)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
authors serve on scientific advisory boards for corporations, Some authors have received research funding from infant formula manufacturers Study follow-up: 3-5 years Original, same study, or follow-up studies: Smithers, 2008[104]; Makrides, 2009[116]; Manley, 2011[118]; Collins, 2011[105]; Atwell, 2013[119]; Collins, 2015[120]	Race of Mother: White European (90%)		Arm 2: DHA Description: DHA-rich tuna oil capsules or high-DHA formula Manufacturer: Clover Corporation Dose: six 500 mg capsules per day DHA: Capsules: Achieved breast milk concentration of 1.0%. Formula: 1.0% AA: Capsules: Did not change AA in breast-milk. Formula 0.6% Other dose 1: DHA-rich tuna oil capsules to achieve a breast milk DHA concentration that was approximately 1% of total fatty acids without altering the naturally occurring concentration of arachidonic acid (AA) in breast milk	
Smithers et al., 2011[53] Study name: DOMInO Study dates: Enrollment from June 2007 to August 2008 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Manufacturer supplied product, Some authors	Study Population: Healthy infants Healthy pregnant women Infants enrolled 185 Infants completers 182 Pregnant age: Tx = 29.5 years, Placebo = 28.7 years (Tx = 5.5 years, Placebo = 5.4 years) NR Infant age: (NA) NA Race of Mother: NR (NR)	Inclusion Criteria: singleton pregnancies at less than 21 weeks' gestation Exclusion Criteria: already taking a prenatal supplement with DHA, fetus had a known major abnormality, mother had a bleeding disorder in which tuna oil was contraindicated, taking anticoagulant therapy, history of	Start time: Pregnant 18 to 21 weeks gestation Duration: Pregnant until birth Arm 1: placebo Description: vegetable oil capsule Manufacturer: Efamol Dose: 3 500 mg capsules Blinding: similar in size, shape, and color Arm 2: Omega 3 supplement Description: fish oil capsule Brand name: Incromega Manufacturer: Croda Chemicals Dose: 3 500 mg capsules DHA: 800/3 mg EPA: 100/3 mg	Outcome domain: Visual function Outcome: VEP Latency: 20 min of arc (ms) (Secondary) Follow-up time: 4 months Arm 1: Sample size 93; mean 133.0; SD (14) Arm 2: Sample size 89; mean 133.0; SD (15) Outcome: VEP Latency: 48 min of arc (ms) (Secondary) Follow-up time: 4 months Arm 1: Sample size 93; mean 121.0; SD (12) Arm 2: Sample size 89; mean 121.0; SD (10) Outcome: VEP Latency: 69 min of arc (ms) (Secondary)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
serve on scientific advisory boards for corporations, Some authors have received research funding from infant formula manufacturers Study follow-up: 4 months Original, same study, or follow-up studies: Makrides, 2010[35]; Palmer, 2012[54]; Zhou, 2012[55]; Palmer, 2013[56]; Makrides, 2014 [57]		drug or alcohol abuse, participating in another fatty acid trial, unable to give written informed consent, or English was not the main language spoken at home		Follow-up time: 4 months Arm 1: Sample size 93; mean 116.0; SD (9) Arm 2: Sample size 89; mean 115.0; SD (8) Outcome: VEP acuity (adjusted) (cyc/deg) (Primary) Follow-up time: 4 months Arm 1: Sample size 93; mean 8.55; SD (1.97) Arm 2: Sample size 89; mean 8.37; SD (1.97) Outcome: VEP acuity (unadjusted) (cyc/deg) (Primary) Follow-up time: 4 months Arm 1: Sample size 93; mean 8.55; SD (1.86) Arm 2: Sample size 89; mean 8.37; SD (2.11)
Stein et al., 2011[34] Study name: POSGRAD Study dates: 02. 2005-02.2007 Study design: Trial randomized parallel Location: Mexico Funding source / conflict: Government, Multiple foundations and Societies	Study Population: Healthy infants Pregnant enrolled 1094 Pregnant completers 973 Pregnant age: placebo 26.3; DHA 26.4 (placebo 4.6; DHA 4.9) Infant age: 39.1 (placebo 1.6; DHA 1.8) Race of Mother: NR	Inclusion Criteria: women were 18–35 y, were in gestation wk 18–22, and planned to deliver at the IMSS General Hospital in Cuernavaca, exclusively or predominantly breast-feed for at least 3 mo, and to live in the area for at least 2 y after delivery Exclusion Criteria: NR	Start time: Pregnant 18-22 Gestational week Infants birth Duration: Pregnant birth Arm 1: Placebo Description: Olive oil Manufacturer: Martek Biosciences Dose: 2 capsules olive oil Blinding: Similar in appearance and taste to DHA capsules Arm 2: DHA Description: algal DHA capsules Manufacturer: Martek Biosciences Dose: 2 capsules * 200mg	Outcome domain: Birth weight Outcome: birth weight (g) (Primary) Follow-up time: birth Arm 1: Sample size 370; mean 3220.0; SD (475) Arm 2: Sample size 369; mean 3242.0; SD (441) Outcome domain: Infants born small gestational age Outcome: IUGR (intrauterine growth retardation); birth weight for gestational age < 10th percentile (Secondary) Follow-up time: birth Arm 1: 38/368 (10.3%) Arm 2: 39/369 (10.6%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Original, same study, or follow-up studies: Stein, 2012[33]; Imhoff-Kunsch, 2011[58]; Escamilla-Nunez, 2014[59]; Gonzalez-Casanova, 2015[60]; Ramakrishnan, 2015[61]; Ramakrishnan, 2011[32]			DHA: 400 mg	Outcome domain: LBW Outcome: birthweight <2500g (Secondary) Follow-up time: birth Arm 1: 20/370 (5.4%) Arm 2: 16/369 (4.3%) Outcome domain: duration of gestation Outcome: gestational age (weeks) (Primary) Follow-up time: birth Arm 1: Sample size 368; mean 39.1; SD (1.6) Arm 2: Sample size 369; mean 39.1; SD (1.8) Outcome: incidence of premature birth (Secondary) Follow-up time: birth Arm 1: 30/368 (8.2%) Arm 2: 33/369 (8.9%) Outcome domain: growth Outcome: head circumference (cm) (Primary) Follow-up time: 18 months Arm 1: Sample size 370; mean 47.0; SD (1.4) Arm 2: Sample size 369; mean 47.0; SD (1.5) Outcome: length (cm) (Primary) Follow-up time: 18 months Arm 1: Sample size 370; mean 79.5; SD (2.8) Arm 2: Sample size 369; mean 79.6; SD (2.8) Outcome: weight (kg) (Primary)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Follow-up time: 18 months Arm 1: Sample size 370; mean 10.4; SD (1.2) Arm 2: Sample size 369; mean 10.4; SD (1.1)
Stein et al., 2012[33] Study name: POSGRAD Study dates: Feb 2005-Feb 2007 Study design: Trial randomized parallel Location: NR Funding source / conflict: Government Original, same study, or follow-up studies: Ramakrishnan, 2010[32]; Imhoff-Kunsch, 2011[58]; Escamilla-Nunez, 2014[59]; Gonzalez-Casanova, 2015[60]; Ramakrishnan, 2015[61]	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 1094 Pregnant withdrawals 63 Pregnant completers 900 Pregnant age: 26.3 (4.6-4.8) Infant age: 39.1 (1.7-1.8) Race of Mother: NR (NR)	Inclusion Criteria: Singleton live births without congenital anomalies Exclusion Criteria: 3364: high risk pregnancy, (history and prevalence of pregnancy complications, including abruptio placentae, preeclampsia, pregnancy-induced hypertension, any serious bleeding episode in the current pregnancy, and physician referral); lipid metabolism or absorption disorders, regular intake of fish oil or DHA supplement, or chronic use of certain medication(e.g.. epilepsy medications)	Start time: Pregnant 18-22 wk Duration: Pregnant to birth Arm 1: Placebo Description: A mixture of corn and soy oil Manufacturer: Martek Biosciences Blinding: "Participants and members of the study team were unaware of the treatment scheme throughout the intervention period of the study" Arm 2: DHA Description: DHA 400 mg/d Manufacturer: Martek Biosciences Dose: 2 capsule per day DHA: 2*200mg	Outcome domain: LBW Outcome: birthweight <2500g (Primary) Follow-up time: birth Arm 1: 24/452 (5.3%) Arm 2: 17/448 (3.8%) Outcome domain: Neurological development Outcome: auditory evoked responses: latency 1 (ms) (Primary) Follow-up time: 1 month Arm 1: Sample size 377; mean 1.63; SD (0.14) Arm 2: Sample size 372; mean 1.62; SD (0.16) Follow-up time: 3 months Arm 1: Sample size 334; mean 1.58; SD (0.15) Arm 2: Sample size 330; mean 1.58; SD (0.15) Outcome: auditory evoked responses: latency 1-3 (ms) (Primary) Follow-up time: 1 month Arm 1: Sample size 377; mean 2.57; SD (0.36) Arm 2: Sample size 372; mean 2.56; SD (0.27) Follow-up time: 3 months Arm 1: Sample size 334; mean 2.44; SD (0.28)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 2: Sample size 330; mean 2.45; SD (0.28) Outcome: auditory evoked responses: latency 1-5 (ms) (Primary) Follow-up time: 1 month Arm 1: Sample size 377; mean 4.93; SD (0.36) Arm 2: Sample size 372; mean 4.91; SD (0.39) Follow-up time: 3 months Arm 1: Sample size 334; mean 4.75; SD (0.39) Arm 2: Sample size 330; mean 4.72; SD (0.39) Outcome: auditory evoked responses: latency 3 (ms) (Primary) Follow-up time: 1 month Arm 1: Sample size 377; mean 4.19; SD (0.33) Arm 2: Sample size 372; mean 4.18; SD (0.32) Follow-up time: 3 months Arm 1: Sample size 334; mean 4.02; SD (0.32) Arm 2: Sample size 330; mean 4.03; SD (0.33) Outcome: auditory evoked responses: latency 3-5 (ms) (Primary) Follow-up time: 1 month Arm 1: Sample size 377; mean 2.37; SD (0.3) Arm 2: Sample size 372; mean 2.37; SD (0.34) Follow-up time: 3 months Arm 1: Sample size 334; mean 2.31; SD (0.35)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 2: Sample size 330; mean 2.28; SD (0.33) Outcome: auditory evoked responses: latency 5 (ms) (Primary) Follow-up time: 1 month Arm 1: Sample size 377; mean 6.55; SD (0.42) Arm 2: Sample size 372; mean 6.52; SD (0.48) Follow-up time: 3 months Arm 1: Sample size 334; mean 6.33; SD (0.4) Arm 2: Sample size 330; mean 6.29; SD (0.42) Outcome domain: Visual function Outcome: Visual evoked potential: Amplitude P (mV) (Primary) Follow-up time: 3 months Arm 1: Sample size 342; mean 8.14; SD (6.04) Arm 2: Sample size 337; mean 7.75; SD (5.97) Follow-up time: 6 months Arm 1: Sample size 342; mean 11.3; SD (6.9) Arm 2: Sample size 337; mean 11.2; SD (7.2) Outcome: Visual evoked potential: Latency N1 (ms) (Primary) Follow-up time: 3 months Arm 1: Sample size 342; mean 93.9; SD (17.1) Arm 2: Sample size 337; mean 94.2; SD (16.3) Follow-up time: 6 months

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 1: Sample size 342; mean 91.9; SD (15.1) Arm 2: Sample size 337; mean 90.5; SD (14.6) Outcome: Visual evoked potential: Latency N3 (ms) (Primary) Follow-up time: 3 months Arm 1: Sample size 342; mean 157.1; SD (24.1) Arm 2: Sample size 337; mean 154.8; SD (23.8) Follow-up time: 6 months Arm 1: Sample size 342; mean 154.9; SD (20.2) Arm 2: Sample size 337; mean 154.2; SD (19.9) Outcome: Visual evoked potential: Latency P1 (ms) (Primary) Follow-up time: 3 months Arm 1: Sample size 342; mean 126.3; SD (18.3) Arm 2: Sample size 337; mean 125.8; SD (17.5) Follow-up time: 6 months Arm 1: Sample size 342; mean 123.5; SD (14.3) Arm 2: Sample size 337; mean 122.7; SD (14.6) Outcome domain: duration of gestation Reason results are not reported: duplicate data of id 3364 Outcome: (Primary)
Toelle et al., 2010[169]	Study Population: Healthy infants	Inclusion Criteria: Pregnant women	Start time: Infants birth	Outcome domain: allergies Outcome: atopy (Primary)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study name: CAPS Study dates: 1997-2008 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Manufacturer supplied product Study follow-up: 8 years Original, same study, or follow-up studies: Mihrshahi, 2003[166]; Mihrshahi, 2004[167]; Mihrshahi, 2006[168]; Brew, 2015[165]	Pregnant enrolled 616 Pregnant completers Infants enrolled 616 Infants completers 450 Pregnant age: 28.5 years (5.3 years) Race of Mother: NR (NR)	whose unborn children were at high risk of developing asthma because of a family history (at least one parent or sibling with symptoms of asthma as assessed by screening questionnaire), reasonable fluency in English, telephone at home, reside within 30 km from center of recruitment Exclusion Criteria: Pet cat at home, families on strict vegetarian diet, multiple births, babies born earlier than 36 weeks gestation, birth weight below 2.5 kg, babies requiring surgery, babies requiring hospitalization for more than 1 week, babies with significant neonatal disease, babies with congenital malformations	Duration: Infants 5 years Arm 1: Control Description: Low-n3 capsules and cooking oils Brand name: Sunola Active ingredients: Capsules: 7% n-6 FA, 82% monounsaturated FA, 9% saturated FA, and 1.7% minor FA; cooking oils: 40% n-6 FA, 20% n-9 FA Dose: Designed to maintain the current n-3 to n-6 ingested FA ratio in the general population (1:15 to 1:20) Blinding: Similar appearance Total N-3: Capsules: 0.3%; cooking oil: 1.2% Arm 2: Omega 3 supplementation Description: High n-3 FA capsules and cooking oils Active ingredients: Capsules: 6% n-6 polyunsaturated FA, 24% monounsaturated FA, 28% saturated FA, and 5% minor FA; cooking oil: 6% n-6 FA, 40% n-9 FA Blinding: Similar appearance N-6 N-3: 5:1 Total N-3: Capsules: 37%; cooking oil: 6%	Follow-up time: 8 yrs Arm 1: 99/220 (45.0%) Arm 2: 104/230 (45.1%) Outcome: rhinitis (Secondary) Follow-up time: 8 yrs Arm 1: 65/220 (29.6%) Arm 2: 70/230 (30.4%) Outcome domain: atopic dermatitis Outcome: eczema (Secondary) Follow-up time: 8 yrs Arm 1: 31/220 (14.2%) Arm 2: 35/230 (15.3%) Outcome domain: respiratory illness Outcome: asthma (Primary) Follow-up time: 8 yrs Arm 1: 44/220 (20.0%) Arm 2: 57/230 (24.8%) Outcome: wheeze (Primary) Follow-up time: 8 yrs Arm 1: 51/220 (23.2%) Arm 2: 73/230 (31.7%)
Tofail et al., 2006[77] Study name: NR	Study Population: Healthy infants Healthy pregnant women	Inclusion Criteria: seems as if all pregnant women at 25	Start time: Pregnant 25 weeks gestation Duration: Pregnant until birth	Outcome domain: Birth weight Outcome: birth weight (kg) (Unspecified) Follow-up time: birth

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study dates: Enrollment January to March 2000 Study design: Trial randomized parallel Location: Bangladesh Funding source / conflict: Government Study follow-up: 10 months	Pregnant enrolled 400 Pregnant completers 151 Pregnant age: 22.7 years (4.35 years) NR Race of Mother: Asian (100%)	weeks gestation were enrolled, no inclusion criteria specified Exclusion Criteria: NR	Arm 1: placebo Description: soy oil capsule Dose: 4 one gram capsules per day Blinding: capsules were identical in appearance Other dose 1: LNA 0.27 g Other dose 2: linoleic acid 2.25 g Arm 2: DHA supplement Description: fish oil capsules Dose: 4 one gram capsules per day DHA: 1.2 g EPA: 1.8 g	Arm 1: Sample size 124; mean 2.7; SD (0.4) Arm 2: Sample size 125; mean 2.7; SD (0.4) Outcome domain: Cognitive development Outcome: Bayley Scale of Infant Development (Mental developmental index) (Unspecified) Follow-up time: 10 months Arm 1: Sample size 124; mean 101.5; SD (7.8) Arm 2: Sample size 125; mean 102.5; SD (8) Outcome domain: Neurological development Outcome: Bayley Scale of Infant Development (Psychomotor developmental index) (Unspecified) Follow-up time: 10 months Arm 1: Sample size 124; mean 100.5; SD (10.1) Arm 2: Sample size 125; mean 101.7; SD (10.9) Outcome domain: growth Outcome: head circumference (cm) (Unspecified) Follow-up time: 10 months Arm 1: Sample size 124; mean 43.2; SD (1.4) Arm 2: Sample size 125; mean 43.0; SD (1.4)
Unay et al., 2004[138]	Study Population:	Inclusion Criteria:	Start time: Infants week 1	Outcome domain: Neurological

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Study name: NR Study dates: 2000-2001 Study design: Trial randomized parallel Location: Turkey Funding source / conflict: NR	Healthy infants Infants enrolled 54 Infants completers 44 Infant age: NR (term) Race of Mother: NR (NR)	healthy, full term newborns of appropriate size for gestational age, who were not going to be breast fed because that was the mother's wish or because of maternal illness or medication incompatible with breast feeding just after birth Exclusion Criteria: Perinatal asphyxia, central nervous system infection, congenital malformation, or significant hyperbilirubinaemia	Duration: Infants 16 weeks Arm 1: Formula B Description: Infant formula without added DHA Brand name: Nutrilon I Manufacturer: NV Nutricia Netherlands Active ingredients: Linoleic acid 11.2gm/100gm fat ALA: 2.2g/100g fat AA: Trace Arm 2: Formula A Description: DHA-containing formula Brand name: Farley's First MIlk Manufacturer: HJ Heinz UK Blinding: not reported ALA: 1.2g/100gm DHA: 0.5g/100gm AA: Trace Arm 3: Human milk Description: Breast milk Active ingredients: Linoleic acid: 10.85 gm/100gm fat ALA: 1.03gm/100g fat DHA: 0.25 gm/100gm fat AA: 0.46 gm/100g fat	development Outcome: brainstem auditory evoked potentials: interpeak latency I-III (Unspecified) Follow-up time: 16 weeks Arm 1: Sample size 22; mean decrease 0.25; SD (0.14) Arm 2: Sample size 22; mean decrease 0.34; SD (0.16) Outcome: brainstem auditory evoked potentials: interpeak latency I-V (Unspecified) Follow-up time: 16 weeks Arm 1: Sample size 22; mean decrease 0.33; SD (0.16) Arm 2: Sample size 22; mean decrease 0.47; SD (0.2) Outcome: brainstem auditory evoked potentials: interpeak latency III-V (Unspecified) Follow-up time: 16 weeks Arm 1: Sample size 22; mean decrease 0.08; SD (0.07) Arm 2: Sample size 22; mean decrease 0.14; SD (0.1) Outcome: brainstem auditory evoked potentials: wave I (Unspecified) Follow-up time: 16 weeks Arm 1: Sample size 22; mean decrease 0.27; SD (0.14) Arm 2: Sample size 22; mean decrease 0.35; SD (0.13) Outcome: brainstem auditory evoked potentials: wave III (Unspecified) Follow-up time: 16 weeks Arm 1: Sample size 22; mean decrease

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				0.52; SD (0.15) Arm 2: Sample size 22; mean decrease 0.69; SD (0.16) Outcome: brainstem auditory evoked potentials: wave V (Unspecified) Follow-up time: 16 weeks Arm 1: Sample size 22; mean decrease 0.6; SD (0.11) Arm 2: Sample size 22; mean decrease 0.83; SD (0.18)
Werkman et al., 1996[154] Study name: NR Study dates: 1987-1990 Study design: Trial randomized parallel Location: US Funding source / conflict: Government, Manufacturer supplied product Study follow-up: 12 months	Study Population: Preterm infants Infants enrolled 67 Infants completers 64 Mother age: 23 y (6 y) Infant age: Born at 29 wks gestation (2 wks) Race of Mother: NR (100)	Inclusion Criteria: Preterm infants weighing between 748 and 1398 g at birth. They were eligible for this study when they had tolerated enteral intakes > 462 kJ/kg body weight/day for 5-7 days Exclusion Criteria: Need for mechanical ventilation at that time, intraventricular hemorrhage > grade 2, retinopathy of prematurity > stage 2, surgery for necrotizing enterocolitis, a weight less than the fifth percentile for gestational age, and a history of maternal substance abuse	Start time: Infants 25 days Duration: Infants 25 days - 9 months Arm 1: Placebo term and pre-term infant formulas Active ingredients: n-6: 19.1-33.2% of total FA Dose: Formula remained the infants' major source of nutrients and energy through at least 9 mo past expected term, but other foods were gradually added to the diet beginning at -4 mon past term Blinding: NR Total N-3: Preterm: 3% of total FA; term: 4.8% of total FA Arm 2: DHA-supplemented term and pre-term infant formulas Description: Marine oil replaced fat blend in commercial formulas Brand name: Similac Manufacturer: Ross Products Division Active ingredients: 18.7-32.6% of total FA Dose: Formula remained the infants' major source of nutrients and energy through at least	Outcome domain: Cognitive development Outcome: Fagan Test of Intelligence: average time/look (seconds) (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 1.18; SD (0.05) Arm 2: Sample size 33; mean 1.11; SD (0.05) Follow-up time: 6.5 months Arm 1: Sample size 34; mean 1.75; SD (0.06) Arm 2: Sample size 33; mean 1.62; SD (0.06) Follow-up time: 9 months Arm 1: Sample size 34; mean 1.3; SD (0.06) Arm 2: Sample size 33; mean 1.13; SD (0.05) Outcome: Fagan Test of Intelligence: looks to familiar (number) (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 18.8; SD (0.8) Arm 2: Sample size 33; mean 21.7; SD (0.8)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			9 mo past expected term, but other foods were gradually added to the diet beginning at -4 mon past term ALA: Preterm: 3.1% of total FA; Term: 4.9% of total FA DHA: 0.2% of total FA EPA: 0.3% of total FA Other dose 1: Preterm: 3.6% of total FA; term: 5.4% of total FA	Follow-up time: 6.5 months Arm 1: Sample size 34; mean 18.8; SD (1) Arm 2: Sample size 33; mean 22.1; SD (1) Follow-up time: 9 months Arm 1: Sample size 34; mean 18.2; SD (0.9) Arm 2: Sample size 33; mean 21.4; SD (0.9) Outcome: Fagan Test of Intelligence: looks to novel (number) (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 23.6; SD (0.8) Arm 2: Sample size 33; mean 26.0; SD (0.8) Follow-up time: 6.5 months Arm 1: Sample size 34; mean 22.2; SD (1) Arm 2: Sample size 33; mean 26.0; SD (1) Follow-up time: 9 months Arm 1: Sample size 34; mean 22.1; SD (0.9) Arm 2: Sample size 33; mean 25.2; SD (0.8) Outcome: Fagan Test of Intelligence: novel time (% of total) (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 64.6; SD (1.2) Arm 2: Sample size 33; mean 60.5; SD (1.3) Follow-up time: 6.5 months Arm 1: Sample size 34; mean 60.4; SD (1.4) Arm 2: Sample size 33; mean 59.8; SD (1.3) Follow-up time: 9 months

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Arm 1: Sample size 34; mean 62.2; SD (1.2) Arm 2: Sample size 33; mean 62.2; SD (1.2) Outcome: Fagan Test of Intelligence: time to familiar (seconds) (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 16.3; SD (0.8) Arm 2: Sample size 33; mean 19.3; SD (0.9) Follow-up time: 6.5 months Arm 1: Sample size 34; mean 26.6; SD (1.1) Arm 2: Sample size 33; mean 26.6; SD (1.1) Follow-up time: 9 months Arm 1: Sample size 34; mean 18.2; SD (1) Arm 2: Sample size 33; mean 18.3; SD (0.9) Outcome: Fagan Test of Intelligence: time to novel (seconds) (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 32.6; SD (1.2) Arm 2: Sample size 33; mean 31.9; SD (1.2) Follow-up time: 6.5 months Arm 1: Sample size 34; mean 45.3; SD (1.5) Arm 2: Sample size 33; mean 45.9; SD (1.5) Follow-up time: 9 months Arm 1: Sample size 34; mean 32.9; SD (1.3) Arm 2: Sample size 33; mean 32.6; SD

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(1.3) Outcome: Fagan Test of Intelligence: time/familiar look (seconds) (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 0.85; SD (0.05) Arm 2: Sample size 33; mean 0.91; SD (0.05) Follow-up time: 6.5 months Arm 1: Sample size 34; mean 1.42; SD (0.06) Arm 2: Sample size 33; mean 1.31; SD (0.06) Follow-up time: 9 months Arm 1: Sample size 34; mean 1.04; SD (0.06) Arm 2: Sample size 33; mean 0.91; SD (0.05) Outcome: Fagan Test of Intelligence: time/novel look (seconds) (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 1.43; SD (0.07) Arm 2: Sample size 33; mean 1.27; SD (0.07) Follow-up time: 6.5 months Arm 1: Sample size 34; mean 2.03; SD (0.09) Arm 2: Sample size 33; mean 1.88; SD (0.08) Follow-up time: 9 months Arm 1: Sample size 34; mean 1.51; SD (0.08) Arm 2: Sample size 33; mean 1.33; SD (0.07) Outcome: Fagan Test of Intelligence: total

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				looks (number) (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 42.4; SD (1.3) Arm 2: Sample size 33; mean 47.7; SD (1.4) Follow-up time: 6.5 months Arm 1: Sample size 34; mean 41.0; SD (1.7) Arm 2: Sample size 33; mean 48.2; SD (1.7) Follow-up time: 9 months Arm 1: Sample size 34; mean 40.3; SD (1.5) Arm 2: Sample size 33; mean 47.0; SD (1.5) Outcome: Fagan Test of Intelligence: total time (seconds) (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 48.9; SD (1.4) Arm 2: Sample size 33; mean 51.2; SD (1.4) Follow-up time: 6.5 months Arm 1: Sample size 34; mean 72.0; SD (1.8) Arm 2: Sample size 33; mean 72.6; SD (1.7) Follow-up time: 9 months Arm 1: Sample size 34; mean 51.1; SD (1.6) Arm 2: Sample size 33; mean 50.9; SD (1.5) Outcome domain: Visual function Outcome: number of total looks

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				(Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 38.4; SD (1.6) Arm 2: Sample size 33; mean 38.9; SD (1.7) Follow-up time: 6.5 months Arm 1: Sample size 34; mean 52.6; SD (2.1) Arm 2: Sample size 33; mean 56.3; SD (2) Follow-up time: 9 months Arm 1: Sample size 34; mean 39.1; SD (1.8) Arm 2: Sample size 33; mean 42.0; SD (1.8) Outcome: time/total looks (seconds) (Unspecified) Follow-up time: 12 months Arm 1: Sample size 34; mean 1.39; SD (0.06) Arm 2: Sample size 33; mean 1.34; SD (0.06) Follow-up time: 6.5 months Arm 1: Sample size 34; mean 2.01; SD (0.08) Arm 2: Sample size 33; mean 1.84; SD (0.07) Follow-up time: 9 month
Willatts et al., 2013[170] Study name: NR Study dates: 1992 Study design: Trial	Study Population: Healthy infants Infants enrolled 237 Infants completers 147 Infant age: birth	Inclusion Criteria: Healthy term singletons, 37-42 weeks gestation, 2500-4000g birthweight	Start time: Infants Birth to 1 week Duration: Infants 4 months Arm 1: Non-LC-PUFA Description: Control formula lacking LCPUFA Manufacturer: Milupa GmbH	Outcome domain: Cognitive development Outcome: Wechsler Preschool and Primary Scale of Intelligence: Full-Scale IQ (Secondary) Follow-up time: 6 year Arm 1: Sample size 76; mean 100.9; SD (16.2)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
randomized parallel Location: Italy, UK, Belgium Funding source / conflict: Industry Study follow-up: 6 years	Race of Mother: NR (100)	Exclusion Criteria: NR	Viability: g/100 g fat Dose: NR Blinding: NR ALA: 0.7 DHA: 0 AA: <0.10 Arm 2: LC-PUFA formula Manufacturer: Milupa GmbH Dose: NR ALA: 0.62 g/100g fat DHA: 0.21 g/100g fat AA: 0.35 g/100g fat	Arm 2: Sample size 71; mean 98.0; SD (14.8) Outcome: Wechsler Preschool and Primary Scale of Intelligence: Performance IQ (Secondary) Follow-up time: 6 year Arm 1: Sample size 76; mean 101.3; SD (15.5) Arm 2: Sample size 71; mean 99.6; SD (13.6) Outcome: Wechsler Preschool and Primary Scale of Intelligence: Verbal IQ (Secondary) Follow-up time: 6 year Arm 1: Sample size 76; mean 100.2; SD (16.4) Arm 2: Sample size 71; mean 97.3; SD (17.5)
Zhou et al., 2012[55] Study name: DOMInO Study dates: 10. 2005 - 01. 2008 Study design: Trial randomized parallel Location: Australia Funding source / conflict: Government, Multiple foundations and Societies, Manufacturer supplied product	Study Population: Healthy pregnant women Pregnant enrolled 2399 Race of Mother: White European (88%;88%) Asian (7%;8%) Inuit Eskimo (2%;1%) Other race/ethnicity (NR)	Inclusion Criteria: NR Exclusion Criteria: If already taking a dietary supplement containing DHA, their fetus had a known major abnormality, they had a bleeding disorder for which fish oil was contraindicated, they were receiving anticoagulant therapy, they had a documented history of drug or alcohol abuse,	Start time: Pregnant medium gestational age 19 weeks Duration: Pregnant birth Arm 1: control Description: 500-mg vegetable oil capsules Dose: 3*500mg 3 non-genetically modified oils (rapeseed, sunflower, and palm) in equal proportions Blinding: All capsules were similar in size, shape, and color Arm 2: DHA Description: DHA-rich fish oil Manufacturer: Incromega 500 TG; Croda Chemicals	Outcome domain: Birth weight Outcome: birth weight (g) (Secondary) Follow-up time: birth Arm 1: Sample size 1202; mean 3407.0; SD (576) Arm 2: Sample size 1197; mean 3475.0; SD (564) Outcome domain: Gestational hypertension preeclampsia eclampsia Outcome: preeclampsia (Secondary) Follow-up time: during pregnancy Arm 1: 58/1202 (4.85%) Arm 2: 60/1197 (4.97%) Outcome: pregnancy induced hypertension (Secondary) Follow-up time: during pregnancy

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Original, same study, or follow-up studies: Makrides, 2010[35]; Smithers, 2011[53]; Palmer, 2012[54]; Palmer, 2013[56]; Makrides, 2014[57]		they were participating in another fatty acid trial, or English was not the main language spoken at home	Dose: 3*500mg capsule DHA: 800 mg EPA: 100 mg	Arm 1: 107/1202 (8.88%) Arm 2: 98/1197 (8.18%) Outcome domain: Infants born small gestational age Outcome: SGA for weight (Secondary) Follow-up time: birth Arm 1: 82/1202 (6.83%) Arm 2: 73/1197 (6.13%) Outcome domain: LBW Outcome: birthweight <2500g (Secondary) Follow-up time: birth Arm 1: 63/1202 (5.27%) Arm 2: 41/1197 (3.41%)
de Jong et al., 2010[64] Study name: Groningen LCPUFA study Study dates: 1997-2008 Study design: Trial randomized parallel Location: Netherlands Funding source / conflict: Government Study follow-up: 9 years Original, same study, or follow-up studies: Bouwstra, 2003[62];	Study Population: Healthy infants Infants enrolled 474 Infants completers 341 Infant age: Gestational age 39.6 wk (1.3 weeks) NR Race of Mother: White European (100)	Inclusion Criteria: healthy term infants Exclusion Criteria: Infants who had a congenital disorder that interfered with adequate functioning in daily life, infants from multiple births, infants whose mothers did not have mastery of the Dutch language or suffered from significant illness or disability, adopted and foster infants, and formula-fed infants who had received human milk for >5 d.	Start time: Infants birth Duration: NR Arm 1: control group Description: standard formula Manufacturer: Zoetermeer, Netherlands Active ingredients: linoleic acid (11mol%); ALA 1.27 mol% Blinding: NR Arm 2: Omega 3 group Description: LCPUFA formula Brand name: Nutrilon Premium Manufacturer: Nutricia, Zoetermeer, The Netherlands Dose: NR DHA: 0·30 % (by weight) AA: 0·45 % (by weight)	Outcome domain: Neurological development Outcome: Touwen examination: neurologically normal (Unspecified) Follow-up time: 9 years Arm 1: 56/123 (46.0%) Arm 2: 44/91 (48.0%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
Bouwstra, 2005[63]; de Jong, 2012[65]; van Goor, 2010[36]; Goor, 2011[66]			Arm 3: Breast fed group Description: Breast feeding only - no formula	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
de Jong et al., 2012[65] Study name: Groningen LCPUFA study Study dates: Enrollment from February 1997 through October 1999, follow-up 9 years later Study design: Trial randomized parallel Location: Netherlands Funding source / conflict: Industry, Government, Some authors have received research funding from infant formula manufacturers Study follow-up: 9 years Original, same study, or follow-up studies: Bouwstra, 2003[62]; Bouwstra, 2005[63]; de Jong, 2010[64]; van Goor, 2010[36]; Goor, 2011[66]	Study Population: Healthy infants Infants enrolled 314 Infants completers 214 Mother age: 31 years (5 years) NR Infant age: birth (NA) NA Race of Mother: White European (100%)	Inclusion Criteria: healthy infants Exclusion Criteria: infants who had a congenital disorder that interfered with adequate functioning in daily life, infants from multiple births, infants whose mothers did not have mastery of the Dutch language or suffered from significant illness or disability, adopted and foster infants, and formula-fed infants who had received human milk for >5 d.	Start time: Infants birth Duration: Infants 2 months Arm 1: Control formula Description: Standard formula with no supplemental LCPUFA Brand name: Nutrilon premium Manufacturer: Nutricia, Zoetermeer, Netherlands Active ingredients: linoleic acid (11mol%); ALA 1.27 mol% Blinding: NR Maternal conditions Current smoker 23% during pregnancy Other maternal conditions 1arm_1_maternal_conditions_other1 Other maternal conditions 10 maternal hypertension 17% Arm 2: Omega 3 supplemented formula Description: LCPUFA formula Manufacturer: Nutricia, Zoetermeer, Netherlands Active ingredients: linoleic acid (11mol%); ALA 1.30 mol% Maternal conditions DHA: 0.30% by weight AA: 0.45% by weight Current smoker 32% during pregnancy Other maternal conditions 1arm_2_maternal_conditions_other1 Other maternal conditions 10 maternal hypertension 12%	Outcome domain: Cognitive development Reason results are not reported: No usable data. Outcome: (Secondary)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			Arm 3: breastfeeding comparison group Maternal conditions Current smoker 10% during pregnancy Other maternal conditions 1arm_3_maternal_conditions_other1 Other maternal conditions 10 maternal hypertension 9%	
van Goor et al., 2010[36] Study name: Groningen LCPUFA study Study dates: Enrollment from December 2004 until December 2006 Study design: Trial randomized parallel Location: Netherlands Funding source / conflict: Industry, Government Study follow-up: 12 weeks Original, same study, or follow-up studies: Bouwstra, 2003[62]; Bouwstra, 2005[63]; de Jong, 2010[64]; de Jong, 2012[65]; Goor, 2011[66]	Study Population: Healthy pregnant women Breast-feeding women Pregnant enrolled 183 Pregnant completers 125 Infants completers 119 Pregnant age: 32 years (5 years) Infant age: 14 to 20 weeks gestation Race of Mother: NR (100)	Inclusion Criteria: healthy women with a first or second low-risk singleton pregnancy Exclusion Criteria: women with vegetarian or vegan diets and women with diabetes mellitus	Start time: Pregnant 14 to 20 weeks gestation Infants 14 to 20 weeks gestation Duration: Pregnant until 3 months after delivery Infants until 3 months of age Arm 1: placebo Description: soybean oil capsule Manufacturer: Wuhan Alking Bioengineering Active ingredients: standard dose vitamins and minerals Dose: 2 capsules Maternal conditions ALA: 60 mg DHA: 0 EPA: 0 AA: 0 Other dose 1: LA 535 mg Current smoker 2% Arm 2: DHA group Description: DHA fish oil capsule Manufacturer: Wuhan Alking Bioengineering Active ingredients: standard dose vitamins and minerals Dose: 2 capsules Maternal conditions ALA: 32 mg	Outcome domain: Neurological development Outcome: general movements: number definitely abnormal (Secondary) Follow-up time: 12 weeks Arm 1: 0/36 (0.0%) Arm 2: 1/42 (2.38%) Arm 3: 0/41 (0.0%) Follow-up time: 2 weeks Arm 1: 1/36 (2.78%) Arm 2: 0/42 (0.0%) Arm 3: 0/41 (0.0%) Outcome: general movements: number mildly abnormal (Secondary) Follow-up time: 12 weeks Arm 1: 11/36 (30.56%) Arm 2: 25/42 (59.52%) Arm 3: 14/41 (34.15%) Follow-up time: 2 weeks Arm 1: 11/36 (30.56%) Arm 2: 20/42 (47.62%) Arm 3: 15/41 (36.59%) Outcome: general movements: number normal optimal (Secondary) Follow-up time: 12 weeks Arm 1: 2/36 (5.56%) Arm 2: 0/42 (0.0%) Arm 3: 1/41 (2.44%)

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
			DHA: 220 mg EPA: 34 mg AA: 15 mg Other dose 2: LA 274 mg Current smoker 2% Arm 3: DHA + AA group Description: DHA + AA capsule Brand name: Marinol D40 Manufacturer: Lipid Nutrition B.V., Wormerveer, The Netherlands Active ingredients: standard dose vitamins and minerals Dose: 2 capsules Maternal conditions ALA: 7 mg DHA: 220 mg EPA: 36 mg AA: 220 mg Other dose 2: LA 46 mg Current smoker 3%	Follow-up time: 2 weeks Arm 1: 1/36 (2.78%) Arm 2: 0/42 (0.0%) Arm 3: 1/41 (2.44%) Outcome: general movements: number normal suboptimal (Secondary) Follow-up time: 12 weeks Arm 1: 23/36 (63.89%) Arm 2: 16/42 (38.1%) Arm 3: 26/41 (63.41%) Follow-up time: 2 weeks Arm 1: 19/36 (52.78%) Arm 2: 17/42 (40.48%) Arm 3: 22/41 (53.66%) Outcome: neonatal neurological classification: number definitely abnormal (Secondary) Follow-up time: 2 weeks Arm 1: 0/36 (0.0%) Arm 2: 0/42 (0.0%) Arm 3: 0/41 (0.0%) Outcome: neonatal neurological classification: number mildly abnormal (Secondary) Follow-up time: 2 weeks Arm 1: 7/36 (19.44%) Arm 2: 6/42 (14.29%) Arm 3: 8/41 (19.51%) Outcome: neonatal neurological classification: number normal (Secondary) Follow-up time: 2 weeks Arm 1: 28/36 (77.78%) Arm 2: 35/42 (83.33%) Arm 3: 33/41 (80.49%) Outcome domain: duration of gestation

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Start time, Duration, Arms	Results
				Outcome: gestational age birth (weeks) (Secondary) Follow-up time: birth Arm 1: Sample size 36; mean 40.2; SD (1) Arm 2: Sample size 42; mean 40.2; SD (1.1) Arm 3: Sample size 41; mean 40.2; SD (1.1)

Appendix D. Evidence Table for Observational Studies

Table D1. Evidence table for observational studies

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Badart-Smook, et al., 1997[47] Study dates: NR Study design: Observational prospective Location: Netherlands Funding source / conflict: NR	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 610 Pregnant withdrawals 240 Pregnant completers 370 Pregnant age: 29 (4) Race of Mother: White European (100)	Inclusion Criteria: White race, intention to give birth to the baby in one of the three hospitals involved in the study Exclusion Criteria: Women with diastolic blood pressure of 90mm or higher, women suffering from any metabolic, cardiovascular, neurological, or renal disorder	Adjustments: Maternal(pregnancy) body weight, height, age, smoking habits, education, parity, and sex of the infant were included in each multiple regression model as possible confounding factors; except for the regression equation with gestational age as a dependent variable, gestational age at birth was also added as a confounder

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Badart-Smook 1997[47]	Birth weight N Total: 370		Sum of n-3 PUFAs+AA n-3 Measure: FFQ			
	Length of gestation N Total: 370		Sum of n-3 PUFAs+AA n-3 Measure: FFQ			

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Bakker, et al., 2003[163] Study name: Maastricht Essential Fatty Acid Birth (MEFAB) Cohort Study dates: Recruitment December 1990 to January 1994 Study design: Observational prospective Location: Netherlands Funding source / conflict: Government Follow-up: 7 years Original, same study, or follow-up studies: Bakker, 2009[134] and two articles in original report: Ghys, 2002 and Al, 1995	Study Population: Healthy infants Infants enrolled 750 Infants withdrawals 444 Infants completers 306 Pregnant age: 29.8 (4.1) Infant age: birth Race of Mother: White European (100)	Inclusion Criteria: 750 Caucasian children, 7 y old, born between December 1990 and January 1994 in the course of an earlier study on maternal and neonatal LCPUFA status and pregnancy outcome Exclusion Criteria: Not reported	Adjustments: Social class, maternal intelligence, parenting skills, maternal smoking and drinking habits during pregnancy, breastfeeding duration, and the child's sex, birth order and birthweight

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Bakker 2003[163]	Cognitive function K-ABC Mental	7 years	AA n-3 Measure: Umbilical plasma n-3 Units: %wt/wt	All	Coefficient Estimate: -0.223 95% CI(-1.051,-0.605)	
	Cognitive function K-ABC Mental N Total: 306	7 years	DHA n-3 Measure: Umbilical plasma n-3 Units: % wt/wt	All	Coefficient Estimate: -0.517 95% CI(-1.471, -0.437)	
	Cognitive function K-ABC Sequential	7 years	AA n-3 Measure: Umbilical plasma	All	Coefficient Estimate: 0.035 95% CI(-0.886, -0.956)	
	Cognitive function K-ABC Sequential	7 years	DHA n-3 Measure: Umbilical plasma	All	Coefficient Estimate: -0.072 95% CI(-1.104, – 0.960)	
	Cognitive function K-ABC Simultaneous	7 years	AA n-3 Measure: Umbilical plasma	All	Coefficient Estimate: -0.34 95% CI(-1.156, 0.476)	
	Cognitive function K-ABC Simultaneous	7 years	DHA n-3 Measure: Umbilical plasma	All	Coefficient Estimate: -0.61 95% CI(-1.557, -0.337)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Bakker, et al., 2009[134] Study dates: 12/90-1/94 Study design: Observational prospective Location: Netherlands Funding source / conflict: Government Follow-up: 7 years Original, same study, or follow-up studies: Bakker, 2003[80] and two articles in original report: Ghys, 2002 and Al, 1995	Study Population: Healthy infants Infants enrolled 750 Infants withdrawals 444 Infants completers 306 Pregnant age: 29.8 (4.1) Infant age: gestational age: boys: 39.8; girls 40.0 (boys 1.7; girls 1.4) Race of Mother: White European (100)	Inclusion Criteria: 750 Caucasian children of 7 y old, born between December 1990 and January 1994 in the course of an earlier study on maternal and neonatal LCPUFA status and pregnancy outcome Exclusion Criteria: Not reported	Adjustments: Gender, cognitive function, gestational age, age at measurement

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Bakker 2009[134]	Maastricht Motor test quality score N Total: 306	7 years	AA n-3 Measure: Umbilical plasma n-3 Units: %wt/wt		Coefficient	P value: P=0.052
	Maastricht Motor test quality score N Total: 306	7 years	DHA n-3 Measure: Umbilical plasma n-3 Units: %wt/wt		Coefficient	P value: P=0.01
	Maastricht Motor test quantity score N Total: 306	7 years	AA n-3 Measure: Umbilical plasma n-3 Units: %wt/wt		Coefficient	P value: P=0.78
	Maastricht Motor test quantity score N Total: 306	7 years	DHA n-3 Measure: Umbilical plasma n-3 Units: %wt/wt		Coefficient	P value: P=0.30
	Maastricht Motor test total score N Total: 306	7 years	AA n-3 Measure: Umbilical plasma n-3 Units: %wt/wt		Coefficient	P value: P=0.069
	Maastricht Motor test total score N Total: 306	7 years	DHA n-3 Measure: Umbilical plasma n-3 Units: %wt/wt		Coefficient	P value: P=0.01

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Bernard, et al., 2013[89] Study name: EDEN Study dates: Recruitment 2003 to 2005 Study design: Observational prospective Location: NR Funding source / conflict: Industry, Government Follow-up: 2 and 3 years Original, same study, or follow-up studies: Drouillet, 2009[80]	Study Population: Healthy pregnant women Pregnant enrolled 2,002 Pregnant completers 1,882 Infants enrolled 1.882 Infants completers 1,510 Pregnant age: 29.2 years (at conception) (4.8 years) NR Infant age: < 24 weeks gestation (NR) NR Race of Mother: NR (100)	Inclusion Criteria: < 24 weeks amenorrhea Exclusion Criteria: multiple pregnancies, known diabetes before pregnancy, illiteracy, and intention to move outside the region in the next 3 years	Adjustments: Center, child gender & age, gestational age, maternal age, obesity, energy intake, tobacco & alcohol consumption, parental education & income, first born, main daytime caregiver, and frequency of maternal stimulations

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Bernard, 2013[89]	Ages and Stages Questionnaire - Breastfed children N Total: 786	3 years	(LC)PUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -0.19 95% CI(-0.76, 0.38)	P value: 0.51
	Ages and Stages Questionnaire - Breastfed children N Total: 786	3 years	AA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -0.09 95% CI(-29.53, 29.35)	P value: 1
	Ages and Stages Questionnaire - Breastfed children N Total: 786	3 years	ALA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 3.29 95% CI(-8.41, 14.99)	P value: 0.58
	Ages and Stages Questionnaire - Breastfed children N Total: 786	3 years	DHA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 7.48 95% CI(-10.51, 25.47)	P value: 0.42
	Ages and Stages Questionnaire - Breastfed children N Total: 786	3 years	EPA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 15.28 95% CI(-18.63, 49.19)	P value: 0.38
	Ages and Stages Questionnaire - Breastfed children N Total: 786	3 years	LA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -0.23 95% CI(-0.82, 0.36)	P value: 0.45
	Ages and Stages Questionnaire - Breastfed children N Total: 786	3 years	n-3 LCPUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 3.61 95% CI(-4.17, 11.39)	P value: 0.36
	Ages and Stages Questionnaire - Breastfed children N Total: 786	3 years	n-6 LCPUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -0.22 95% CI(-0.81, 0.37)	P value: 0.45
	Ages and Stages Questionnaire - Breastfed children N Total: 786	3 years	n-6:n-3 n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -0.63 95% CI(-1.39, 0.13)	P value: 0.11

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Ages and Stages Questionnaire - Never-breastfed children N Total: 270	3 years	(LC)PUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -1.33 95% CI(-2.58, -0.08)	P value: 0.04
	Ages and Stages Questionnaire - Never-breastfed children N Total: 270	3 years	AA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -104.25 95% CI(-162.11, -46.39)	P value: 0.001
	Ages and Stages Questionnaire - Never-breastfed children N Total: 270	3 years	ALA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -2.39 95% CI(-31.22, 26.44)	P value: 0.87
	Ages and Stages Questionnaire - Never-breastfed children N Total: 270	3 years	DHA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -1.77 95% CI(-49.10, 45.56)	P value: 0.94
	Ages and Stages Questionnaire - Never-breastfed children N Total: 270	3 years	EPA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 24.51 95% CI(-60.08, 109.10)	P value: 0.57
	Ages and Stages Questionnaire - Never-breastfed children N Total: 270	3 years	LA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -1.34 95% CI(-2.65, -0.03)	P value: 0.05
	Ages and Stages Questionnaire - Never-breastfed children N Total: 270	3 years	n-3 LCPUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -2.43 95% CI(-21.52, 16.66)	P value: 0.8
	Ages and Stages Questionnaire - Never-breastfed children N Total: 270	3 years	n-6 LCPUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -1.37 95% CI(-2.68, -0.06)	P value: 0.04
	Ages and Stages Questionnaire - Never-breastfed children N Total: 270	3 years	n-6:n-3 n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -1.52 95% CI(-3.01, -0.03)	P value: 0.05
	Communicative Development Inventory - Never-breastfed children N Total: 309	3 years	(LC)PUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -1.13 95% CI(-2.21, -0.05)	P value: 0.04
	Communicative Development Inventory - Never-breastfed children N Total: 309	3 years	AA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -33.93 95% CI(-83.64, 15.78)	P value: 0.18
	Communicative Development Inventory - Never-breastfed children N Total: 309	3 years	ALA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 13.84 95% CI(-10.21, 37.89)	P value: 0.26
	Communicative Development Inventory - Never-breastfed children N Total: 309	3 years	DHA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 6.14 95% CI(-32.79, 45.07)	P value: 0.76
	Communicative Development Inventory - Never-breastfed children N Total: 309	3 years	EPA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 13.98 95% CI(-57.56, 85.52)	P value: 0.7
	Communicative Development Inventory - Never-breastfed children N Total: 309	3 years	LA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -1.23 95% CI(-2.37, -0.09)	P value: 0.03
	Communicative Development Inventory - Never-breastfed children N Total: 309	3 years	n-3 LCPUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 7.02 95% CI(-9.13, 23.17)	P value: 0.39

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Communicative Development Inventory - Never-breastfed children N Total: 309	3 years	n-6 LCPUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -1.24 95% CI(-2.36, -0.12)	P value: 0.03
	Communicative Development Inventory - Never-breastfed children N Total: 309	3 years	n-6:n-3 n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -2.13 95% CI(-3.40, -0.86)	P value: 0.001
	Communicative Development Inventory -Breastfed children N Total: 901	3 years	(LC)PUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 0.23 95% CI(-0.34, 0.80)	P value: 0.43
	Communicative Development Inventory -Breastfed children N Total: 901	3 years	AA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 6.29 95% CI(-22.56, 35.14)	P value: 0.67
	Communicative Development Inventory -Breastfed children N Total: 901	3 years	ALA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -2.77 95% CI(-14.65, 9.11)	P value: 0.65
	Communicative Development Inventory -Breastfed children N Total: 901	3 years	DHA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -3.63 95% CI(-21.72, 14.46)	P value: 0.69
	Communicative Development Inventory -Breastfed children N Total: 901	3 years	EPA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -8.55 95% CI(-42.77, 25.67)	P value: 0.62
	Communicative Development Inventory -Breastfed children N Total: 901	3 years	LA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 0.25 95% CI(-0.34, 0.84)	P value: 0.4
	Communicative Development Inventory -Breastfed children N Total: 901	3 years	n-3 LCPUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -2.23 95% CI(-10.07, 5.61)	P value: 0.58
	Communicative Development Inventory -Breastfed children N Total: 901	3 years	n-6 LCPUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 0.25 95% CI(-0.34, 0.84)	P value: 0.4
	Communicative Development Inventory -Breastfed children N Total: 901	3 years	n-6:n-3 n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 0.38 95% CI(-0.40, 1.16)	P value: 0.34
	Motor ability N Total: 257	3 years	(LC)PUFAs n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 0.17 95% CI(-0.6924, 1.0324)	
	Motor ability N Total: 257	3 years	AA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 5.07 95% CI(3.8744, 6.2656)	
	Motor ability N Total: 257	3 years	ALA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -1.3 95% CI(-2.8288, 0.2288)	
	Motor ability N Total: 257	3 years	DHA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -4.35 95% CI(-5.526, -3.174)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Motor ability N Total: 257	3 years	EPA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -10.55 95% CI(-11.4908, -9.6092)	
	Motor ability N Total: 257	3 years	LA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 0.17 95% CI(-0.6924, 1.0324)	
	Motor ability N Total: 257	3 years	n-3 LCPUFAs n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -1.72 95% CI(-2.896, -0.544)	
	Motor ability N Total: 257	3 years	n-6 LCPUFAs n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 0.17 95% CI(-0.6728, 1.0128)	
	Motor ability N Total: 257	3 years	n-6:n-3 n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 0.49 95% CI(0.3724, 0.6076)	
	Motor ability N Total: 746	3 years	(LC)PUFAs n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 0.1 95% CI(-0.1156, 0.3156)	
	Motor ability N Total: 746	3 years	AA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -7.67 95% CI(-19.3124, 3.9724)	
	Motor ability N Total: 746	3 years	ALA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 0.29 95% CI(-4.4336, 5.0136)	
	Motor ability N Total: 746	3 years	DHA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -3.26 95% CI(-10.5316, 4.0116)	
	Motor ability N Total: 746	3 years	EPA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -9.8 95% CI(-23.5004, 3.9004)	
	Motor ability N Total: 746	3 years	LA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 0.12 95% CI(-0.1152, 0.3552)	
	Motor ability N Total: 746	3 years	n-3 LCPUFAs n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -1.11 95% CI(-4.2264, 2.0064)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Motor ability N Total: 746	3 years	n-6 LCPUFAs n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 0.12 95% CI(-0.1152, 0.3552)	
	Motor ability N Total: 746	3 years	n-6:n-3 n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 0.3 95% CI(-0.0136, 0.6136)	
	Neurological development N Total: 270	3 years	AA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -104.25 95% CI(-162.1092, -46.3908)	
	Neurological development N Total: 270	3 years	AA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -104.25 95% CI(-162.1092, -46.3908)	
	Neurological development N Total: 270	3 years	ALA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -2.39 95% CI(-31.2216, 26.4416)	
	Neurological development N Total: 270	3 years	ALA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -2.39 95% CI(-31.2216, 26.4416)	
	Neurological development N Total: 270	3 years	DHA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -1.77 95% CI(-49.104, 45.564)	
	Neurological development N Total: 270	3 years	DHA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -1.77 95% CI(-49.104, 45.564)	
	Neurological development N Total: 270	3 years	EPA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 24.51 95% CI(-60.0836, 109.1036)	
	Neurological development N Total: 270	3 years	EPA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 24.51 95% CI(-60.0836, 109.1036)	
	Neurological development N Total: 270	3 years	LA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -1.34 95% CI(-2.6532, -0.0267999999999999)	
	Neurological development N Total: 270	3 years	LA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -1.34 95% CI(-2.6532, -0.0267999999999999)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Neurological development N Total: 270	3 years	LCPUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -1.33 95% CI(-2.5844, -0.0756000000000001)	
	Neurological development N Total: 270	3 years	LCPUFAs n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -1.33 95% CI(-2.5844, -0.0756000000000001)	
	Neurological development N Total: 270	3 years	n-3 LCPUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -2.43 95% CI(-21.5204, 16.6604)	
	Neurological development N Total: 270	3 years	n-3 LCPUFAs n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -2.43 95% CI(-21.5204, 16.6604)	
	Neurological development N Total: 270	3 years	n-6 LCPUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -1.37 95% CI(-2.6832, -0.0568)	
	Neurological development N Total: 270	3 years	n-6 LCPUFAs n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -1.37 95% CI(-2.6832, -0.0568)	
	Neurological development N Total: 270	3 years	n-6:n-3 n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -1.52 95% CI(-3.0096, -0.0304)	
	Neurological development N Total: 270	3 years	n-6:n-3 n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -1.52 95% CI(-3.0096, -0.0304)	
	Neurological development N Total: 309	2 years	AA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -33.93 95% CI(-83.6356, 15.7756)	
	Neurological development N Total: 309	2 years	AA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -33.93 95% CI(-83.6356, 15.7756)	
	Neurological development N Total: 309	2 years	ALA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 13.84 95% CI(-10.2092, 37.8892)	
	Neurological development N Total: 309	2 years	ALA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 13.84 95% CI(-10.2092, 37.8892)	
	Neurological development N Total: 309	2 years	DHA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 6.14 95% CI(-32.7856, 45.0656)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Neurological development N Total: 309	2 years	DHA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 6.14 95% CI(-32.7856, 45.0656)	
	Neurological development N Total: 309	2 years	EPA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 13.98 95% CI(-57.56, 85.52)	
	Neurological development N Total: 309	2 years	EPA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 13.98 95% CI(-57.56, 85.52)	
	Neurological development N Total: 309	2 years	LA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -1.23 95% CI(-2.3668, -0.0932000000000002)	
	Neurological development N Total: 309	2 years	LA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -1.23 95% CI(-2.3668, -0.0932000000000002)	
	Neurological development N Total: 309	2 years	LCPUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -1.13 95% CI(-2.208, -0.0519999999999998)	
	Neurological development N Total: 309	2 years	LCPUFAs n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -1.13 95% CI(-2.208, -0.0519999999999998)	
	Neurological development N Total: 309	2 years	n-3 LCPUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 7.02 95% CI(-9.1304, 23.1704)	
	Neurological development N Total: 309	2 years	n-3 LCPUFAs n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 7.02 95% CI(-9.1304, 23.1704)	
	Neurological development N Total: 309	2 years	n-6 LCPUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -1.24 95% CI(-2.3572, -0.1228)	
	Neurological development N Total: 309	2 years	n-6 LCPUFAs n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -1.24 95% CI(-2.3572, -0.1228)	
	Neurological development N Total: 309	2 years	n-6:n-3 n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -2.13 95% CI(-3.404, -0.856)	
	Neurological development N Total: 309	2 years	n-6:n-3 n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -2.13 95% CI(-3.404, -0.856)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Neurological development N Total: 786	3 years	AA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -0.09 95% CI(-29.5292, 29.3492)	
	Neurological development N Total: 786	3 years	AA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -0.09 95% CI(-29.5292, 29.3492)	
	Neurological development N Total: 786	3 years	ALA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 3.29 95% CI(-8.4112, 14.9912)	
	Neurological development N Total: 786	3 years	ALA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 3.29 95% CI(-8.4112, 14.9912)	
	Neurological development N Total: 786	3 years	DHA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 7.48 95% CI(-10.5128, 25.4728)	
	Neurological development N Total: 786	3 years	DHA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 7.48 95% CI(-10.5128, 25.4728)	
	Neurological development N Total: 786	3 years	EPA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 15.28 95% CI(-18.628, 49.188)	
	Neurological development N Total: 786	3 years	EPA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 15.28 95% CI(-18.628, 49.188)	
	Neurological development N Total: 786	3 years	LA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -0.23 95% CI(-0.818, 0.358)	
	Neurological development N Total: 786	3 years	LA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -0.23 95% CI(-0.818, 0.358)	
	Neurological development N Total: 786	3 years	LCPUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -0.19 95% CI(-0.7584, 0.3784)	
	Neurological development N Total: 786	3 years	LCPUFAs n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -0.19 95% CI(-0.7584, 0.3784)	
	Neurological development N Total: 786	3 years	n-3 LCPUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 3.61 95% CI(-4.1712, 11.3912)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Neurological development N Total: 786	3 years	n-3 LCPUFAs n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 3.61 95% CI(-4.1712, 11.3912)	
	Neurological development N Total: 786	3 years	n-6 LCPUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -0.22 95% CI(-0.808, 0.368)	
	Neurological development N Total: 786	3 years	n-6 LCPUFAs n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -0.22 95% CI(-0.808, 0.368)	
	Neurological development N Total: 786	3 years	n-6:n-3 n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -0.63 95% CI(-1.3944, 0.1344)	
	Neurological development N Total: 786	3 years	n-6:n-3 n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -0.63 95% CI(-1.3944, 0.1344)	
	Neurological development N Total: 901	2 years	AA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 6.29 95% CI(-22.5612, 35.1412)	
	Neurological development N Total: 901	2 years	AA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 6.29 95% CI(-22.5612, 35.1412)	
	Neurological development N Total: 901	2 years	ALA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -2.77 95% CI(-14.6476, 9.1076)	
	Neurological development N Total: 901	2 years	ALA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -2.77 95% CI(-14.6476, 9.1076)	
	Neurological development N Total: 901	2 years	DHA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -3.63 95% CI(-21.7208, 14.4608)	
	Neurological development N Total: 901	2 years	DHA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -3.63 95% CI(-21.7208, 14.4608)	
	Neurological development N Total: 901	2 years	EPA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -8.55 95% CI(-42.7716, 25.6716)	
	Neurological development N Total: 901	2 years	EPA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -8.55 95% CI(-42.7716, 25.6716)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Neurological development N Total: 901	2 years	LA n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 0.25 95% CI(-0.338, 0.838)	
	Neurological development N Total: 901	2 years	LA n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 0.25 95% CI(-0.338, 0.838)	
	Neurological development N Total: 901	2 years	LCPUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 0.23 95% CI(-0.3384, 0.7984)	
	Neurological development N Total: 901	2 years	LCPUFAs n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 0.23 95% CI(-0.3384, 0.7984)	
	Neurological development N Total: 901	2 years	n-3 LCPUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: -2.23 95% CI(-10.07, 5.61)	
	Neurological development N Total: 901	2 years	n-3 LCPUFAs n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: -2.23 95% CI(-10.07, 5.61)	
	Neurological development N Total: 901	2 years	n-6 LCPUFAs n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 0.25 95% CI(-0.338, 0.838)	
	Neurological development N Total: 901	2 years	n-6 LCPUFAs n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 0.25 95% CI(-0.338, 0.838)	
	Neurological development N Total: 901	2 years	n-6:n-3 n-3 Measure: FFQ n-3 Units: g/d		Coefficient Estimate: 0.38 95% CI(-0.404, 1.164)	
	Neurological development N Total: 901	2 years	n-6:n-3 n-3 Measure: Maternal food frequency questionnaire n-3 Units: g/d	All	Coefficient Estimate: 0.38 95% CI(-0.404, 1.164)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Bouwstra, et al., 2006[133] Study dates: 1997-1999 Study design: NR Location: Netherlands Funding source / conflict: Industry Follow-up: 3 months Original, same study, or follow-up studies: Bouwstra, 2003[62]	Study Population: Healthy infants Infants enrolled 317 Infants completers 269 Pregnant age: 30 (4.3) Infant age: 3 months (NR) Race of Mother: White European (100)	Inclusion Criteria: All infants were born at 37–42 wk of gestation, had a native West European origin, and were born between February 1997 and October 1999. Exclusion Criteria: children with a congenital disorder interfering with adequate functioning in daily life, children from multiple births, children whose mother did not master the Dutch language or had significant illness or disability, and adopted and fostered children	Adjustments: Type of postnatal feeding and potential confounders such as the postnatal age of the infant at GM assessment, paternal smoking, and the total Obstetric Optimality Score

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Bouwstra 2003[133]	General movement (mildly abnormal) N Total: 269	3 months	AA n-3 Measure: umbilical artery	All	Standardized coefficients Estimate: 0.81 95% CI(0.68, 0.98)	
	General movement (mildly abnormal) N Total: 269	3 months	DHA deficiency index n-3 Measure: umbilical artery	All	Standardized coefficients Estimate: 2 95% CI(0.73, 5.2)	
	General movement (mildly abnormal) N Total: 269	3 months	DHA n-3 Measure: umbilical artery	All	Standardized coefficients Estimate: 0.74 95% CI(0.48, 1.1)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Brantsaeter, et al., 2012[81] Study name: Norwegian Mother and Child Cohort Study (MoBa) Study dates: 2002-2009 Study design: Observational prospective Location: Norway Funding source / conflict: Government	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 76218 Pregnant completers 62099 Race of Mother: NR	Inclusion Criteria: first participation for women with multiple participation in MoBa and women with singleton births. Exclusion Criteria: participants with a pregnancy duration <28 weeks or >42 weeks (n=628), if the birth weight of the baby had not been recorded or if the birth weight was, <600 g (n = 35). We also excluded participants who had not given birth to a live baby (n 153). Lastly, we excluded women having improbable energy intakes, i.e. energy intake , >4·5 MJ or .<20 MJ (n 1063)	Adjustments: Adjusted for maternal age, height, pre-pregnant BMI, parity, pregnancy duration, maternal education, smoking status, mother tongue other than Norwegian and total energy intake, and with intakes of seafood/seafood items and supplementary n-3 mutually adjusted

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Brantsaeter 2012[81]	Birth weight N Total: 61387		n-3 supplement n-3 Measure: FFQ n-3 Units: g/day	0 (No) N Quantile: NR N Cases: NR		
	Birth weight N Total: 61387		n-3 supplement n-3 Measure: FFQ n-3 Units: g/day	0.40 - 6.9 N Quantile: NR N Cases: NR	0.74 95% CI(-7.6, 9.07)	
	Birth weight N Total: 61387		n-3 supplement n-3 Measure: FFQ n-3 Units: g/day	< 0.39 N Quantile: NR N Cases: NR	-2.03 95% CI(-10.4, 6.29)	
	Birth weight N Total: 61387		n-3 supplement n-3 Measure: FFQ n-3 Units: g/day	Per g increase N Quantile: NR N Cases: NR	Coefficient Estimate: 0.53 95% CI(-3.25, 4.31)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Chong, et al., 2015[95] Study dates: 2009-2010 Study design: Observational prospective Location: NR Funding source / conflict: Industry, Government Follow-up: 3 months postpartum	Study Population: Healthy pregnant women Postpartum women Pregnant enrolled 997 Pregnant completers 698 Pregnant age: NR (NR) Race of Mother: Asian (100)	Inclusion Criteria: Within range of 18-50 years, recruited from 2 major public maternity units in NUH and KKH. Were Singaporean citizens or permanent resident of Chinese, Malay, Indian ethnicity with parents of homogeneous ethnic background, with the intention to deliver in the two hospitals and residing in Singapore for next 5 years and willing to donate birth tissues including cord, placenta, cord blood at delivery Exclusion Criteria: pre-existing health conditions such as type 1 diabetes, depression, or mental health related disorders self-reported during recruitment	Adjustments: Adjusted for ethnicity, parity, education level, marital status, maternal body mass index at 26-28 week's gestation, maternal age, employment status, obstetric and neonatal complications, smoking status and smoke exposure before and during pregnancy, alcohol consumption before and during pregnancy, history of abortion, miscarriage, stillbirth, exercise frequency, and reported fish oil supplementation

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Chong 2015[95]	Antenatal and Postpartum Depression N Total: 698	26- 28 wk	Log plasma AA:DHA ratio n-3 Measure: Maternal	All N Quantile: na N Cases: na	OR Estimate: 1.05 95% CI(0.08, 13.44)	
	Antenatal and Postpartum Depression N Total: 698	26- 28 wk	Log plasma AA:DPA ratio n-3 Measure: Maternal	All N Quantile: na N Cases: na	OR Estimate: 1.65 95% CI(0.12, 23.39)	
	Antenatal and Postpartum Depression N Total: 698	26- 28 wk	Log plasma AA:EPA ratio n-3 Measure: Maternal	All N Quantile: na N Cases: na	OR Estimate: 1.38 95% CI(0.31, 6.18)	
	Antenatal and Postpartum Depression N Total: 698	26- 28 wk	Log plasma total omega-3 n-3 Measure: Maternal n-3 Units: ug/ml	All N Quantile: na N Cases: na	OR Estimate: 1.4 95% CI(0.29, 6.73)	
	Antenatal and Postpartum Depression N Total: 698	3 month postpartum	Log plasma AA:DHA ratio n-3 Measure: Maternal	All N Quantile: na N Cases: na	OR Estimate: 0.74 95% CI(0.08, 6.69)	
	Antenatal and Postpartum Depression N Total: 698	3 month postpartum	Log plasma AA:DPA ratio n-3 Measure: Maternal	All N Quantile: na N Cases: na	OR Estimate: 3.81 95% CI(0.39, 37.06)	
	Antenatal and Postpartum Depression N Total: 698	3 month postpartum	Log plasma AA:EPA ratio n-3 Measure: Maternal	All N Quantile: na N Cases: na	OR Estimate: 0.54 95% CI(0.16, 1.85)	
	Antenatal and Postpartum Depression N Total: 698	3 month postpartum	Log plasma total omega-4 n-3 Measure: Maternal n-3 Units: ug/ml	All N Quantile: na N Cases: na	OR Estimate: 1.48 95% CI(0.40, 5055)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Clausen, et al., 2001[68] Study dates: 12/94-8/96 Study design: Observational prospective Location: Norway Funding source / conflict: NR	Study Population: Healthy pregnant women Pregnant enrolled 3,771 Pregnant completers 3,133 Pregnant age: 29.8 (4.5) Race of Mother: White European (100)	Inclusion Criteria: Caucasian women seen at Aker University Hospital for prenatal care and who agreed to undergo ultrasound at their first prenatal visit and who completed a FFQ Exclusion Criteria: Pregestational diabetes, abortion, twin or triplet pregnancies, patients who give birth at other hospitals, missing records, loss to follow-up	Adjustments: Age, smoking (yes or no), BMI (<=20, 20-25, 25-30, >30), systolic blood pressure before 20 weeks' gestation, and nullipara (yes or no)

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Clausen 2001[68]	Preeclampsia N Total: 3133		n-3 fatty acids n-3 Measure: FFQ n-3 Units: Energy %	T1 <=0.9 N Cases: 39	OR	
	Preeclampsia N Total: 3133		n-3 fatty acids n-3 Measure: FFQ n-3 Units: Energy %	T2 0.9 - 1.6 N Cases: 35	OR Estimate: 1.4 95% CI(0.9, 2.3)	
	Preeclampsia N Total: 3133		n-3 fatty acids n-3 Measure: FFQ n-3 Units: Energy %	T3 >1.6 N Cases: 11	OR Estimate: 1.9 95% CI(0.9, 3.8)	
	Preeclampsia N Total: 3133		n-6 fatty acids n-3 Measure: FFQ n-3 Units: Energy %	T1 <=3.8 N Cases: 34	OR	
	Preeclampsia N Total: 3133		n-6 fatty acids n-3 Measure: FFQ n-3 Units: Energy %	T2 3.8 - 5.8 N Cases: 38	OR Estimate: 1.5 95% CI(0.9, 2.4)	
	Preeclampsia N Total: 3133		n-6 fatty acids n-3 Measure: FFQ n-3 Units: Energy %	T3 >5.8 N Cases: 13	OR Estimate: 2.2 95% CI(1.1, 4.4)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Dirix, et al., 2009[84] Study name: Maastricht Essential Fatty Acid Birth (MEFAB) Cohort Study dates: 1990-1997 Study design: Observational prospective Location: Netherlands Funding source / conflict: Government	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 1238 Pregnant completers 782 Infants enrolled 1238 Infants completers 782 Pregnant age: 29.0 26.2-31.7 Infant age: 40.1 wk 39.3-41.0 Race of Mother: White European (100)	Inclusion Criteria: gestational age of <16 weeks at study entry, singleton pregnancy, Caucasian race, diastolic blood pressure, 90 mmHg and the absence of any metabolic, cardiovascular, neurological or renal disorder at the time of recruitment Exclusion Criteria: excluded if infants were born preterm (gestational age < 37 weeks,), mothers had diabetes or developed pregnancy-induced hypertension, mothers had reported specific health problems in the past (e.g. diabetes mellitus, hypertension and heart, kidney, liver, gall bladder or thyroid gland disorders, one or both parents were non-Caucasians or values for any of the afore-mentioned exclusion criteria were missing. The mother – infant pairs were also excluded if fatty acid analyses were not reported or values were missing for birth weight, birth length and head circumference	Adjustments: Infant sex, gestational age, maternal height

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Dirix 2009[84]	Birth weight N Total: 782		DHA @ 16 weeks n-3 Measure: Maternal plasma phospholipids n-3 Units: per %, w/w plasma phospholipids increase	N Quantile: 665 N Cases: NR	Coefficient Estimate: 52.1 95% CI(20.4, 83.8)	
	Birth weight N Total: 782		DHA @ 22 weeks n-3 Measure: Maternal plasma phospholipids n-3 Units: per %, w/w plasma phospholipids increase	N Quantile: 623 N Cases: NR	Coefficient Estimate: 31.18 95% CI(-4.301, 66.67)	
	Birth weight N Total: 782		DHA @ 32 weeks n-3 Measure: Maternal plasma phospholipids n-3 Units: per %, w/w plasma phospholipids increase	N Quantile: 644 N Cases: NR	Coefficient Estimate: 33.08 95% CI(-5.699, 71.86)	
	Birth weight N Total: 782		DHA @ delivery n-3 Measure: Maternal plasma phospholipids n-3 Units: per %, w/w plasma phospholipids increase	N Quantile: 608 N Cases: NR	Coefficient Estimate: 3.423 95% CI(-34.95, 41.8)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Drouillet, et al., 2009[80] Study name: EDEN Study dates: February 2003 - September 2003 Study design: Observational prospective Location: NR Funding source / conflict: Industry, Government, Multiple foundations and Societies Original, same study, or follow-up studies: Bernard, 2013[89]	Study Population: Healthy pregnant women Pregnant enrolled 2002 Pregnant completers 1446 Pregnant age: 29.2 (4.8) Race of Mother: NR	Inclusion Criteria: NR Exclusion Criteria: twin pregnancies, known diabetes before pregnancy, not being able to speak and read French, and planned moving away from the region	Adjustments: Centre, mother's age and height, smoking habits, parity, gestational age, newborn's sex, delay between birth and anthropometric measures, and BMI

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Drouillet 2009[80]	Birth weight N Total: 1446		Increase of 1 SD of the intake consumed per d n-3 Measure: FFQ n-3 Units: n-3 FA (% PUFA intake)		Coefficient Estimate: 6.4 95% CI(NR)	P value: P=0.54

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Guxens, et al., 2011[144] Study name: INMA Study dates: Recruitment: July 2004 to July 2006 Follow-up: 14 months Study design: Observational prospective Location: Spain Funding source / conflict: Government, Multiple foundations and Societies Follow-up: 14 months Original, same study, or follow-up studies: Julvez, 2014[143]	Study Population: Healthy infants Breast-feeding women Pregnant enrolled 657 Pregnant completers 622 Lactating enrolled 622 Lactating completers 582 Infants enrolled 622 Infants completers 582 (319 with LCPUFA data) Lactating enrolled 622 Lactating completers 582 Lactating age: 31.6 years (4.2 years) Infant age: 2 to 5 days postpartum Race of Mother: NR (NR)	Inclusion Criteria: age older than 16 years, intent to deliver at the reference hospital, singleton pregnancy Exclusion Criteria: no problems of communication, no assisted conception	Adjustments: Child's age, maternal and paternal: education, social class, attachment to child, mental health; maternal age, maternal alcohol use during pregnancy, use of gas stove, child age of food introduction

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Guxens, 2011[144]	Cognitive Development N Total: 504	14 months	ALA n-3 Measure: Biomarker (colostrum) n-3 Units: weight (%)	High versus low levels dichotomized at median	Coefficient Estimate: 1.25 95% CI(-1.43, 3.93)	
	Cognitive Development N Total: 504	14 months	ALA n-3 Measure: Biomarker (colostrum) n-3 Units: weight (%)	Sample divided into only 2 groups - High vs Low levels	Coefficient Estimate: 1.25 95% CI(-1.43, 3.93)	
	Cognitive Development N Total: 504	14 months	DHA n-3 Measure: Biomarker (colostrum) n-3 Units: weight (%)	High versus low levels dichotomized at median	Coefficient Estimate: 0.58 95% CI(-2.08, 3.23)	
	Cognitive Development N Total: 504	14 months	DHA n-3 Measure: Biomarker (colostrum) n-3 Units: weight (%)	Sample divided into only 2 groups - High vs Low levels	Coefficient Estimate: 0.58 95% CI(-2.08, 3.23)	
	Cognitive Development N Total: 504	14 months	DPA n-3 Measure: Biomarker (colostrum) n-3 Units: weight (%)	High versus low levels dichotomized at median	Coefficient Estimate: 1.35 95% CI(-1.39, 4.08)	
	Cognitive Development N Total: 504	14 months	DPA n-3 Measure: Biomarker (colostrum) n-3 Units: weight (%)	Sample divided into only 2 groups - High vs Low levels	Coefficient Estimate: 1.35 95% CI(-1.39, 4.08)	
	Cognitive Development N Total: 504	14 months	EPA n-3 Measure: Biomarker (colostrum) n-3 Units: weight (%)	High versus low levels dichotomized at median	Coefficient Estimate: 0.63 95% CI(-2.18, 3.44)	
	Cognitive Development N Total: 504	14 months	EPA n-3 Measure: Biomarker (colostrum) n-3 Units: weight (%)	Sample divided into only 2 groups - High vs Low levels	Coefficient Estimate: 0.63 95% CI(-2.18, 3.44)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Cognitive Development N Total: 504	14 months	Total n-3 n-3 Measure: Biomarker (colostrum) n-3 Units: weight (%)	High versus low levels dichotomized at median	Coefficient Estimate: 1.76 95% CI(-0.88, 4.4)	
	Cognitive Development N Total: 504	14 months	Total n-3 n-3 Measure: Biomarker (colostrum) n-3 Units: weight (%)	Sample divided into only 2 groups - High vs Low levels	Coefficient Estimate: 1.76 95% CI(-0.88, 4.4)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Jordi Julvez, et al., 2014[143] Study name: INMA Study dates: Enrollment conducted July 2004 to July 2006 Follow-up: 4 years Study design: Observational prospective Location: Spain Funding source / conflict: Government, Multiple foundations and Societies Follow-up: 4 years Original, same study, or follow-up studies: Guxens, 2011[144]	Study Population: Breast-feeding women Pregnant enrolled 657 Pregnant completers 622 Lactating enrolled 622 Lactating completers 582 Infants enrolled 622 Infants completers 434 Lactating enrolled 622 Lactating completers 582 Lactating age: 31.6 years (4.2 years) Infant age: 2 to 5 days after birth Race of Mother: NR (NR)	Inclusion Criteria: age older than 16 years, intent to deliver at the reference hospital, singleton pregnancy Exclusion Criteria: no problems with communication, no assisted conception	Adjustments: Test conditions, child age & sex, parental age, parity, alcohol consumption and smoking during pregnancy, day care attendance, country of birth, maternal education, social class, mental health, attachment to child, and perceptive performance IQ at 14 months, maternal psych symptoms, verbal IQ at 4 years, pollutant exposure during pregnancy.

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Julvez, 2013[143]	Neuropsychological development N Total: 434	4 years	Total n-3 fatty acids n-3 Measure: Biomarker (colostrum) n-3 Units: NR	Tertile 2 vs. Tertile 1	Coefficient Estimate: 0.5 95% CI(-2.9, 3.9)	
	Neuropsychological development N Total: 434	4 years	Total n-3 fatty acids n-3 Measure: Biomarker (colostrum) n-3 Units: NR	Tertile 2 vs. Tertile 2	Coefficient Estimate: 1.8 95% CI(-1.7, 5.4)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Keim, et al., 2012[162] Study name: Pregnancy, Infection and Nutrition Study Study dates: Recruitment between January 2001 and June 2005 Follow-up: 1 year Study design: Observational prospective Location: US Funding source / conflict: Government Follow-up: 12 months	Study Population: Healthy infants Breast-feeding women Pregnant enrolled 1,169 Pregnant completers 689 Infants enrolled 408 Infants completers 358 Pregnant age: NR Infant age: 20 weeks gestation NA Race of Mother: White European (79.1%) Other race/ethnicity (21.0)	Inclusion Criteria: health women at less than 20 weeks of pregnancy Exclusion Criteria: pregnant with multiple fetuses, unable to communicate in English, under age 16 years, no access to a telephone, intention to go elsewhere for future care or delivery	Adjustments: Laboratory, infant sex, race, parity, maternal smoking, education, breastfeeding status and preterm status

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Keim, 2012[162]	Mullen Scales of Early Learning - composite score N Total: 266	12 months	AA n-3 Measure: breast milk and formula n-3 Units: a change in fatty acid concentration of 1.0%.		Coefficient Estimate: 0.9 95% CI(-1.5, 3.4)	
	Mullen Scales of Early Learning - composite score N Total: 266	12 months	DHA n-3 Measure: breast milk and formula n-3 Units: a change in fatty acid concentration of 1.0%.		Coefficient Estimate: -0.5 95% CI(-2.7, 1.7)	
	Mullen Scales of Early Learning - expressive language scale N Total: 266	12 months	AA n-3 Measure: breast milk and formula n-3 Units: a change in fatty acid concentration of 1.0%.		Coefficient Estimate: 0.7 95% CI(-0.9, 2.3)	
	Mullen Scales of Early Learning - expressive language scale N Total: 266	12 months	DHA n-3 Measure: breast milk and formula n-3 Units: a change in fatty acid concentration of 1.0%.		Coefficient Estimate: -0.6 95% CI(-2.1, 0.8)	
	Mullen Scales of Early Learning - fine motor scale N Total: 266	12 months	AA n-3 Measure: breast milk and formula n-3 Units: a change in fatty acid concentration of 1.0%.		Coefficient Estimate: 0 95% CI(-2, 2)	
	Mullen Scales of Early Learning - fine motor scale N Total: 266	12 months	DHA n-3 Measure: breast milk and formula n-3 Units: a change in fatty acid concentration of 1.0%.		Coefficient Estimate: 0.2 95% CI(-1.7, 2)	
	Mullen Scales of Early Learning - gross motor scale N Total: 266	12 months	AA n-3 Measure: breast milk and formula n-3 Units: a change in fatty acid concentration of 1.0%.		Coefficient Estimate: 1.2 95% CI(-1.1, 3.4)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Mullen Scales of Early Learning - gross motor scale N Total: 266	12 months	DHA n-3 Measure: breast milk and formula n-3 Units: a change in fatty acid concentration of 1.0%.		Coefficient Estimate: 1.1 95% CI(-0.9, 3.1)	
	Mullen Scales of Early Learning - receptive language scale N Total: 266	12 months	AA n-3 Measure: breast milk and formula n-3 Units: a change in fatty acid concentration of 1.0%.		Coefficient Estimate: 0.3 95% CI(-1.2, 1.7)	
	Mullen Scales of Early Learning - receptive language scale N Total: 266	12 months	DHA n-3 Measure: breast milk and formula n-3 Units: a change in fatty acid concentration of 1.0%.		Coefficient Estimate: -0.1 95% CI(-1.4, 1.2)	
	Mullen Scales of Early Learning - visual reception scale N Total: 266	12 months	AA n-3 Measure: breast milk and formula n-3 Units: a change in fatty acid concentration of 1.0%.		Coefficient Estimate: 0.7 95% CI(-1.3, 2.8)	
	Mullen Scales of Early Learning - visual reception scale N Total: 266	12 months	DHA n-3 Measure: breast milk and formula n-3 Units: a change in fatty acid concentration of 1.0%.		Coefficient Estimate: -0.1 95% CI(-2, 1.8)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Klebanoff, et al., 2011[49] Study dates: Jan 2005- Oct 2006 Study design: Observational prospective Location: US Funding source / conflict: Government Original, same study, or follow-up studies: Harper, 2010[29]	Study Population: Healthy pregnant women Pregnant enrolled 852 Pregnant completers 852 Pregnant age: <1/month, 27.1 (5.6) 0.5-3 per week, 28.0 (5.6) >3 per week, 27.3 (5.7) (<1/month, 27.1 (5.6) 0.5-3 per week, 28.0 (5.6) >3 per week, 27.3 (5.7)) Race of Mother: NR	Inclusion Criteria: at least one prior singleton preterm delivery between 20 0/7 and 36 6/7 weeks of gestation after spontaneous preterm labor or premature rupture of the membranes, and a current singleton pregnancy between 16 and 21 6/7 weeks of gestation Exclusion Criteria: evidence of a major fetal anomaly, intake of a fish oil supplement in excess of 500 mg per week at any time during the preceding month, allergy to fish, anticoagulation therapy, hypertension, White's classification D or higher diabetes, drug or alcohol abuse, seizure disorder, uncontrolled thyroid disease, clotting disorder, current or planned cerclage, or a plan to deliver either elsewhere or before 37 weeks of gestation	Adjustments: Study center, number of previous preterm births, gestation of earliest prior spontaneous preterm birth, receipt of omega-3 versus placebo supplement, smoking, age, education, body mass index and ethnicity

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Klebanoff 2011[49]	Preterm birth N Total: 852		Erythrocyte DHA + EPA n-3 Measure: Maternal red blood cells n-3 Units: % of total fatty acids	Q1 <3.052 - N Cases: 176	OR	
	Preterm birth N Total: 852		Erythrocyte DHA + EPA n-3 Measure: Maternal red blood cells n-3 Units: % of total fatty acids	Q2 3.052 - 3.719 N Cases: 175	OR Estimate: 0.59 95% CI(0.37, 0.94)	
	Preterm birth N Total: 852		Erythrocyte DHA + EPA n-3 Measure: Maternal red blood cells n-3 Units: % of total fatty acids	Q3 3.723 - 4.426 N Cases: 175	OR Estimate: 0.84 95% CI(0.53, 1.32)	
	Preterm birth N Total: 852		Erythrocyte DHA + EPA n-3 Measure: Maternal red blood cells n-3 Units: % of total fatty acids	Q4 >4.426 N Cases: 175	OR Estimate: 0.71 95% CI(0.45, 1.15)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Leung, et al., 2013[94] Study name: Alberta Pregnancy Outcomes and Nutrition (APrON) study Study dates: %n Study design: Observational prospective Location: Canada Funding source / conflict: NR	Study Population: Healthy pregnant women Pregnant enrolled 600 Pregnant withdrawals 125 Pregnant completers 475 Pregnant age: 31.2 not depressed 31.6 depressed (4.16 not depressed 4.7 depressed) not reported Race of Mother: White European (87%) Other race/ethnicity (13%)	Inclusion Criteria: at least 16 years old with gestational age =27 weeks. Women must be in the first (T1) or second (T2) trimester Exclusion Criteria: Any woman who was 28 weeks or beyond, Non-English speakers, known drug and alcohol abusers, and those planning to move out of the region within 6 months	Adjustments: Born in Canada, prenatal and postnatal social support, prenatal EPDS, selenium

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Leung 2013[94]	PPD N Total: 475		Biomarkers	N Cases: 59	OR Estimate: 1 95% CI(0.99, 1)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Lim, et al., 2015[71] Study dates: 2009-2012 Study design: Observational prospective Location: NR Funding source / conflict: Industry, Government	Study Population: Healthy pregnant women Pregnant enrolled 1162 Pregnant completers 751 Infants completers Pregnant age: 1st tertile 29.9 2nd tertile 30.0 3rd tertile 31.7 _ (1st tertile 5. 2 2nd tertile 5.2, 3rd tertile 4.8) Race of Mother: Asian (100)	Inclusion Criteria: Healthy women in early pregnancy at one of 3 tertiary care hospitals in Singapore Exclusion Criteria: receiving chemotherapy, taking psychotropic drugs, or having type 1 diabetes	Adjustments: Adjusted for age, ethnicity, education, exercise, alcohol intake, smoking status, BMI, and height at the 26th to the 28th week of gestation, gestational diabetes, and heart rate, fish oil supplementation

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Lim 2015[71]	Gestational hypertension N Total: 751	26-28 weeks	AA n-3 Measure: Biomarker (maternal plasma) n-3 Units: 1% increase in % total FA	All N Quantile: NR N Cases: 28	OR Estimate: 1.07 95% CI(0.95, 1.22)	
	Gestational hypertension N Total: 751	26-28 weeks	Total n-3 PUFAs n-3 Measure: Biomarker (maternal plasma) n-3 Units: 1% increase in % total FA	All N Quantile: NR N Cases: 28	OR Estimate: 0.76 95% CI(0.60, 0.97)	
	Gestational hypertension N Total: 751	26-28 weeks	n-3 LCPUFA n-3 Measure: Biomarker (maternal plasma) n-3 Units: 1% increase in % total FA	All N Quantile: NR N Cases: 28	OR Estimate: 0.77 95% CI(0.60, 0.98)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Lumia, et al., 2011[188] Study name: Finnish Type 1 Diabetes Prediction and Prevention Nutrition Study Study dates: 1997-2004 Study design: NR Location: Finland Funding source / conflict: Industry, Government, Multiple foundations and Societies, None Follow-up: 5 years	Study Population: NR Infants enrolled 2908 Infants completers 2679 Pregnant age: 14.8% <25 years at birth 35.4% 25-29 years 30.4% 30-34 years 19.5% =35 years Race of Mother: White European (100%)	Inclusion Criteria: infants at three university hospitals in Finland (Turku, Tampere and Oulu) whose cord blood was screened for HLA-conferred genetic susceptibility to type 1 diabetes (HLA-DQB1) and were found to have high or moderate genetic risk of type 1 diabetes Exclusion Criteria: Severe congenital malformations or diseases, parents of non-Caucasian origin or parents who did not have a working knowledge of Finnish, Swedish or English	Adjustments: Maternal age, mode of delivery, duration of gestation, number of earlier deliveries, birth weight, sex of the child, area of birth, maternal smoking during pregnancy, parental asthma or allergic rhinitis, maternal vocational education, pets at home, farming, contact with cow stable during the first year of life and the duration of total breastfeeding

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Lumia 2011[188]	Asthma N Total: 2679	5 years	AA n-3 Measure: Maternal FFQ n-3 Units: g/d	Q1 - <0.06 N Quantile: NR N Cases: NR	RR Estimate: 0.52 95% CI(0.32, 0.84)	P value: 0.025
	Asthma N Total: 2679	5 years	AA n-3 Measure: Maternal FFQ n-3 Units: g/d	Q2,Q3 0.06- 0.11 N Quantile: NR N Cases: NR	RR	
	Asthma N Total: 2679	5 years	AA n-3 Measure: Maternal FFQ n-3 Units: g/d	Q4 >0.11- N Quantile: NR N Cases: NR	RR Estimate: 0.77 95% CI(0.51, 1.17)	
	Asthma N Total: 2679	5 years	ALA n-3 Measure: Maternal FFQ n-3 Units: g/d	Q1 - <1.83 N Quantile: NR N Cases: NR	RR Estimate: 1.7 95% CI(1.14, 2.53)	P value: 0.022
	Asthma N Total: 2679	5 years	ALA n-3 Measure: Maternal FFQ n-3 Units: g/d	Q2,Q3 1.83- 3.18 N Quantile: NR N Cases: NR	RR	
	Asthma N Total: 2679	5 years	ALA n-3 Measure: Maternal FFQ n-3 Units: g/d	Q4 >3.18- N Quantile: NR N Cases: NR	RR Estimate: 1.06 95% CI(0.68, 1.65)	
	Asthma N Total: 2679	5 years	DHA n-3 Measure: Maternal FFQ n-3 Units: g/d	Q1 - <0.10 N Quantile: NR N Cases: NR	RR Estimate: 0.8 95% CI(0.52, 1.23)	P value: 0.467
	Asthma N Total: 2679	5 years	DHA n-3 Measure: Maternal FFQ n-3 Units: g/d	Q2,Q3 0.1- 0.32 N Quantile: NR N Cases: NR	RR	
	Asthma N Total: 2679	5 years	DHA n-3 Measure: Maternal FFQ n-3 Units: g/d	Q4 >0.32- N Quantile: NR N Cases: NR	RR Estimate: 0.83 95% CI(0.53, 1.29)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Asthma N Total: 2679	5 years	EPA n-3 Measure: Maternal FFQ n-3 Units: g/d	Q1 - <0.04 N Quantile: NR N Cases: NR	RR Estimate: 1.09 95% CI(0.72, 1.65)	P value: 0.604
	Asthma N Total: 2679	5 years	EPA n-3 Measure: Maternal FFQ n-3 Units: g/d	Q2,Q3 0.04- 1.13 N Quantile: NR N Cases: NR	RR	
	Asthma N Total: 2679	5 years	EPA n-3 Measure: Maternal FFQ n-3 Units: g/d	Q4 >1.13- N Quantile: NR N Cases: NR	RR Estimate: 0.84 95% CI(0.54, 1.31)	
	Asthma N Total: 2679	5 years	n-3 PUFAs n-3 Measure: Maternal FFQ n-3 Units: g/d	Q1 - <2.24 N Quantile: NR N Cases: NR	RR Estimate: 1.66 95% CI(1.11, 2.48)	P value: 0.036
	Asthma N Total: 2679	5 years	n-3 PUFAs n-3 Measure: Maternal FFQ n-3 Units: g/d	Q2,Q3 2.24- 3.84 N Quantile: NR N Cases: NR	RR	
	Asthma N Total: 2679	5 years	n-3 PUFAs n-3 Measure: Maternal FFQ n-3 Units: g/d	Q4 >3.84- N Quantile: NR N Cases: NR	RR Estimate: 1.09 95% CI(0.7, 1.7)	
	Asthma N Total: 2679	5 years	n-6/n-3 PUFAs n-3 Measure: Maternal FFQ n-3 Units: g/d	Q1 - <3.07 N Quantile: NR N Cases: NR	RR Estimate: 0.95 95% CI(0.62, 1.46)	P value: 0.835
	Asthma N Total: 2679	5 years	n-6/n-3 PUFAs n-3 Measure: Maternal FFQ n-3 Units: g/d	Q2,Q3 3.07- 3.82 N Quantile: NR N Cases: NR	RR	
	Asthma N Total: 2679	5 years	n-6/n-3 PUFAs n-3 Measure: Maternal FFQ n-3 Units: g/d	Q4 >3.82- N Quantile: NR N Cases: NR	RR Estimate: 1.1 95% CI(0.72, 1.68)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Lyall, et al., 2013[171] Study name: Nurses Health Study Study dates: Births 1991 to 2007 Study design: NR Location: US Funding source / conflict: Government	Study Population: Healthy pregnant women Pregnant enrolled 18,045 Pregnant completers 5,884 Pregnant age: Q1 34.7y Q4 33.7 y NR Infant age: birth Race of Mother: White European (Q1: 96%; Q4: 98%) Other race/ethnicity (Q1 4%; Q4 2%)	Inclusion Criteria: female nurses who were 25–42 years of age in 1989, with index births between 1991 (the year of first collection of dietary information) and 2007; women reported a child with ASD either in 2005 or 2009 not both, if 1) the reason for non-reporting on the other questionnaire was on participation in that questionnaire year; 2) the nurse confirmed the diagnosis in a previous substudy; or 3) for women reporting on the 2009 questionnaire only, the child was born after 2000 (in which case, the child might have been too young for report of diagnosis by the 2005 questionnaire mailing) Exclusion Criteria: Women reporting competing diagnoses (fragile X syndrome, Rett Syndrome, tuberous sclerosis, Down syndrome, trisomy 18; in a previous sub-study were not included.. women without food frequency questionnaire data or without autism diagnosis info on child	Adjustments: Adjusted for total energy intake, maternal age, child's year of birth, income level, race, body mass index, and pre-pregnancy smoking status. Removal of adjustment for smoking did not affect results. Additional adjustment for child birth order, maternal physical activity level, spouse's education level, or multivitamin use, or for trans-fat in PUFA model, did not materially alter estimates

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Lyall, 2013[171]	Autism Spectrum Disorders N Total: 17728		Total LCPUFA n-3 Measure: FFQ	Q1 7.8	RR	P value: P<0.008
	Autism Spectrum Disorders N Total: 17728		Total LCPUFA n-3 Measure: FFQ	Q2 9.5	RR Estimate: 0.97 95% CI(0.73, 1.3)	
	Autism Spectrum Disorders N Total: 17728		Total LCPUFA n-3 Measure: FFQ	Q3 11	RR Estimate: 0.82 95% CI(0.82, 1.11)	
	Autism Spectrum Disorders N Total: 17728		Total LCPUFA n-3 Measure: FFQ	Q4 13.4	RR Estimate: 0.67 95% CI(0.49, 0.92)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Miyake, et al., 2009[182] Study name: Osaka maternal and child health study Study dates: 2002-2003 Study design: Observational prospective Location: Japan Funding source / conflict: Government, None	Study Population: Healthy infants Pregnant enrolled 1,002 Pregnant completers 763 Infants enrolled 1,002 Infants completers 763 Pregnant age: 30.0 (4.0) Race of Mother: NR (100)	Inclusion Criteria: pregnant women living in Neyagawa City, Osaka Prefecture or the surrounding cities Exclusion Criteria: Not reported	Adjustments: Maternal age, gestation at baseline, residential municipality, family income, maternal and paternal education, maternal and paternal history of asthma, atopic eczema and allergic rhinitis, maternal intake of vitamins D and E during pregnancy, changes in maternal diet in the previous 1 month, season when data at baseline were collected, maternal smoking during pregnancy, baby's older siblings, baby's sex, baby's birth weight, household smoking in the same room as the infant, breastfeeding duration and time of delivery before the third survey

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Miyake 2009[182]	Eczema N Total: 763	16-24 months	ALA n-3 Measure: FFQ n-3 Units: median, g/d	Q1 1.3 N Quantile: NR N Cases: 35	OR	P value: 0.06
	Eczema N Total: 763	16-24 months	ALA n-3 Measure: FFQ n-3 Units: median, g/d	Q2 1.6 N Quantile: NR N Cases: 33	OR Estimate: 1.28 95% CI(0.71, 2.29)	
	Eczema N Total: 763	16-24 months	ALA n-3 Measure: FFQ n-3 Units: median, g/d	Q3 1.9 N Quantile: NR N Cases: 35	OR Estimate: 1.69 95% CI(0.91, 3.13)	
	Eczema N Total: 763	16-24 months	ALA n-3 Measure: FFQ n-3 Units: median, g/d	Q4 2.3 N Quantile: NR N Cases: 39	OR Estimate: 1.79 95% CI(0.93, 3.5)	
	Eczema N Total: 763	16-24 months	DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q1 0.15 N Quantile: NR N Cases: 40	OR	P value: 0.57
	Eczema N Total: 763	16-24 months	DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q2 0.24 N Quantile: NR N Cases: 40	OR Estimate: 1.5 95% CI(0.76, 3.02)	
	Eczema N Total: 763	16-24 months	DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q3 0.32 N Quantile: NR N Cases: 32	OR Estimate: 1.11 95% CI(0.49, 2.54)	
	Eczema N Total: 763	16-24 months	DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q4 0.46 N Quantile: NR N Cases: 30	OR Estimate: 0.86 95% CI(0.33, 2.28)	
	Eczema N Total: 763	16-24 months	EPA n-3 Measure: FFQ n-3 Units: median, g/d	Q1 0.08 N Quantile: NR N Cases: 39	OR	P value: 0.95

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Eczema N Total: 763	16-24 months	EPA n-3 Measure: FFQ n-3 Units: median, g/d	Q2 0.13 N Quantile: NR N Cases: 36	OR Estimate: 0.99 95% CI(0.51, 1.89)	
	Eczema N Total: 763	16-24 months	EPA n-3 Measure: FFQ n-3 Units: median, g/d	Q3 0.18 N Quantile: NR N Cases: 33	OR Estimate: 1.12 95% CI(0.52, 2.45)	
	Eczema N Total: 763	16-24 months	EPA n-3 Measure: FFQ n-3 Units: median, g/d	Q4 0.28 N Quantile: NR N Cases: 34	OR Estimate: 0.98 95% CI(0.39, 2.5)	
	Eczema N Total: 763	16-24 months	n-3 PUFA n-3 Measure: FFQ n-3 Units: median, g/d	Q1 1.7 N Quantile: NR N Cases: 35	OR	P value: 0.2
	Eczema N Total: 763	16-24 months	n-3 PUFA n-3 Measure: FFQ n-3 Units: median, g/d	Q2 2.2 N Quantile: NR N Cases: 38	OR Estimate: 1.72 95% CI(0.95, 3.13)	
	Eczema N Total: 763	16-24 months	n-3 PUFA n-3 Measure: FFQ n-3 Units: median, g/d	Q3 2.5 N Quantile: NR N Cases: 33	OR Estimate: 1.63 95% CI(0.83, 3.22)	
	Eczema N Total: 763	16-24 months	n-3 PUFA n-3 Measure: FFQ n-3 Units: median, g/d	Q4 3 N Quantile: NR N Cases: 36	OR Estimate: 1.74 95% CI(0.82, 3.73)	
	Eczema N Total: 763	16-24 months	n-3/n-6 n-3 Measure: FFQ n-3 Units: median, g/d	Q1 0.17 N Quantile: NR N Cases: 31	OR	P value: 0.18
	Eczema N Total: 763	16-24 months	n-3/n-7 n-3 Measure: FFQ n-3 Units: median, g/d	Q2 0.19 N Quantile: NR N Cases: 33	OR Estimate: 1.24 95% CI(0.68, 2.28)	
	Eczema N Total: 763	16-24 months	n-3/n-8 n-3 Measure: FFQ n-3 Units: median, g/d	Q3 0.21 N Quantile: NR N Cases: 46	OR Estimate: 2.13 95% CI(1.17, 3.96)	
	Eczema N Total: 763	16-24 months	n-3/n-9 n-3 Measure: FFQ n-3 Units: median, g/d	Q4 0.24 N Quantile: NR N Cases: 32	OR Estimate: 1.32 95% CI(0.65, 2.71)	
	Wheeze N Total: 763	16-24 months	ALA n-3 Measure: FFQ n-3 Units: median, g/d	Q1 1.3 N Quantile: NR N Cases: 53	OR	P value: 0.08
	Wheeze N Total: 763	16-24 months	ALA n-3 Measure: FFQ n-3 Units: median, g/d	Q2 1.6 N Quantile: NR N Cases: 38	OR Estimate: 0.63 95% CI(0.37, 1.07)	
	Wheeze N Total: 763	16-24 months	ALA n-3 Measure: FFQ n-3 Units: median, g/d	Q3 1.9 N Quantile: NR N Cases: 45	OR Estimate: 0.78 95% CI(0.45, 1.35)	
	Wheeze N Total: 763	16-24 months	ALA n-3 Measure: FFQ n-3 Units: median, g/d	Q4 2.3 N Quantile: NR N Cases: 33	OR	
	Wheeze N Total: 763	16-24 months	DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q1 0.15 N Quantile: NR N Cases: 55	OR	P value: 0.14

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Wheeze N Total: 763	16-24 months	DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q2 0.24 N Quantile: NR N Cases: 29	OR Estimate: 0.41 95% CI(0.2, 0.81)	
	Wheeze N Total: 763	16-24 months	DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q3 0.32 N Quantile: NR N Cases: 50	OR Estimate: 0.72 95% CI(0.33, 1.57)	
	Wheeze N Total: 763	16-24 months	DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q4 0.46 N Quantile: NR N Cases: 35	OR	
	Wheeze N Total: 763	16-24 months	EPA n-3 Measure: FFQ n-3 Units: median, g/d	Q1 0.08 N Quantile: NR N Cases: 48	OR	P value: 0.58
	Wheeze N Total: 763	16-24 months	EPA n-3 Measure: FFQ n-3 Units: median, g/d	Q2 0.13 N Quantile: NR N Cases: 39	OR Estimate: 0.77 95% CI(0.42, 1.41)	
	Wheeze N Total: 763	16-24 months	EPA n-3 Measure: FFQ n-3 Units: median, g/d	Q3 0.18 N Quantile: NR N Cases: 38	OR Estimate: 0.76 95% CI(0.37, 1.58)	
	Wheeze N Total: 763	16-24 months	EPA n-3 Measure: FFQ n-3 Units: median, g/d	Q4 0.28 N Quantile: NR N Cases: 44	OR Estimate: 0.76 95% CI(0.33, 1.8)	
	Wheeze N Total: 763	16-24 months	n-3 PUFA n-3 Measure: FFQ n-3 Units: median, g/d	Q1 1.7 N Quantile: NR N Cases: 53	OR	P value: 0.13
	Wheeze N Total: 763	16-24 months	n-3 PUFA n-3 Measure: FFQ n-3 Units: median, g/d	Q2 2.2 N Quantile: NR N Cases: 38	OR Estimate: 0.57 95% CI(0.33, 0.99)	
	Wheeze N Total: 763	16-24 months	n-3 PUFA n-3 Measure: FFQ n-3 Units: median, g/d	Q3 2.5 N Quantile: NR N Cases: 42	OR Estimate: 0.66 95% CI(0.36, 1.22)	
	Wheeze N Total: 763	16-24 months	n-3 PUFA n-3 Measure: FFQ n-3 Units: median, g/d	Q4 3 N Quantile: NR N Cases: 36	OR Estimate: 0.53 95% CI(0.26, 1.08)	
	Wheeze N Total: 763	16-24 months	n-3/n-6 n-3 Measure: FFQ n-3 Units: median, g/d	Q1 0.17 N Quantile: NR N Cases: 46	OR	P value: 0.38
	Wheeze N Total: 763	16-24 months	n-3/n-7 n-3 Measure: FFQ n-3 Units: median, g/d	Q2 0.19 N Quantile: NR N Cases: 44	OR Estimate: 0.88 95% CI(0.52, 1.51)	
	Wheeze N Total: 763	16-24 months	n-3/n-8 n-3 Measure: FFQ n-3 Units: median, g/d	Q3 0.21 N Quantile: NR N Cases: 37	OR Estimate: 0.69 95% CI(0.39, 1.23)	
	Wheeze N Total: 763	16-24 months	n-3/n-9 n-3 Measure: FFQ n-3 Units: median, g/d	Q4 0.24 N Quantile: NR N Cases: 42	OR Estimate: 0.81 95% CI(0.42, 1.55)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Miyake, et al., 2013[183] Study name: Kyushu Okinawa Maternal and Child Health Study Study dates: 2007-2010 Study design: Observational prospective Location: Japan Funding source / conflict: Industry, Government, Multiple foundations and Societies Follow-up: 23-29 months	Study Population: Healthy infants Pregnant enrolled 1757 Pregnant completers 1354 Infants enrolled 1757 Infants completers 1354 Pregnant age: 31.5 (4.1) Race of Mother: NR (100)	Inclusion Criteria: Women living in one of 7 prefectures on Kyushu Island who became pregnant from 2007-2008 Exclusion Criteria: Failure to complete the study surveys	Adjustments: Maternal age, gestation at baseline, residential municipality, family income, maternal and paternal education, maternal and paternal history of asthma, atopic eczema and allergic rhinitis, maternal intake of vitamins D and E during pregnancy, changes in maternal diet in the previous 1 month, season when data at baseline were collected, maternal smoking during pregnancy, baby's older siblings, baby's sex, baby's birth weight, household smoking in the same room as the infant, breastfeeding duration and time of delivery before the third survey

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Miyake 2013[183]	Eczema N Total: 763	23-29 months	AA n-3 Measure: FFQ n-3 Units: median, g/d	Q1 0.09 N Quantile: NR N Cases: 56	OR	
	Eczema N Total: 763	23-29 months	AA n-3 Measure: FFQ n-3 Units: median, g/d	Q2 0.12 N Quantile: NR N Cases: 61	OR Estimate: 1.08 95% CI(0.72, 1.63)	
	Eczema N Total: 763	23-29 months	AA n-3 Measure: FFQ n-3 Units: median, g/d	Q3 0.14 N Quantile: NR N Cases: 61	OR Estimate: 1.07 95% CI(0.71, 1.6)	
	Eczema N Total: 763	23-29 months	AA n-3 Measure: FFQ n-3 Units: median, g/d	Q4 0.18 N Quantile: NR N Cases: 51	OR Estimate: 0.87 95% CI(0.57, 1.33)	
	Eczema N Total: 763	23-29 months	ALA n-3 Measure: FFQ n-3 Units: median, g/d	Q1 1.2 N Quantile: NR N Cases: 61	OR	
	Eczema N Total: 763	23-29 months	ALA n-3 Measure: FFQ n-3 Units: median, g/d	Q2 1.5 N Quantile: NR N Cases: 52	OR Estimate: 0.82 95% CI(0.54, 1.24)	
	Eczema N Total: 763	23-29 months	ALA n-3 Measure: FFQ n-3 Units: median, g/d	Q3 1.8 N Quantile: NR N Cases: 61	OR Estimate: 0.97 95% CI(0.65, 1.45)	
	Eczema N Total: 763	23-29 months	ALA n-3 Measure: FFQ n-3 Units: median, g/d	Q4 2.2 N Quantile: NR N Cases: 55	OR Estimate: 0.86 95% CI(0.57, 1.29)	
	Eczema N Total: 763	23-29 months	DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q1 0.15 N Quantile: NR N Cases: 45	OR	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Eczema N Total: 763	23-29 months	DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q2 0.23 N Quantile: NR N Cases: 64	OR Estimate: 1.51 95% CI(0.99, 2.32)	
	Eczema N Total: 763	23-29 months	DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q3 0.3 N Quantile: NR N Cases: 58	OR Estimate: 1.35 95% CI(0.88, 2.08)	
	Eczema N Total: 763	23-29 months	DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q4 0.45 N Quantile: NR N Cases: 62	OR Estimate: 1.45 95% CI(0.95, 2.24)	
	Eczema N Total: 763	23-29 months	EPA+DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q1 0.22 N Quantile: NR N Cases: 48	OR	
	Eczema N Total: 763	23-29 months	EPA+DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q2 0.35 N Quantile: NR N Cases: 62	OR Estimate: 1.35 95% CI(0.89, 2.06)	
	Eczema N Total: 763	23-29 months	EPA+DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q3 0.47 N Quantile: NR N Cases: 55	OR Estimate: 1.18 95% CI(0.77, 1.82)	
	Eczema N Total: 763	23-29 months	EPA+DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q4 0.73 N Quantile: NR N Cases: 64	OR Estimate: 1.42 95% CI(0.93, 2.17)	
	Eczema N Total: 763	23-29 months	EPA n-3 Measure: FFQ n-3 Units: median, g/d	Q1 0.07 N Quantile: NR N Cases: 54	OR	
	Eczema N Total: 763	23-29 months	EPA n-3 Measure: FFQ n-3 Units: median, g/d	Q2 0.13 N Quantile: NR N Cases: 56	OR Estimate: 1.03 95% CI(0.68, 1.57)	
	Eczema N Total: 763	23-29 months	EPA n-3 Measure: FFQ n-3 Units: median, g/d	Q3 0.17 N Quantile: NR N Cases: 55	OR	
	Eczema N Total: 763	23-29 months	EPA n-3 Measure: FFQ n-3 Units: median, g/d	Q4 0.28 N Quantile: NR N Cases: 64	OR Estimate: 1.21 95% CI(0.8, 1.83)	
	Eczema N Total: 763	23-29 months	n-3-PUFA n-3 Measure: FFQ n-3 Units: median, g/d	Q1 1.6 N Quantile: NR N Cases: 56	OR	
	Eczema N Total: 763	23-29 months	n-3-PUFA n-3 Measure: FFQ n-3 Units: median, g/d	Q2 2.1 N Quantile: NR N Cases: 53	OR Estimate: 0.93 95% CI(0.61, 1.41)	
	Eczema N Total: 763	23-29 months	n-3-PUFA n-3 Measure: FFQ n-3 Units: median, g/d	Q3 2.4 N Quantile: NR N Cases: 68	OR Estimate: 1.21 95% CI(0.81, 1.81)	
	Eczema N Total: 763	23-29 months	n-3-PUFA n-3 Measure: FFQ n-3 Units: median, g/d	Q4 2.9 N Quantile: NR N Cases: 52	OR Estimate: 0.89 95% CI(0.58, 1.35)	
	Eczema N Total: 763	23-29 months	n-3:n-6 n-3 Measure: FFQ n-3 Units: median, g/d	Q1 0.17 N Quantile: NR N Cases: 50	OR	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Eczema N Total: 763	23-29 months	n-3:n-7 n-3 Measure: FFQ n-3 Units: median, g/d	Q2 0.19 N Quantile: NR N Cases: 59	OR Estimate: 1.21 95% CI(0.8, 1.85)	
	Eczema N Total: 763	23-29 months	n-3:n-8 n-3 Measure: FFQ n-3 Units: median, g/d	Q3 0.21 N Quantile: NR N Cases: 57	OR Estimate: 1.14 95% CI(0.75, 1.76)	
	Eczema N Total: 763	23-29 months	n-3:n-9 n-3 Measure: FFQ n-3 Units: median, g/d	Q4 0.25 N Quantile: NR N Cases: 63	OR Estimate: 1.28 95% CI(0.84, 1.95)	
	Wheeze N Total: 763	23-29 months	AA n-3 Measure: FFQ n-3 Units: median, g/d	Q1 0.09 N Quantile: NR N Cases: 91	OR	
	Wheeze N Total: 763	23-29 months	AA n-3 Measure: FFQ n-3 Units: median, g/d	Q2 0.12 N Quantile: NR N Cases: 99	OR Estimate: 1.12 95% CI(0.79, 1.59)	
	Wheeze N Total: 763	23-29 months	AA n-3 Measure: FFQ n-3 Units: median, g/d	Q3 0.14 N Quantile: NR N Cases: 92	OR Estimate: 1.04 95% CI(0.74, 1.48)	
	Wheeze N Total: 763	23-29 months	AA n-3 Measure: FFQ n-3 Units: median, g/d	Q4 0.18 N Quantile: NR N Cases: 91	OR Estimate: 0.95 95% CI(0.66, 1.34)	
	Wheeze N Total: 763	23-29 months	ALA n-3 Measure: FFQ n-3 Units: median, g/d	Q1 1.2 N Quantile: NR N Cases: 91	OR	
	Wheeze N Total: 763	23-29 months	ALA n-3 Measure: FFQ n-3 Units: median, g/d	Q2 1.5 N Quantile: NR N Cases: 92	OR Estimate: 1.02 95% CI(0.72, 1.44)	
	Wheeze N Total: 763	23-29 months	ALA n-3 Measure: FFQ n-3 Units: median, g/d	Q3 1.8 N Quantile: NR N Cases: 97	OR Estimate: 1.06 95% CI(0.75, 1.5)	
	Wheeze N Total: 763	23-29 months	ALA n-3 Measure: FFQ n-3 Units: median, g/d	Q4 2.2 N Quantile: NR N Cases: 93	OR Estimate: 0.96 95% CI(0.68, 1.36)	
	Wheeze N Total: 763	23-29 months	DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q1 0.15 N Quantile: NR N Cases: 98	OR	
	Wheeze N Total: 763	23-29 months	DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q2 0.23 N Quantile: NR N Cases: 107	OR Estimate: 1.14 95% CI(0.81, 1.6)	
	Wheeze N Total: 763	23-29 months	DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q3 0.3 N Quantile: NR N Cases: 86	OR Estimate: 0.82 95% CI(0.58, 1.17)	
	Wheeze N Total: 763	23-29 months	DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q4 0.45 N Quantile: NR N Cases: 82	OR Estimate: 0.77 95% CI(0.54, 1.1)	
	Wheeze N Total: 763	23-29 months	EPA+DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q1 0.22 N Quantile: NR N Cases: 100	OR	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Wheeze N Total: 763	23-29 months	EPA+DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q2 0.35 N Quantile: NR N Cases: 103	OR Estimate: 1.07 95% CI(0.76, 1.51)	
	Wheeze N Total: 763	23-29 months	EPA+DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q3 0.47 N Quantile: NR N Cases: 93	OR Estimate: 0.87 95% CI(0.62, 1.25)	
	Wheeze N Total: 763	23-29 months	EPA+DHA n-3 Measure: FFQ n-3 Units: median, g/d	Q4 0.73 N Quantile: NR N Cases: 77	OR Estimate: 0.7 95% CI(0.49, 1.003)	
	Wheeze N Total: 763	23-29 months	EPA n-3 Measure: FFQ n-3 Units: median, g/d	Q1 0.07 N Quantile: NR N Cases: 100	OR	
	Wheeze N Total: 763	23-29 months	EPA n-3 Measure: FFQ n-3 Units: median, g/d	Q2 0.13 N Quantile: NR N Cases: 109	OR Estimate: 1.19 95% CI(0.84, 1.67)	
	Wheeze N Total: 763	23-29 months	EPA n-3 Measure: FFQ n-3 Units: median, g/d	Q3 0.17 N Quantile: NR N Cases: 86	OR Estimate: 0.79 95% CI(0.55, 1.13)	
	Wheeze N Total: 763	23-29 months	EPA n-3 Measure: FFQ n-3 Units: median, g/d	Q4 0.28 N Quantile: NR N Cases: 78	OR Estimate: 0.73 95% CI(0.5, 1.04)	
	Wheeze N Total: 763	23-29 months	n-3-PUFA n-3 Measure: FFQ n-3 Units: median, g/d	Q1 1.6 N Quantile: NR N Cases: 95	OR	
	Wheeze N Total: 763	23-29 months	n-3-PUFA n-3 Measure: FFQ n-3 Units: median, g/d	Q2 2.1 N Quantile: NR N Cases: 99	OR Estimate: 1.05 95% CI(0.75, 1.49)	
	Wheeze N Total: 763	23-29 months	n-3-PUFA n-3 Measure: FFQ n-3 Units: median, g/d	Q3 2.4 N Quantile: NR N Cases: 96	OR Estimate: 0.97 95% CI(0.69, 1.38)	
	Wheeze N Total: 763	23-29 months	n-3-PUFA n-3 Measure: FFQ n-3 Units: median, g/d	Q4 2.9 N Quantile: NR N Cases: 83	OR Estimate: 0.79 95% CI(0.55, 1.12)	
	Wheeze N Total: 763	23-29 months	n-3:n-6 n-3 Measure: FFQ n-3 Units: median, g/d	Q1 0.17 N Quantile: NR N Cases: 90	OR	
	Wheeze N Total: 763	23-29 months	n-3:n-7 n-3 Measure: FFQ n-3 Units: median, g/d	Q2 0.19 N Quantile: NR N Cases: 104	OR Estimate: 1.24 95% CI(0.88, 1.75)	
	Wheeze N Total: 763	23-29 months	n-3:n-8 n-3 Measure: FFQ n-3 Units: median, g/d	Q3 0.21 N Quantile: NR N Cases: 97	OR Estimate: 1.08 95% CI(0.76, 1.54)	
	Wheeze N Total: 763	23-29 months	n-3:n-9 n-3 Measure: FFQ n-3 Units: median, g/d	Q4 0.25 N Quantile: NR N Cases: 82	OR Estimate: 0.85 95% CI(0.59, 1.22)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Mohanty, et al., 2015[85] Study dates: 1996-2008 Study design: Observational prospective Location: US Funding source / conflict: Government	Study Population: Healthy infants Healthy pregnant women Pregnant completers 534 Race of Mother: White European (88)	Inclusion Criteria: initiated prenatal care at or before 20 weeks gestation, were aged = 18 years, able to speak and read English, planned to carry the pregnancy to term, and to deliver at either of the two hospitals Exclusion Criteria: multi-fetal pregnancies, implausible total energy intake of <500 or >3500 kcal/day, pregnancies complicated by fetal demise (after 20 weeks of gestation), missing labor and delivery information, missing information on fetal growth indices, missing seafood intake information	Adjustments: Adjusted for maternal age (years), non-Hispanic white race, post high-school education, unmarried marital status, pre-pregnancy body mass index (indicator variables: 18.5-24.9, 25-29.9, =30 kg/m2), total energy (kcal/day), current recreational physical activity, current smoking, current alcohol intake, nulliparity, intake of red/processed meats (servings/day), male infant sex.

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Mohanty 2015[85]	Birth weight N Total: 534		Erythrocyte DHA + EPA n-3 Measure: Maternal n-3 Units: % total fatty acids	Q1 2.28-4.49 N Quantile: 133	Mean difference	
	Birth weight N Total: 534		Erythrocyte DHA + EPA n-3 Measure: Maternal n-3 Units: % total fatty acids	Q2 4.49-5.25 N Quantile: 134	Mean difference Estimate: -59 95% CI(-207.5, 89.6)	
	Birth weight N Total: 534		Erythrocyte DHA + EPA n-3 Measure: Maternal n-3 Units: % total fatty acids	Q3 5.26-6.07 N Quantile: 133	Mean difference Estimate: 49.6 95% CI(-100.9, 200.1)	
	Birth weight N Total: 534		Erythrocyte DHA + EPA n-3 Measure: Maternal n-3 Units: % total fatty acids	Q4 6.07-9.55 N Quantile: 134	Mean difference Estimate: -39.4 95% CI(-194.5, 115.7)	
	Head circumference N Total: 534		Erythrocyte DHA + EPA n-3 Measure: Maternal n-3 Units: % total fatty acids	Q1 2.28-4.49 N Quantile: 133	Mean difference	
	Head circumference N Total: 534		Erythrocyte DHA + EPA n-3 Measure: Maternal n-3 Units: % total fatty acids	Q2 4.49-5.25 N Quantile: 134	Mean difference Estimate: 0.3 95% CI(-0.3, 0.9)	
	Head circumference N Total: 534		Erythrocyte DHA + EPA n-3 Measure: Maternal n-3 Units: % total fatty acids	Q3 5.26-6.07 N Quantile: 133	Mean difference Estimate: 0.5 95% CI(-0.1, 1.1)	
	Head circumference N Total: 534		Erythrocyte DHA + EPA n-3 Measure: Maternal n-3 Units: % total fatty acids	Q4 6.07-9.55 N Quantile: 134	Mean difference Estimate: 0.2 95% CI(-0.4, 0.9)	
	Length N Total: 534		Erythrocyte DHA + EPA n-3 Measure: Maternal n-3 Units: % total fatty acids	Q1 2.28-4.49 N Quantile: 133	Mean difference	
	Length N Total: 534		Erythrocyte DHA + EPA n-3 Measure: Maternal n-3 Units: % total fatty acids	Q2 4.49-5.25 N Quantile: 134	Mean difference Estimate: -0.1 95% CI(-0.9, 0.6)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Length N Total: 534		Erythrocyte DHA + EPA n-3 Measure: Maternal n-3 Units: % total fatty acids	Q3 5.26-6.07 N Quantile: 133	Mean difference Estimate: -0.1 95% CI(-0.9, 0.6)	
	Length N Total: 534		Erythrocyte DHA + EPA n-3 Measure: Maternal n-3 Units: % total fatty acids	Q4 6.07-9.55 N Quantile: 134	Mean difference Estimate: 0 95% CI(-0.9, 0.8)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Molto-Puigmarti, et al., 2014[48] Study name: KOALA Birth Cohort Study Study dates: 2000-2002 Study design: Observational prospective Location: Netherlands Funding source / conflict: Multiple foundations and Societies	Study Population: Healthy pregnant women Pregnant enrolled 2669 Pregnant completers 1516 Infants enrolled 2669 Infants completers 1515 Pregnant age: years (.7yrs) Race of Mother: NR (100)	Inclusion Criteria: nr, Described in Ref 37 Exclusion Criteria: nr	Adjustments: Adjusted for child gender, study recruitment group, maternal education, parity, maternal smoking status during pregnancy, maternal alcohol use in pregnancy, and maternal age at delivery

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Molto-Puigmarti 2014[48]	Birth weight N Total: 2606		DHA n-3 Measure: Maternal n-3 Units: mg/d	All N Quantile: na N Cases: na	Coefficient Estimate: 0.16 95% CI(0.008, 0.313)	
	Pregnancy duration N Total: 2606		DHA n-3 Measure: Maternal n-3 Units: mg/d	All N Quantile: na N Cases: na	Coefficient Estimate: 0.004 95% CI(0.001, 0.007)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Morales, et al., 2012[184] Study name: INfancia y Medio Ambiente (INMA) Project Study dates: 2004-2007 Study design: Observational prospective Location: Spain Funding source / conflict: Government Follow-up: 14 months	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 622 Pregnant completers 580 Infants enrolled 622 Infants completers 580 Mother age: 31.6 (4.2) Race of Mother: NR (100)	Inclusion Criteria: to be resident in the study area, to be at least 16 years old, to have a singleton pregnancy, to not have followed any programme of assisted reproduction, to wish to deliver in the reference hospital, and to have no communication problems Exclusion Criteria: NR	Adjustments: Child gender, maternal social class, siblings at birth, maternal smoking in pregnancy, and DDE levels in cord blood for wheezing outcome

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Morales 2012[184]	Wheezing N Total: 197	6 &14 months	AA n-3 Measure: Colostrum fatty acid concentration n-3 Units: weight-percentage (wt%, mg/100 mg) of total fatty acids	Highest vs. lowest tertile odds ratios N Quantile: NR	OR Estimate: 1.34 95% CI(0.44, 4.06)	
	Wheezing N Total: 197	6 &14 months	ALA n-3 Measure: Colostrum fatty acid concentration n-3 Units: weight-percentage (wt%, mg/100 mg) of total fatty acids	Highest vs. lowest tertile odds ratios N Quantile: NR	OR Estimate: 1.57 95% CI(0.42, 5.84)	
	Wheezing N Total: 197	6 &14 months	All n-3 n-3 Measure: Colostrum fatty acid concentration n-3 Units: weight-percentage (wt%, mg/100 mg) of total fatty acids	Highest vs. lowest tertile odds ratios N Quantile: NR	OR Estimate: 1.08 95% CI(0.37, 3.18)	
	Wheezing N Total: 197	6 &14 months	DHA n-3 Measure: Colostrum fatty acid concentration n-3 Units: weight-percentage (wt%, mg/100 mg) of total fatty acids	Highest vs. lowest tertile odds ratios N Quantile: NR	OR Estimate: 0.91 95% CI(0.31, 2.67)	
	Wheezing N Total: 197	6 &14 months	EPA n-3 Measure: Colostrum fatty acid concentration n-3 Units: weight-percentage (wt%, mg/100 mg) of total fatty acids	Highest vs. lowest tertile odds ratios N Quantile: NR	OR Estimate: 0.56 95% CI(0.15, 2.08)	
	Wheezing N Total: 269	7-14 months	AA n-3 Measure: Colostrum fatty acid concentration n-3 Units: weight-percentage (wt%, mg/100 mg) of total fatty acids	Highest vs. lowest tertile odds ratios N Quantile: NR	OR Estimate: 1.36 95% CI(0.69, 2.65)	
	Wheezing N Total: 269	7-14 months	ALA n-3 Measure: Colostrum fatty acid concentration n-3 Units: weight-percentage (wt%, mg/100 mg) of total fatty acids	Highest vs. lowest tertile odds ratios N Quantile: NR	OR Estimate: 0.82 95% CI(0.4, 1.69)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Wheezing N Total: 269	7-14 months	All n-3 n-3 Measure: Colostrum fatty acid concentration n-3 Units: weight-percentage (wt%, mg/100 mg) of total fatty acids	Highest vs. lowest tertile odds ratios N Quantile: NR	OR Estimate: 0.72 95% CI(0.36, 1.44)	
	Wheezing N Total: 269	7-14 months	DHA n-3 Measure: Colostrum fatty acid concentration n-3 Units: weight-percentage (wt%, mg/100 mg) of total fatty acids	Highest vs. lowest tertile odds ratios N Quantile: NR	OR Estimate: 0.94 95% CI(0.48, 1.86)	
	Wheezing N Total: 269	7-14 months	EPA n-3 Measure: Colostrum fatty acid concentration n-3 Units: weight-percentage (wt%, mg/100 mg) of total fatty acids	Highest vs. lowest tertile odds ratios N Quantile: NR	OR Estimate: 0.58 95% CI(0.27, 1.24)	
	Wheezing N Total: 272	0-6 months	AA n-3 Measure: Colostrum fatty acid concentration n-3 Units: weight-percentage (wt%, mg/100 mg) of total fatty acids	Highest vs. lowest tertile odds ratios N Quantile: NR	OR Estimate: 1.19 95% CI(0.51, 2.76)	
	Wheezing N Total: 272	0-6 months	ALA n-3 Measure: Colostrum fatty acid concentration n-3 Units: weight-percentage (wt%, mg/100 mg) of total fatty acids	Highest vs. lowest tertile odds ratios N Quantile: NR	OR Estimate: 1.54 95% CI(0.62, 3.78)	
	Wheezing N Total: 272	0-6 months	All n-3 n-3 Measure: Colostrum fatty acid concentration n-3 Units: weight-percentage (wt%, mg/100 mg) of total fatty acids	Highest vs. lowest tertile odds ratios N Quantile: NR	OR Estimate: 1.35 95% CI(0.58, 3.13)	
	Wheezing N Total: 272	0-6 months	DHA n-3 Measure: Colostrum fatty acid concentration n-3 Units: weight-percentage (wt%, mg/100 mg) of total fatty acids	Highest vs. lowest tertile odds ratios N Quantile: NR	OR Estimate: 0.91 95% CI(0.41, 2.03)	
	Wheezing N Total: 272	0-6 months	EPA n-3 Measure: Colostrum fatty acid concentration n-3 Units: weight-percentage (wt%, mg/100 mg) of total fatty acids	Highest vs. lowest tertile odds ratios N Quantile: NR	OR Estimate: 2.24 95% CI(0.76, 6.55)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Much, et al., 2013[101] Study name: INFAT Study dates: Recruitment: 2006-2009 Follow-up: 1 year Study design: Observational prospective Location: Germany Funding source / conflict: Industry, Government, Some authors employed by industry (companies that make the supplements) Follow-up: 1 year Original, same study, or follow-up studies: Hauner, 2012[37]	Study Population: Healthy infants Breast-feeding women Pregnant enrolled 208 Lactating enrolled 152 at 6 weeks/120 at 4 months Infants enrolled 56 at 4 months/31 at 12 months Lactating enrolled 152 at 6 weeks/120 at 4 months Pregnant age: Intervention: 31.9 Control: 31.6 (Intervention: 4.9 Control: 4.5) Race of Mother: NR (NR)	Inclusion Criteria: Gestational age =15th wk of gestation, between 18 and 43 y of age, pre-pregnancy BMI (in kg/m2) between 18 and 30, willingness to implement the dietary recommendations, sufficient German language skills, and written informed consent Exclusion Criteria: High-risk pregnancy (multiple pregnancy, rhesus incompatibility, hepatitis B infection, or parity >4); hypertension; chronic diseases (e.g., diabetes) or gastrointestinal disorders accompanied by maldigestion, malabsorption, or elevated energy and nutritional requirements (e.g., gluten enteropathy); known metabolic defects (e.g., phenylketonuria); psychiatric diseases; hyperemesis gravidarum; supplementation with n–3 LCPUFAs before randomization; and alcohol abuse and smoking	Adjustments: Gestational age, parity, infant sex, group, ponderal index at birth, breastfeeding status of infants at 6 wk, 4 mo, and 1 yr.

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Much 2013[101]	BMI at 1 yr N Total: 117	1 y	DHA n-3 Measure: Breast milk at 4 mo postpartum n-3 Units: % wt		Coefficient Estimate: 0.86 95% CI(0.11, 1.62)	
	Length at 1 yr N Total: 117	1 y	EPA n-3 Measure: Breast milk at 4 mo postpartum n-3 Units: % wt		Coefficient Estimate: -12.43 95% CI(-20.36, -4.231)	
	Length at 4 mo N Total: 119	4 mo	EPA n-3 Measure: Breast milk at 4 mo postpartum n-3 Units: % wt		Coefficient Estimate: -7.85 95% CI(-14.94, -0.73)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Much, et al., 2013[83] Study name: INFAT Study dates: >2009-<2013 Study design: Observational prospective Location: Germany Funding source / conflict: Industry, Government, Some authors employed by industry (companies that make the supplements), Multiple foundations and Societies, None	Study Population: Healthy infants Breast-feeding women Pregnant enrolled 208 Infants completers 187 Race of Mother: NR (NR)	Inclusion Criteria: Healthy pregnant women at 14th week of gestation Exclusion Criteria: None reported	Adjustments: Pregnancy duration, group, parity, and sex

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Much 2013 [83]	Birth weight N Total: 187		DHA at 32 wks gestation n-3 Measure: Maternal red blood cells n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 24.38 95% CI(0.42, 48.33)	
	Birth weight N Total: 187		n-3 LCPUFA at 32 wks gestation n-3 Measure: Maternal red blood cells n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 20.38 95% CI(2.78, 37.99)	
Much 2013[83]	BMI N Total: 169	12 mo	DHA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: -0.04 95% CI(-0.11, 0.04)	
	BMI N Total: 169	12 mo	n-3 LCPUFA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: -0.02 95% CI(-0.08, 0.04)	
	BMI N Total: 172	4 mo	DHA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 0.04 95% CI(-0.04, 0.12)	
	BMI N Total: 172	4 mo	n-3 LCPUFA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 0.03 95% CI(-0.03, 0.09)	
	BMI N Total: 177	6 wks	DHA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 0.05 95% CI(-0.02, 0.12)	
	BMI N Total: 177	6 wks	n-3 LCPUFA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 0.04 95% CI(-0.01, 0.09)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	BMI N Total: 187	Birth	DHA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 0.04 95% CI(-0.03, 0.1)	
	BMI N Total: 187	Birth	n-3 LCPUFA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 0.03 95% CI(-0.02, 0.08)	
	Head circumference N Total: 169	12 mo	DHA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 0.01 95% CI(-0.08, 0.22)	
	Head circumference N Total: 169	12 mo	n-3 LCPUFA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 0.01 95% CI(-0.05, 0.08)	
	Head circumference N Total: 172	4 mo	DHA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 0.02 95% CI(-0.04, 0.09)	
	Head circumference N Total: 172	4 mo	n-3 LCPUFA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 0.03 95% CI(-0.02, 0.08)	
	Head circumference N Total: 177	6 wks	DHA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 0.02 95% CI(-0.04, 0.1)	
	Head circumference N Total: 177	6 wks	n-3 LCPUFA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 0.02 95% CI(-0.02, 0.07)	
	Head circumference N Total: 187	Birth	DHA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 0.07 95% CI(0, 0.14)	
	Head circumference N Total: 187	Birth	n-3 LCPUFA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 0.06 95% CI(0.01, 0.12)	
	Length N Total: 169	12 mo	DHA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 0.07 95% CI(-0.08, 0.22)	
	Length N Total: 169	12 mo	n-3 LCPUFA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 0.04 95% CI(-0.07, 0.15)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Length N Total: 172	4 mo	DHA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 0.03 95% CI(-0.09, 0.15)	
	Length N Total: 172	4 mo	n-3 LCPUFA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 0.02 95% CI(-0.07, 0.11)	
	Length N Total: 177	6 wks	DHA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 0.05 95% CI(-0.07, 0.18)	
	Length N Total: 177	6 wks	n-3 LCPUFA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 0.05 95% CI(-0.04, 0.15)	
	Length N Total: 187	Birth	DHA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 0.12 95% CI(-0.01, 0.24)	
	Length N Total: 187	Birth	n-3 LCPUFA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 0.1 95% CI(0.01, 0.19)	
	Weight N Total: 169	12 mo	DHA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: -0.99 95% CI(-58.1, 56.12)	
	Weight N Total: 169	12 mo	n-3 LCPUFA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 1.4 95% CI(-40.7, 43.5)	
	Weight N Total: 172	4 mo	DHA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 19.72 95% CI(-19.25, 58.69)	
	Weight N Total: 172	4 mo	n-3 LCPUFA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 15.17 95% CI(-13.49, 43.84)	
	Weight N Total: 177	6 wks	DHA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 24.16 95% CI(-8.96, 57.29)	
	Weight N Total: 177	6 wks	n-3 LCPUFA n-3 Measure: Maternal red blood cells at 32 wks gestation n-3 Units: per unit increase in % of total FA		Coefficient Estimate: 21.53 95% CI(-2.81, 45.86)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Muthayya, et al., 2009[72] Study dates: Jan 2002- Mar 2006 Study design: Observational prospective Location: NR Funding source / conflict: Industry, Government	Study Population: Healthy pregnant women Pregnant enrolled 829 Pregnant completers 676 Pregnant age: group 1, 23 group 2, 23 group 3, 23 total, 24 group 1, 21-26 group 2, 21-27 group 3, 23-29 total: 21-27 Race of Mother: Asian (Indian, 100%)	Inclusion Criteria: pregnant women aged 17–40 years and at <20 weeks of gestation, registered for antenatal screening at the Department of Obstetrics and Gynecology at St John's Medical College Hospital, Exclusion Criteria: Women with multiple pregnancies, those with a clinical diagnosis of chronic illness such as diabetes mellitus, hypertension, heart disease and thyroid disease, those who tested positive for HbSAg/HIV/VDRL infection or who anticipated moving out of the city before delivery were excluded	Adjustments: Adjusted for maternal age, maternal education, parity, maternal weight/maternal weight gain per week and gestational age

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Muthayya 2009[72]	Low birth weight N Total: 419		EPA @ 3rd trimester n-3 Measure: FFQ n-3 Units: mg/day	T1 0.28 N Cases: 133	AOR Estimate: 2.75 95% CI(1.26, 6.02)	
	Low birth weight N Total: 419		EPA @ 3rd trimester n-3 Measure: FFQ n-3 Units: mg/day	T2 3.03 N Cases: 148	AOR Estimate: 2.54 95% CI(1.17, 5.5)	
	Low birth weight N Total: 419		EPA @ 3rd trimester n-3 Measure: FFQ n-3 Units: mg/day	T3 9.53 N Cases: 138	AOR	
	Low birth weight N Total: 675		EPA @ 1st trimester n-3 Measure: FFQ n-3 Units: mg/day	T1 0.24 N Cases: 225	AOR Estimate: 1.61 95% CI(0.92, 2.8)	
	Low birth weight N Total: 675		EPA @ 1st trimester n-3 Measure: FFQ n-3 Units: mg/day	T2 2.1 N Cases: 224	AOR Estimate: 1.05 95% CI(0.59, 1.9)	
	Low birth weight N Total: 675		EPA @ 1st trimester n-3 Measure: FFQ n-3 Units: mg/day	T3 9.37 N Cases: 226	AOR	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Newson, et al., 2004[176] Study name: Avon Longitudinal Study of Parents and Children (ALSPAC) Study dates: Recruitment: April 1, 1991 to December 31, 1992 Follow-up: 42 months Study design: Observational prospective Location: UK Funding source / conflict: Government, Multiple foundations and Societies Follow-up: 42 months Original, same study, or follow-up studies: Golding et al., 2001 (ALSPAC)	Study Population: Healthy infants Pregnant enrolled 4136 Infants enrolled 4202 Infants completers 1762 Infant age: Prenatal Race of Mother: NR (100%)	Inclusion Criteria: Pregnant women with expected date of delivery between April 1, 1991, and December 31, 1992, and place of residence within the 3 Bristol-based health districts of the former county of Avon, United Kingdom Exclusion Criteria: NR for enrollment. Exclusion for analysis: multiple pregnancies or in small missing value categories for various confounders.	Adjustments: Child's sex, gestational age at birth, and birth weight, and for the mother's age, education level, housing tenure, parity, ethnicity, and smoking in pregnancy (for variable categories see Table EI in the Journal's Online Repository at http://www.mosby.com/jaci), as well as maternal atopic disease (asthma, eczema, rhinoconjunctivitis), child's head circumference at birth (< 33 cm, 33-34.99 cm, 35-36.99 cm, 37+ cm, unknown), child's crown to heel length at birth (< 48 cm, 48-50.99 cm, 51-53.99 cm, 54+ cm, unknown), mother's body mass index (from pre-pregnancy self-reported weight and height; < 18.5 kg/m2 , 18.5-24.99 kg/m2 , 25-29.99 kg/m2 , 30+ kg/m2 , unknown), breast-feeding

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Newson 2004[176]	Eczema N Total: 1238	30 months	18:3 n-3 ALA n-3 Measure: Cord blood n-3 Units: % of total RBC membrane phospholipid	All	Per doubling OR Estimate: 1 95% CI(0.9, 1.11)	
	Eczema N Total: 1238	30 months	20:4 n-6 AA n-3 Measure: Cord blood n-3 Units: % of total RBC membrane phospholipid	All	Per doubling OR Estimate: 1.08 95% CI(0.93, 1.25)	
	Eczema N Total: 1238	30 months	20:5 n-3 EPA n-3 Measure: Cord blood n-3 Units: % of total RBC membrane phospholipid	All	Per doubling OR Estimate: 0.95 95% CI(0.86, 1.06)	
	Eczema N Total: 1238	30 months	22:6 n-3 DHA n-3 Measure: Cord blood n-3 Units: % of total RBC membrane phospholipid	All	Per doubling OR Estimate: 1 95% CI(0.91, 1.1)	
	Eczema N Total: 1238	30 months	AA: EPA n-3 Measure: Cord blood n-3 Units: % of total RBC membrane phospholipid	All	Per doubling OR Estimate: 1.14 95% CI(1, 1.31)	
	Eczema N Total: 2945	30 months	18:3 n-3 ALA n-3 Measure: Maternal blood n-3 Units: % of total RBC membrane phospholipid	All	Per doubling OR Estimate: 1 95% CI(0.91, 1.09)	
	Eczema N Total: 2945	30 months	20:4 n-6 AA n-3 Measure: Maternal blood n-3 Units: % of total RBC membrane phospholipid	All	Per doubling OR Estimate: 0.98 95% CI(0.88, 1.1)	
	Eczema N Total: 2945	30 months	20:5 n-3 EPA n-3 Measure: Maternal blood n-3 Units: % of total RBC membrane phospholipid	All	Per doubling OR Estimate: 1.03 95% CI(0.94, 1.12)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Eczema N Total: 2945	30 months	22:6 n-3 DHA n-3 Measure: Maternal blood n-3 Units: % of total RBC membrane phospholipid	All	Per doubling OR Estimate: 1.02 95% CI(0.94, 1.12)	
	Eczema N Total: 2945	30 months	AA: EPA n-3 Measure: Maternal blood n-3 Units: % of total RBC membrane phospholipid	All	Per doubling OR Estimate: 0.95 95% CI(0.85, 1.05)	
	Wheezing N Total: 1191	42 months	18:3 n-3 ALA n-3 Measure: Cord blood n-3 Units: % of total RBC membrane phospholipid	All	Per doubling OR Estimate: 0.99 95% CI(0.85, 1.15)	
	Wheezing N Total: 1191	42 months	20:4 n-6 AA n-3 Measure: Cord blood n-3 Units: % of total RBC membrane phospholipid	All	Per doubling OR Estimate: 1.05 95% CI(0.86, 1.27)	
	Wheezing N Total: 1191	42 months	20:5 n-3 EPA n-3 Measure: Cord blood n-3 Units: % of total RBC membrane phospholipid	All	Per doubling OR Estimate: 1.01 95% CI(0.87, 1.17)	
	Wheezing N Total: 1191	42 months	22:6 n-3 DHA n-3 Measure: Cord blood n-3 Units: % of total RBC membrane phospholipid	All	Per doubling OR Estimate: 1.05 95% CI(0.93, 1.19)	
	Wheezing N Total: 1191	42 months	AA: EPA n-3 Measure: Cord blood n-3 Units: % of total RBC membrane phospholipid	All	Per doubling OR Estimate: 1.01 95% CI(0.85, 1.21)	
	Wheezing N Total: 2764	42 months	18:3 n-3 ALA n-3 Measure: Maternal blood n-3 Units: % of total RBC membrane phospholipid	All	Per doubling OR Estimate: 1.03 95% CI(0.91, 1.16)	
	Wheezing N Total: 2764	42 months	20:4 n-6 AA n-3 Measure: Maternal blood n-3 Units: % of total RBC membrane phospholipid	All	Per doubling OR Estimate: 1.02 95% CI(0.86, 1.2)	
	Wheezing N Total: 2764	42 months	20:5 n-3 EPA n-3 Measure: Maternal blood n-3 Units: % of total RBC membrane phospholipid	All	Per doubling OR Estimate: 0.94 95% CI(0.84, 1.06)	
	Wheezing N Total: 2764	42 months	22:6 n-3 DHA n-3 Measure: Maternal blood n-3 Units: % of total RBC membrane phospholipid	All	Per doubling OR Estimate: 0.99 95% CI(0.86, 1.13)	
	Wheezing N Total: 2764	42 months	AA: EPA n-3 Measure: Maternal blood n-3 Units: % of total RBC membrane phospholipid	All	Per doubling OR Estimate: 1.11 95% CI(0.95, 1.3)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Notenboom, et al., 2011[179] Study name: KOALA Birth Cohort Study Study dates: Recruitment from October 2000 onwards and Follow-up: 6-7 years Study design: Observational prospective Location: Netherlands Funding source / conflict: Industry, Government, Multiple foundations and Societies Follow-up: 3 - 84 months	Study Population: Healthy infants Healthy pregnant women Infants enrolled 1275 Infants completers 1253 (samples for 815) Mother age: 32.6 (3.8) Race of Mother: White European (Dutch 96.3%)	Inclusion Criteria: Conventional participants: participation in ongoing study of pelvic girdle pain Alternative participants: frequented locations associated with organic diet and similar lifestyles Subsample: participants recruited from January 2002 onwards who consented to biosampling. Exclusion Criteria: Current multiple pregnancy n=9 Prematurity n=15 Perinatal infant death n=2 Down syndrome n=4 No response after birth n=51	Adjustments: Adjusted for recruitment group, maternal age, maternal ethnicity, maternal education level, maternal smoking during pregnancy, parental history of atopy, term of gestation, season of birth, gender, birth weight, mode of delivery, exposure to environmental tobacco, presence of older siblings and sibling atopy, breastfeeding, child day care, and pets at home

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Notenboom 2011[179]	Allergic rhinoconjunctivitis N Total: 951	6-7 years	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -6.46 N Quantile: 192 N Cases: 13	OR	
	Allergic rhinoconjunctivitis N Total: 951	6-7 years	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 6.47-7.15 N Quantile: 199 N Cases: 14	OR Estimate: 1.04 95% CI(0.47, 2.27)	
	Allergic rhinoconjunctivitis N Total: 951	6-7 years	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 7.16-7.85 N Quantile: 190 N Cases: 15	OR Estimate: 1.17 95% CI(0.54, 2.53)	
	Allergic rhinoconjunctivitis N Total: 951	6-7 years	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 7.86-8.6 N Quantile: 199 N Cases: 12	OR Estimate: 0.87 95% CI(0.39, 1.197)	
	Allergic rhinoconjunctivitis N Total: 951	6-7 years	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 8.61- N Quantile: 171 N Cases: 15	OR Estimate: 1.3 95% CI(0.59, 2.83)	
	Allergic rhinoconjunctivitis N Total: 951	6-7 years	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -60.72 N Quantile: 176 N Cases: 14	OR	
	Allergic rhinoconjunctivitis N Total: 951	6-7 years	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 60.73-72.35 N Quantile: 189 N Cases: 16	OR Estimate: 1.07 95% CI(0.51, 2.26)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Allergic rhinoconjunctivitis N Total: 951	6-7 years	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 72.36-82.29 N Quantile: 191 N Cases: 8	OR Estimate: 0.51 95% CI(0.21, 1.25)	
	Allergic rhinoconjunctivitis N Total: 951	6-7 years	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 83.3-102.69 N Quantile: 205 N Cases: 15	OR Estimate: 0.92 95% CI(0.43, 2)	
	Allergic rhinoconjunctivitis N Total: 951	6-7 years	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 102.7- N Quantile: 190 N Cases: 16	OR Estimate: 1.09 95% CI(0.51, 2.31)	
	Allergic rhinoconjunctivitis N Total: 951	6-7 years	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -1.91 N Quantile: 195 N Cases: 8	OR	
	Allergic rhinoconjunctivitis N Total: 951	6-7 years	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 1.92-2.24 N Quantile: 194 N Cases: 14	OR Estimate: 1.81 95% CI(0.74, 4.41)	
	Allergic rhinoconjunctivitis N Total: 951	6-7 years	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 2.25-2.52 N Quantile: 187 N Cases: 18	OR Estimate: 2.48 95% CI(1.05, 5.85)	
	Allergic rhinoconjunctivitis N Total: 951	6-7 years	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 2.53-2.84 N Quantile: 183 N Cases: 12	OR Estimate: 1.62 95% CI(0.64, 4.06)	
	Allergic rhinoconjunctivitis N Total: 951	6-7 years	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 2.85- N Quantile: 192 N Cases: 17	OR Estimate: 2.24 95% CI(0.94, 5.34)	
	Allergic rhinoconjunctivitis N Total: 951	6-7 years	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -3.93 N Quantile: 195 N Cases: 19	OR	
	Allergic rhinoconjunctivitis N Total: 951	6-7 years	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 3.94-4.44 N Quantile: 185 N Cases: 10	OR Estimate: 0.53 95% CI(0.24, 1.17)	
	Allergic rhinoconjunctivitis N Total: 951	6-7 years	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 4.45-4.93 N Quantile: 182 N Cases: 16	OR Estimate: 0.89 95% CI(0.44, 1.79)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Allergic rhinoconjunctivitis N Total: 951	6-7 years	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 4.94-5.64 N Quantile: 191 N Cases: 16	OR Estimate: 0.85 95% CI(0.42, 1.71)	
	Allergic rhinoconjunctivitis N Total: 951	6-7 years	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 5.65- N Quantile: 198 N Cases: 8	OR Estimate: 0.4 95% CI(0.17, 0.92)	
	Allergic sensitization N Total: 768	24 months	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -6.46 N Quantile: 156 N Cases: 45	OR	
	Allergic sensitization N Total: 768	24 months	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 6.47-7.15 N Quantile: 159 N Cases: 42	OR Estimate: 0.81 95% CI(0.48, 1.34)	
	Allergic sensitization N Total: 768	24 months	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 7.16-7.85 N Quantile: 159 N Cases: 52	OR Estimate: 1.15 95% CI(0.7, 1.9)	
	Allergic sensitization N Total: 768	24 months	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 7.86-8.6 N Quantile: 153 N Cases: 41	OR Estimate: 0.86 95% CI(0.51, 1.46)	
	Allergic sensitization N Total: 768	24 months	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 8.61- N Quantile: 141 N Cases: 33	OR Estimate: 0.69 95% CI(0.39, 1.23)	
	Allergic sensitization N Total: 768	24 months	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -60.72 N Quantile: 152 N Cases: 44	OR	
	Allergic sensitization N Total: 768	24 months	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 60.73-72.35 N Quantile: 158 N Cases: 42	OR Estimate: 0.88 95% CI(0.53, 1.49)	
	Allergic sensitization N Total: 768	24 months	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 72.36-82.29 N Quantile: 152 N Cases: 41	OR Estimate: 0.96 95% CI(0.57, 1.62)	
	Allergic sensitization N Total: 768	24 months	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 83.3-102.69 N Quantile: 151 N Cases: 47	OR Estimate: 1.1 95% CI(0.65, 1.85)	
	Allergic sensitization N Total: 768	24 months	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 102.7- N Quantile: 155 N Cases: 39	OR Estimate: 0.82 95% CI(0.48, 1.4)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Allergic sensitization N Total: 768	24 months	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -1.91 N Quantile: 143 N Cases: 40	OR	
	Allergic sensitization N Total: 768	24 months	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 1.92-2.24 N Quantile: 150 N Cases: 42	OR Estimate: 1.01 95% CI(0.59, 1.72)	
	Allergic sensitization N Total: 768	24 months	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 2.25-2.52 N Quantile: 155 N Cases: 44	OR Estimate: 1.03 95% CI(0.6, 1.76)	
	Allergic sensitization N Total: 768	24 months	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 2.53-2.84 N Quantile: 167 N Cases: 44	OR Estimate: 0.92 95% CI(0.53, 1.6)	
	Allergic sensitization N Total: 768	24 months	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 2.85- N Quantile: 153 N Cases: 43	OR Estimate: 1.04 95% CI(0.6, 1.8)	
	Allergic sensitization N Total: 768	24 months	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -3.93 N Quantile: 169 N Cases: 51	OR	
	Allergic sensitization N Total: 768	24 months	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 3.94-4.44 N Quantile: 146 N Cases: 39	OR Estimate: 0.79 95% CI(0.47, 1.33)	
	Allergic sensitization N Total: 768	24 months	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 4.45-4.93 N Quantile: 154 N Cases: 43	OR Estimate: 0.83 95% CI(0.5, 1.4)	
	Allergic sensitization N Total: 768	24 months	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 4.94-5.64 N Quantile: 159 N Cases: 38	OR Estimate: 0.73 95% CI(0.44, 1.24)	
	Allergic sensitization N Total: 768	24 months	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 5.65- N Quantile: 140 N Cases: 42	OR Estimate: 0.94 95% CI(0.56, 1.6)	
	Asthma N Total: 951	6-7 years	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -6.46 N Quantile: NR N Cases: NR	OR	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Asthma N Total: 951	6-7 years	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 6.47-7.15 N Quantile: NR N Cases: NR	OR Estimate: 1.69 95% CI(0.7, 4.1)	
	Asthma N Total: 951	6-7 years	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 7.16-7.85 N Quantile: NR N Cases: NR	OR Estimate: 1.29 95% CI(0.52, 3.2)	
	Asthma N Total: 951	6-7 years	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 7.86-8.6 N Quantile: NR N Cases: NR	OR Estimate: 0.82 95% CI(0.31, 2.15)	
	Asthma N Total: 951	6-7 years	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 8.61- N Quantile: NR N Cases: NR	OR Estimate: 1.7 95% CI(0.67, 4.33)	
	Asthma N Total: 951	6-7 years	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -60.72 N Quantile: NR N Cases: NR	OR	
	Asthma N Total: 951	6-7 years	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 60.73-72.35 N Quantile: NR N Cases: NR	OR Estimate: 1.14 95% CI(0.51, 2.55)	
	Asthma N Total: 951	6-7 years	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 72.36-82.29 N Quantile: NR N Cases: NR	OR Estimate: 0.55 95% CI(0.21, 1.45)	
	Asthma N Total: 951	6-7 years	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 83.3-102.69 N Quantile: NR N Cases: NR	OR Estimate: 1.08 95% CI(0.47, 2.49)	
	Asthma N Total: 951	6-7 years	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 102.7- N Quantile: NR N Cases: NR	OR Estimate: 0.6 95% CI(0.23, 1.56)	
	Asthma N Total: 951	6-7 years	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -1.91 N Quantile: NR N Cases: NR	OR	
	Asthma N Total: 951	6-7 years	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 1.92-2.24 N Quantile: NR N Cases: NR	OR Estimate: 1.12 95% CI(0.43, 2.89)	
	Asthma N Total: 951	6-7 years	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 2.25-2.52 N Quantile: NR N Cases: NR	OR Estimate: 1.47 95% CI(0.56, 3.85)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Asthma N Total: 951	6-7 years	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 2.53-2.84 N Quantile: NR N Cases: NR	OR Estimate: 2.07 95% CI(0.82, 5.24)	
	Asthma N Total: 951	6-7 years	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 2.85- N Quantile: NR N Cases: NR	OR Estimate: 1.87 95% CI(0.76, 4.63)	
	Asthma N Total: 951	6-7 years	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -3.93 N Quantile: NR N Cases: NR	OR	
	Asthma N Total: 951	6-7 years	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 3.94-4.44 N Quantile: NR N Cases: NR	OR Estimate: 1.85 95% CI(0.83, 4.12)	
	Asthma N Total: 951	6-7 years	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 4.45-4.93 N Quantile: NR N Cases: NR	OR Estimate: 1.12 95% CI(0.45, 2.71)	
	Asthma N Total: 951	6-7 years	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 4.94-5.64 N Quantile: NR N Cases: NR	OR Estimate: 0.92 95% CI(0.37, 2.29)	
	Asthma N Total: 951	6-7 years	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 5.65- N Quantile: NR N Cases: NR	OR Estimate: 0.85 95% CI(0.34, 2.16)	
	Atopic dermatitis N Total: 807	24 months	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -6.46 N Quantile: 161 N Cases: 20	OR	
	Atopic dermatitis N Total: 807	24 months	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 6.47-7.15 N Quantile: 166 N Cases: 23	OR Estimate: 1.15 95% CI(0.59, 2.28)	
	Atopic dermatitis N Total: 807	24 months	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 7.16-7.85 N Quantile: 166 N Cases: 24	OR Estimate: 1.24 95% CI(0.63, 2.44)	
	Atopic dermatitis N Total: 807	24 months	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 7.86-8.6 N Quantile: 162 N Cases: 26	OR Estimate: 1.35 95% CI(0.79, 2.65)	
	Atopic dermatitis N Total: 807	24 months	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 8.61- N Quantile: 152 N Cases: 18	OR Estimate: 0.94 95% CI(0.44, 1.98)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Atopic dermatitis N Total: 807	24 months	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -60.72 N Quantile: 159 N Cases: 18	OR	
	Atopic dermatitis N Total: 807	24 months	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 60.73-72.35 N Quantile: 163 N Cases: 18	OR Estimate: 0.89 95% CI(0.43, 1.85)	
	Atopic dermatitis N Total: 807	24 months	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 72.36-82.29 N Quantile: 156 N Cases: 24	OR Estimate: 1.63 95% CI(0.81, 3.27)	
	Atopic dermatitis N Total: 807	24 months	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 83.3-102.69 N Quantile: 161 N Cases: 31	OR Estimate: 2.17 95% CI(1.1, 4.27)	
	Atopic dermatitis N Total: 807	24 months	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 102.7- N Quantile: 168 N Cases: 20	OR Estimate: 1.16 95% CI(0.56, 2.39)	
	Atopic dermatitis N Total: 807	24 months	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -1.91 N Quantile: 155 N Cases: 23	OR	
	Atopic dermatitis N Total: 807	24 months	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 1.92-2.24 N Quantile: 154 N Cases: 21	OR Estimate: 0.94 95% CI(0.49, 1.83)	
	Atopic dermatitis N Total: 807	24 months	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 2.25-2.52 N Quantile: 162 N Cases: 24	OR Estimate: 1.21 95% CI(0.63, 2.35)	
	Atopic dermatitis N Total: 807	24 months	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 2.53-2.84 N Quantile: 175 N Cases: 22	OR Estimate: 0.98 95% CI(0.49, 2)	
	Atopic dermatitis N Total: 807	24 months	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 2.85- N Quantile: 162 N Cases: 21	OR Estimate: 0.9 95% CI(0.45, 1.81)	
	Atopic dermatitis N Total: 807	24 months	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -3.93 N Quantile: 174 N Cases: 22	OR	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Atopic dermatitis N Total: 807	24 months	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 3.94-4.44 N Quantile: 155 N Cases: 24	OR Estimate: 1.24 95% CI(0.64, 2.42)	
	Atopic dermatitis N Total: 807	24 months	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 4.45-4.93 N Quantile: 163 N Cases: 24	OR Estimate: 1.1 95% CI(0.56, 2.17)	
	Atopic dermatitis N Total: 807	24 months	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 4.94-5.64 N Quantile: 164 N Cases: 21	OR Estimate: 1 95% CI(0.5, 1.98)	
	Atopic dermatitis N Total: 807	24 months	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 5.65- N Quantile: 151 N Cases: 20	OR Estimate: 0.92 95% CI(0.46, 1.86)	
	Eczema N Total: 951	6-7 years	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -6.46 N Quantile: NR N Cases: NR	OR	
	Eczema N Total: 951	6-7 years	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 6.47-7.15 N Quantile: NR N Cases: NR	OR Estimate: 0.94 95% CI(0.67, 1.31)	
	Eczema N Total: 951	6-7 years	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 7.16-7.85 N Quantile: NR N Cases: NR	OR Estimate: 1.03 95% CI(0.73, 1.44)	
	Eczema N Total: 951	6-7 years	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 7.86-8.6 N Quantile: NR N Cases: NR	OR Estimate: 0.77 95% CI(0.55, 1.09)	
	Eczema N Total: 951	6-7 years	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 8.61- N Quantile: NR N Cases: NR	OR Estimate: 0.81 95% CI(0.56, 1.15)	
	Eczema N Total: 951	6-7 years	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -60.72 N Quantile: NR N Cases: NR	OR	
	Eczema N Total: 951	6-7 years	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 60.73-72.35 N Quantile: NR N Cases: NR	OR Estimate: 1.04 95% CI(0.73, 1.47)	
	Eczema N Total: 951	6-7 years	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 72.36-82.29 N Quantile: NR N Cases: NR	OR Estimate: 1.12 95% CI(0.8, 1.57)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Eczema N Total: 951	6-7 years	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 83.3-102.69 N Quantile: NR N Cases: NR	OR Estimate: 0.83 95% CI(0.58, 1.19)	
	Eczema N Total: 951	6-7 years	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 102.7- N Quantile: NR N Cases: NR	OR Estimate: 0.94 95% CI(0.66, 1.34)	
	Eczema N Total: 951	6-7 years	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -1.91 N Quantile: NR N Cases: NR	OR	
	Eczema N Total: 951	6-7 years	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 1.92-2.24 N Quantile: NR N Cases: NR	OR Estimate: 0.72 95% CI(0.51, 1)	
	Eczema N Total: 951	6-7 years	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 2.25-2.52 N Quantile: NR N Cases: NR	OR Estimate: 0.68 95% CI(0.49, 0.96)	
	Eczema N Total: 951	6-7 years	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 2.53-2.84 N Quantile: NR N Cases: NR	OR Estimate: 0.7 95% CI(0.49, 0.98)	
	Eczema N Total: 951	6-7 years	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 2.85- N Quantile: NR N Cases: NR	OR Estimate: 0.6 95% CI(0.42, 0.87)	
	Eczema N Total: 951	6-7 years	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -3.93 N Quantile: NR N Cases: NR	OR	
	Eczema N Total: 951	6-7 years	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 3.94-4.44 N Quantile: NR N Cases: NR	OR Estimate: 1.21 95% CI(0.85, 1.73)	
	Eczema N Total: 951	6-7 years	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 4.45-4.93 N Quantile: NR N Cases: NR	OR Estimate: 1.02 95% CI(0.71, 1.47)	
	Eczema N Total: 951	6-7 years	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 4.94-5.64 N Quantile: NR N Cases: NR	OR Estimate: 1.3 95% CI(0.91, 1.85)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Eczema N Total: 951	6-7 years	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 5.65- N Quantile: NR N Cases: NR	OR Estimate: 1.29 95% CI(0.91, 1.83)	
	High total IgE N Total: 776	24 months	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -6.46 N Quantile: 158 N Cases: 57	OR	
	High total IgE N Total: 776	24 months	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 6.47-7.15 N Quantile: 159 N Cases: 44	OR Estimate: 0.69 95% CI(0.42, 1.15)	
	High total IgE N Total: 776	24 months	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 7.16-7.85 N Quantile: 162 N Cases: 67	OR Estimate: 1.29 95% CI(0.8, 2.09)	
	High total IgE N Total: 776	24 months	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 7.86-8.6 N Quantile: 153 N Cases: 49	OR Estimate: 0.83 95% CI(0.5, 1.37)	
	High total IgE N Total: 776	24 months	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 8.61- N Quantile: 144 N Cases: 39	OR Estimate: 0.72 95% CI(0.42, 1.24)	
	High total IgE N Total: 776	24 months	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -60.72 N Quantile: 152 N Cases: 47	OR	
	High total IgE N Total: 776	24 months	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 60.73-72.35 N Quantile: 158 N Cases: 43	OR Estimate: 0.82 95% CI(0.5, 1.41)	
	High total IgE N Total: 776	24 months	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 72.36-82.29 N Quantile: 154 N Cases: 51	OR Estimate: 1.04 95% CI(0.63, 1.72)	
	High total IgE N Total: 776	24 months	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 83.3-102.69 N Quantile: 153 N Cases: 63	OR Estimate: 1.42 95% CI(0.86, 2.35)	
	High total IgE N Total: 776	24 months	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 102.7- N Quantile: 159 N Cases: 52	OR Estimate: 0.88 95% CI(0.53, 1.47)	
	High total IgE N Total: 776	24 months	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -1.91 N Quantile: 147 N Cases: 51	OR	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	High total IgE N Total: 776	24 months	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 1.92-2.24 N Quantile: 150 N Cases: 46	OR Estimate: 0.83 95% CI(0.5, 1.39)	
	High total IgE N Total: 776	24 months	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 2.25-2.52 N Quantile: 155 N Cases: 53	OR Estimate: 0.97 95% CI(0.58, 1.61)	
	High total IgE N Total: 776	24 months	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 2.53-2.84 N Quantile: 169 N Cases: 50	OR Estimate: 0.84 95% CI(0.5, 1.42)	
	High total IgE N Total: 776	24 months	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 2.85- N Quantile: 155 N Cases: 56	OR Estimate: 1.02 95% CI(0.61, 1.71)	
	High total IgE N Total: 776	24 months	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -3.93 N Quantile: 169 N Cases: 63	OR	
	High total IgE N Total: 776	24 months	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 3.94-4.44 N Quantile: 149 N Cases: 44	OR Estimate: 0.74 95% CI(0.45, 1.22)	
	High total IgE N Total: 776	24 months	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 4.45-4.93 N Quantile: 156 N Cases: 54	OR Estimate: 0.93 95% CI(0.57, 1.52)	
	High total IgE N Total: 776	24 months	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 4.94-5.64 N Quantile: 159 N Cases: 48	OR Estimate: 0.79 95% CI(0.48, 1.3)	
	High total IgE N Total: 776	24 months	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 5.65- N Quantile: 143 N Cases: 47	OR Estimate: 0.88 95% CI(0.53, 1.46)	
	Wheeze N Total: 951	6-7 years	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -6.46 N Quantile: NR N Cases: NR	OR	
	Wheeze N Total: 951	6-7 years	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 6.47-7.15 N Quantile: NR N Cases: NR	OR Estimate: 1.23 95% CI(0.87, 1.73)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Wheeze N Total: 951	6-7 years	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 7.16-7.85 N Quantile: NR N Cases: NR	OR Estimate: 1.08 95% CI(0.78, 1.5)	
	Wheeze N Total: 951	6-7 years	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 7.86-8.6 N Quantile: NR N Cases: NR	OR Estimate: 1.08 95% CI(0.78, 1.49)	
	Wheeze N Total: 951	6-7 years	AA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 8.61- N Quantile: NR N Cases: NR	OR Estimate: 1.03 95% CI(0.74, 1.44)	
	Wheeze N Total: 951	6-7 years	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -60.72 N Quantile: NR N Cases: NR	OR	
	Wheeze N Total: 951	6-7 years	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 60.73-72.35 N Quantile: NR N Cases: NR	OR Estimate: 1.04 95% CI(0.76, 1.42)	
	Wheeze N Total: 951	6-7 years	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 72.36-82.29 N Quantile: NR N Cases: NR	OR Estimate: 0.87 95% CI(0.64, 1.19)	
	Wheeze N Total: 951	6-7 years	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 83.3-102.69 N Quantile: NR N Cases: NR	OR Estimate: 0.9 95% CI(0.66, 1.23)	
	Wheeze N Total: 951	6-7 years	Ratio LA to ALA n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 102.7- N Quantile: NR N Cases: NR	OR Estimate: 0.91 95% CI(0.68, 1.23)	
	Wheeze N Total: 951	6-7 years	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -1.91 N Quantile: NR N Cases: NR	OR	
	Wheeze N Total: 951	6-7 years	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 1.92-2.24 N Quantile: NR N Cases: NR	OR Estimate: 0.88 95% CI(0.63, 1.23)	
	Wheeze N Total: 951	6-7 years	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 2.25-2.52 N Quantile: NR N Cases: NR	OR Estimate: 1.03 95% CI(0.75, 1.42)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Wheeze N Total: 951	6-7 years	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 2.53-2.84 N Quantile: NR N Cases: NR	OR Estimate: 0.83 95% CI(0.59, 1.18)	
	Wheeze N Total: 951	6-7 years	Ratio n-6 LCPs (LGLA and AA) to n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 2.85- N Quantile: NR N Cases: NR	OR Estimate: 0.97 95% CI(0.7, 1.35)	
	Wheeze N Total: 951	6-7 years	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q1 -3.93 N Quantile: NR N Cases: NR	OR	
	Wheeze N Total: 951	6-7 years	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q2 3.94-4.44 N Quantile: NR N Cases: NR	OR Estimate: 0.96 95% CI(0.7, 1.31)	
	Wheeze N Total: 951	6-7 years	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q3 4.45-4.93 N Quantile: NR N Cases: NR	OR Estimate: 1.12 95% CI(0.82, 1.53)	
	Wheeze N Total: 951	6-7 years	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q4 4.94-5.64 N Quantile: NR N Cases: NR	OR Estimate: 1.15 95% CI(0.85, 1.57)	
	Wheeze N Total: 951	6-7 years	n-3 LCPs (EPA, DPA n-3, DHA) n-3 Measure: maternal venous plasma phospholipids n-3 Units: wt%	Q5 5.65- N Quantile: NR N Cases: NR	OR Estimate: 0.98 95% CI(0.7, 1.37)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Nwaru, et al., 2012[180] Study name: Finnish Type 1 Diabetes Prediction and Prevention Nutrition Study Study dates: Infants recruited between 20 October 1997 and 29 February 2004; Follow-up to 5 years of age Study design: Observational prospective Location: Finland Funding source / conflict: Government, Multiple foundations and Societies Follow-up: 5 years	Study Population: NR Pregnant enrolled NR Pregnant completers 3523 Infants enrolled 3253 Infants completers 2441 Infant age: birth Race of Mother: White European (100%)	Inclusion Criteria: Newborn infants with human leucocyte antigen (HLA)- conferred susceptibility to type 1 diabetes recruited from three university hospitals in Finland Exclusion Criteria: Infants with severe systemic disease or anomalies, or both parents non-Caucasian	Adjustments: Sex of child, hospital of birth, duration of gestation, maternal age at delivery, maternal basic education, maternal smoking during pregnancy, mode of delivery, number of siblings at the time of the child's birth, parental asthma, parental allergic rhinitis, pets at home by 1 year of age. A second adjusted model was computed for the FA in which potentially confounding nutrients, vitamin C, Zn, Se, vitamin D and vitamin E were included as additional covariates

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Nwaru 2012[180]	Allergic rhinitis N Total: 2441	5 years	ALA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q1 -4.45 N Quantile: NR N Cases: NR	OR Estimate: 1.01 95% CI(0.79, 1.29)	
	Allergic rhinitis N Total: 2441	5 years	ALA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q2 & Q3 4.45-6.4 N Quantile: NR N Cases: NR	OR	
	Allergic rhinitis N Total: 2441	5 years	ALA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q4 6.4-8.9 N Quantile: NR N Cases: NR	OR Estimate: 0.74 95% CI(0.56, 0.99)	
	Allergic rhinitis N Total: 2441	5 years	DHA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q1 -0.19 N Quantile: NR N Cases: NR	OR Estimate: 0.94 95% CI(0.72, 1.22)	
	Allergic rhinitis N Total: 2441	5 years	DHA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q2 & Q3 0.19-0.6 N Quantile: NR N Cases: NR	OR	
	Allergic rhinitis N Total: 2441	5 years	DHA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q4 0.6-3.5 N Quantile: NR N Cases: NR	OR Estimate: 0.93 95% CI(0.72, 1.21)	
	Allergic rhinitis N Total: 2441	5 years	EPA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q1 -0.07 N Quantile: NR N Cases: NR	OR Estimate: 0.99 95% CI(0.76, 1.29)	
	Allergic rhinitis N Total: 2441	5 years	EPA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q2 & Q3 0.07-0.23 N Quantile: NR N Cases: NR	OR	
	Allergic rhinitis N Total: 2441	5 years	EPA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q4 0.23-1.25 N Quantile: NR N Cases: NR	OR Estimate: 0.99 95% CI(0.76, 1.28)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Allergic rhinitis N Total: 2441	5 years	Ratio of n-6 to n-3 PUFA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q1 NR-NR N Quantile: NR N Cases: NR	OR Estimate: 1.09 95% CI(0.84, 1.43)	
	Allergic rhinitis N Total: 2441	5 years	Ratio of n-6 to n-3 PUFA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q2 & Q3 NR-NR N Quantile: NR N Cases: NR	OR	
	Allergic rhinitis N Total: 2441	5 years	Ratio of n-6 to n-3 PUFA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q4 NR-NR N Quantile: NR N Cases: NR	OR Estimate: 1.35 95% CI(1.05, 1.73)	
	Allergic rhinitis N Total: 2441	5 years	n-3 PUFA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q1 -5.55 N Quantile: NR N Cases: NR	OR Estimate: 0.89 95% CI(0.69, 1.15)	
	Allergic rhinitis N Total: 2441	5 years	n-3 PUFA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q2 & Q3 5.55-7.34 N Quantile: NR N Cases: NR	OR	
	Allergic rhinitis N Total: 2441	5 years	n-3 PUFA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q4 7.35-11.28 N Quantile: NR N Cases: NR	OR Estimate: 0.82 95% CI(0.63, 1.08)	
	Atopic eczema N Total: 2441	5 years	ALA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q1 -4.45 N Quantile: NR N Cases: NR	OR Estimate: 1.05 95% CI(0.86, 1.3)	
	Atopic eczema N Total: 2441	5 years	ALA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q2 & Q3 4.45-6.4 N Quantile: NR N Cases: NR	OR	
	Atopic eczema N Total: 2441	5 years	ALA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q4 6.4-8.9 N Quantile: NR N Cases: NR	OR Estimate: 0.99 95% CI(0.8, 1.23)	
	Atopic eczema N Total: 2441	5 years	DHA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q1 -0.19 N Quantile: NR N Cases: NR	OR Estimate: 1.18 95% CI(0.95, 1.46)	
	Atopic eczema N Total: 2441	5 years	DHA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q2 & Q3 0.19-0.6 N Quantile: NR N Cases: NR	OR	
	Atopic eczema N Total: 2441	5 years	DHA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q4 0.6-3.5 N Quantile: NR N Cases: NR	OR Estimate: 0.98 95% CI(0.79, 1.2)	
	Atopic eczema N Total: 2441	5 years	EPA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q1 -0.07 N Quantile: NR N Cases: NR	OR Estimate: 1.07 95% CI(0.86, 1.33)	
	Atopic eczema N Total: 2441	5 years	EPA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q2 & Q3 0.07-0.23 N Quantile: NR N Cases: NR	OR	
	Atopic eczema N Total: 2441	5 years	EPA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q4 0.23-1.25 N Quantile: NR N Cases: NR	OR Estimate: 0.94 95% CI(0.76, 1.16)	
	Atopic eczema N Total: 2441	5 years	Ratio of n-6 to n-3 PUFA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q1 NR-NR N Quantile: NR N Cases: NR	OR Estimate: 0.99 95% CI(0.8, 1.22)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Atopic eczema N Total: 2441	5 years	Ratio of n-6 to n-3 PUFA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q2 & Q3 NR-NR N Quantile: NR N Cases: NR	OR	
	Atopic eczema N Total: 2441	5 years	Ratio of n-6 to n-3 PUFA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q4 NR-NR N Quantile: NR N Cases: NR	OR Estimate: 1.01 95% CI(0.82, 1.24)	
	Atopic eczema N Total: 2441	5 years	n-3 PUFA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q1 -5.55 N Quantile: NR N Cases: NR	OR Estimate: 1.03 95% CI(0.84, 1.27)	
	Atopic eczema N Total: 2441	5 years	n-3 PUFA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q2 & Q3 5.55-7.34 N Quantile: NR N Cases: NR	OR	
	Atopic eczema N Total: 2441	5 years	n-3 PUFA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q4 7.35-11.28 N Quantile: NR N Cases: NR	OR Estimate: 0.93 95% CI(0.75, 1.14)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Oken, et al., 2004[46] Study name: Project Viva Study dates: 1999-2002 Study design: Observational prospective Location: US Funding source / conflict: Government, Multiple foundations and Societies	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 2109 Pregnant completers 2109 Pregnant age: 14-<20, 3% 20-<25, 6% 25-<30, 21% 30-<35, 42% 35=<40, 23% >=40, 4% (14-44) Race of Mother: White European (66) Black (16) Asian (6) Hispanic (7) Other race/ethnicity (4)	Inclusion Criteria: delivered a live infant, and completed at least one dietary questionnaire Exclusion Criteria: taking cod liver or fish oil supplement	Adjustments: Enrollment site, infant sex, and maternal age, height, intrapartum weight gain, pre-pregnancy BMI, race/ethnicity, smoking during pregnancy, education, and gravidity

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Oken 2004[46]	Birth weight N Total: 1663		DHA+EPA n-3 Measure: FFQ n-3 Units: g/day	Q1 0.02 N Quantile: 416 N Cases: NR	50 95% CI(-19, 119)	
	Birth weight N Total: 1663		DHA+EPA n-3 Measure: FFQ n-3 Units: g/day	Q2 0.09 N Quantile: 416 N Cases: NR	49 95% CI(-19, 117)	
	Birth weight N Total: 1663		DHA+EPA n-3 Measure: FFQ n-3 Units: g/day	Q3 0.18 N Quantile: 416 N Cases: NR	-23 95% CI(-92, 47)	
	Birth weight N Total: 1663		DHA+EPA n-3 Measure: FFQ n-3 Units: g/day	Q4 0.38 N Quantile: 416 N Cases: NR		
	Birth weight N Total: 1797		DHA+EPA n-3 Measure: FFQ n-3 Units: g/day	Q1 0.02 N Quantile: 449 N Cases: NR	94 95% CI(23, 166)	
	Birth weight N Total: 1797		DHA+EPA n-3 Measure: FFQ n-3 Units: g/day	Q2 0.09 N Quantile: 449 N Cases: NR	35 95% CI(-36, 107)	
	Birth weight N Total: 1797		DHA+EPA n-3 Measure: FFQ n-3 Units: g/day	Q3 0.18 N Quantile: 449 N Cases: NR	32 95% CI(-39, 103)	
	Birth weight N Total: 1797		DHA+EPA n-3 Measure: FFQ n-3 Units: g/day	Q4 0.36 N Quantile: 449 N Cases: NR		
	Birth weight N Total: 2070		DHA+EPA n-3 Measure: FFQ n-3 Units: g/day	Q1+Q2 0.05 N Quantile: 1035 N Cases: NR	90 95% CI(33, 147)	
	Birth weight N Total: 2070		DHA+EPA n-3 Measure: FFQ n-3 Units: g/day	Q3 0.09 N Quantile: 518 N Cases: NR	11 95% CI(-58, 81)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Birth weight N Total: 2070		DHA+EPA n-3 Measure: FFQ n-3 Units: g/day	Q4 0.27 N Quantile: 518 N Cases: NR		
	Length of gestation N Total: 1663		DHA+EPA @ 2nd trimester n-3 Measure: FFQ n-3 Units: g/day	Q1 0.02 N Quantile: 416 N Cases: NR	Q1-Q4 (difference in weeks) Estimate: 0.3 95% CI(-1.4, 2.1)	
	Length of gestation N Total: 1663		DHA+EPA @ 2nd trimester n-3 Measure: FFQ n-3 Units: g/day	Q2 0.09 N Quantile: 416 N Cases: NR	Q2-Q4 (difference in weeks) Estimate: -0.4 95% CI(-2.1, 1.3)	
	Length of gestation N Total: 1663		DHA+EPA @ 2nd trimester n-3 Measure: FFQ n-3 Units: g/day	Q3 0.18 N Quantile: 416 N Cases: NR	Q3-Q4 (difference in weeks) Estimate: 0.3 95% CI(-1.4, 2)	
	Length of gestation N Total: 1663		DHA+EPA @ 2nd trimester n-3 Measure: FFQ n-3 Units: g/day	Q4 0.38 N Quantile: 416 N Cases: NR		
	Length of gestation N Total: 1797		DHA+EPA @ 1st trimester n-3 Measure: FFQ n-3 Units: g/day	Q1 0.02 N Quantile: 449 N Cases: NR	Q1-Q4 (difference in weeks) Estimate: 0.3 95% CI(-1.3, 19)	
	Length of gestation N Total: 1797		DHA+EPA @ 1st trimester n-3 Measure: FFQ n-3 Units: g/day	Q1 vs. Q4	OR Estimate: 1.1 95% CI(0.7, 1.9)	
	Length of gestation N Total: 1797		DHA+EPA @ 1st trimester n-3 Measure: FFQ n-3 Units: g/day	Q2 0.09 N Quantile: 449 N Cases: NR	Q2-Q4 (difference in weeks) Estimate: -0.3 95% CI(-1.9, 1.3)	
	Length of gestation N Total: 1797		DHA+EPA @ 1st trimester n-3 Measure: FFQ n-3 Units: g/day	Q3 0.18 N Quantile: 449 N Cases: NR	Q3-Q4 (difference in weeks) Estimate: 0.6 95% CI(-1, 2.2)	
	Length of gestation N Total: 1797		DHA+EPA @ 1st trimester n-3 Measure: FFQ n-3 Units: g/day	Q4 0.36 N Quantile: 449 N Cases: NR		
	Length of gestation N Total: 2070		DHA+EPA @ 3rd trimester n-3 Measure: FFQ n-3 Units: g/day	Q1+Q2 0.05 N Quantile: 1035 N Cases: NR	Q1+Q2-Q4 (difference in weeks) Estimate: 0.5 95% CI(-0.7, 1.7)	
	Length of gestation N Total: 2070		DHA+EPA @ 3rd trimester n-3 Measure: FFQ n-3 Units: g/day	Q3 0.09 N Quantile: 518 N Cases: NR	Q3-Q4 (difference in weeks) Estimate: -0.7 95% CI(-2.2, 0.8)	
	Length of gestation N Total: 2070		DHA+EPA @ 3rd trimester n-3 Measure: FFQ n-3 Units: g/day	Q4 0.27 N Quantile: 518 N Cases: NR		

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Oken, et al., 2007[69] Study name: Project Viva Study dates: Recruitment 1999-2002 Study design: Observational prospective Location: US Funding source / conflict: Government, Multiple foundations and Societies	Study Population: Healthy pregnant women Pregnant enrolled 2,128 Pregnant completers 1,718 Pregnant age: 93% were 20-40 years Race of Mother: White European (72%) Black (12%) Hispanic (6%) Other race/ethnicity (10%)	Inclusion Criteria: 1st trimester pregnant women attending 1st prenatal visit Exclusion Criteria: Post hoc: no live birth, no medical records, failure to complete dietary questionnaires, pre-existing chronic hypertension and no subsequent preeclampsia	Adjustments: Maternal age, pre-pregnancy BMI, 1st trimester sBp, race/ethnicity, education, parity; nutrients adjusted for total energy intake

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Oken 2007[69]	Gestational HTN N Total: 1718	Term	AA n-3 Measure: FFQ n-3 Units: per 100 mg	N Quantile: NR N Cases: 119	OR Estimate: 1.03 95% CI(0.97, 1.1)	
	Gestational HTN N Total: 1718	Term	ALA n-3 Measure: FFQ n-3 Units: per g	N Quantile: NR N Cases: 119	OR Estimate: 1.14 95% CI(0.68, 1.92)	
	Gestational HTN N Total: 1718	Term	DHA+EPA/AA n-3 Measure: calculated n-3 Units: ratio	N Quantile: NR N Cases: 119	OR Estimate: 0.99 95% CI(0.93, 1.07)	
	Gestational HTN N Total: 1718	Term	DHA+EPA n-3 Measure: FFQ n-3 Units: per 100 mg	N Quantile: NR N Cases: 119	OR Estimate: 1.01 95% CI(0.95, 1.08)	
	Gestational HTN N Total: 1718	Term	LA n-3 Measure: FFQ n-3 Units: per g	N Quantile: NR N Cases: 119	OR Estimate: 1.01 95% CI(0.95, 1.08)	
	Gestational HTN N Total: 1718	Term	Total n-3 n-3 Measure: FFQ n-3 Units: per g	N Quantile: NR N Cases: 119	OR Estimate: 1.13 95% CI(0.79, 1.61)	
	Gestational HTN N Total: 1718	Term	n-3/n-6 n-3 Measure: calculated n-3 Units: ratio	N Quantile: NR N Cases: 119	OR Estimate: 1.02 95% CI(0.96, 1.08)	
	Preeclampsia N Total: 1718	Term	AA n-3 Measure: FFQ n-3 Units: per 100 mg	N Quantile: NR N Cases: 59	OR Estimate: 0.99 95% CI(0.91, 1.08)	
	Preeclampsia N Total: 1718	Term	ALA n-3 Measure: FFQ n-3 Units: per g	N Quantile: NR N Cases: 59	OR Estimate: 1.35 95% CI(0.66, 2.74)	
	Preeclampsia N Total: 1718	Term	DHA+EPA/AA n-3 Measure: calculated n-3 Units: ratio	N Quantile: NR N Cases: 59	OR Estimate: 0.82 95% CI(0.66, 1.01)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Preeclampsia N Total: 1718	Term	DHA+EPA n-3 Measure: FFQ n-3 Units: per 100 mg	N Quantile: NR N Cases: 59	OR Estimate: 0.84 95% CI(0.69, 1.03)	
	Preeclampsia N Total: 1718	Term	LA n-3 Measure: FFQ n-3 Units: per g	N Quantile: NR N Cases: 59	OR Estimate: 0.99 95% CI(0.91, 1.08)	
	Preeclampsia N Total: 1718	Term	Total n-3 n-3 Measure: FFQ n-3 Units: per g	N Quantile: NR N Cases: 59	OR Estimate: 1.01 95% CI(0.55, 1.85)	
	Preeclampsia N Total: 1718	Term	n-3/n-6 n-3 Measure: calculated n-3 Units: ratio	N Quantile: NR N Cases: 59	OR Estimate: 0.99 95% CI(0.89, 1.11)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Olafsdottir, et al., 2005[82] Study dates: 1999-2001 Study design: Observational prospective Location: NR Funding source / conflict: Government, Multiple foundations and Societies	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 436 Pregnant completers 436 Pregnant age: No 27.8; Yes 29.6 (no 4.9; yes 4.6) Race of Mother: NR	Inclusion Criteria: absence of pre-eclampsia, hypertension or diabetes mellitus Exclusion Criteria: women whose personal data could not be found or who moved abroad before giving birth (n 8), had a miscarriage or stillbirth (n 17), twins or triplets (n 5), a preterm birth hypertension/pre-eclampsia (n 62) or gestational diabetes mellitus (n=4)	Adjustments: Gender, gestational age, mother's height, BMI, hemoglobin, alcohol consumption in first trimester, parity, smoking during pregnancy, weight gain during pregnancy

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Olafsdottir 2005[82]	Birth weight N Total: 350		Liquid cod liver oil in first trimester (y/n) n-3 Measure: FFQ n-3 Units: grams	Yes vs. no N Quantile: NR N Cases: NR	Coefficient Estimate: 132.1 95% CI(18.3, 246)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Olafsdottir, et al., 2006[70] Study dates: 1999-2001 Study design: Observational prospective Location: NR Funding source / conflict: Government, Multiple foundations and Societies	Study Population: Healthy pregnant women Pregnant enrolled 549 Pregnant completers 488 Pregnant age: 28 (5) Race of Mother: White European (NR)	Inclusion Criteria: Pregnant women attending first prenatal visit at Center of Prenatal Care in Reykjavik from 1999-2001, who gave birth to full-term babies completed the study. Exclusion Criteria: Essential hypertension, gestational diabetes, miscarriage/stillbirth, twins/triplets, preterm birth, loss of personal data, moved, missing data,	Adjustments: Weight gain during pregnancy, BMI X weight gain, smoking, parity and diastolic and systolic blood pressure early in pregnancy

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Olafsdottir 2005[70]	Gestational hypertension or preeclampsia		n-3 LCPUFAs (0.1-0.23g/d) n-3 Units: g/d	11th-50th N Cases: NR	OR	
	Gestational hypertension or preeclampsia		n-3 LCPUFAs (0.24-0.87g/d) n-3 Units: g/d	51st-90th N Cases: NR	OR	
	Gestational hypertension or preeclampsia		n-3 LCPUFAs (<0.9g/d) n-3 Units: g/d	10th centile N Cases: NR	OR	
	Gestational hypertension or preeclampsia		n-3 LCPUFAs (>0.87g/d) n-3 Units: g/d	>90th N Cases: NR	OR	
	Gestational hypertension or preeclampsia N Total: 488		n-3 LCPUFAs n-3 Units: yes/no	All N Cases: 49	OR Estimate: 4.7 95% CI(1.8, 12.6)	
	Gestational hypertension N Total: 488		Cod liver oil liquid n-3 Measure: FFQ yes/no n-3 Units: yes/no	All N Cases: 30	OR Estimate: 5.2 95% CI(1.5, 17.8)	
	Preeclampsia N Total: 488		Yes/no	All N Cases: 19	OR Estimate: 4.2 95% CI(0.8, 20.9)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Parker, et al., 2015[97] Study dates: NR Study design: Observational prospective Location: Australia Funding source / conflict: Government	Study Population: Healthy pregnant women Postpartum women Pregnant enrolled 1232 Pregnant completers 831 Pregnant age: 31.0 (5.7) Race of Mother: NR (100)	Inclusion Criteria: Women between 34 and37 weeks of pregnancy and attending an obstetric service. Participants had to be more than 18 years of age, be proficient in English and able to provide informed consent Exclusion Criteria: nr	Adjustments: Age, education level, income level, marital status, number of children, neuroticism scores, the presence or absence of a lifetime mood disorder, coffee drinking, cigarette smoking and alcohol intake, as well as stress levels during pregnancy

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Parker 2015[97]	Postnatal depression measured by EPDS N Total: 773		PUFA variables: total omega-6; total omega-3; omega-6/omega-3 ratio; DHA; DPA; DPE; EPA+DHA; AA n-3 Measure: Maternal RBC phospholipids at 36 weeks of pregnancy n-3 Units: percentage of total fatty acids in erythrocyte phospholipids	NR N Cases: 138	OR	
	Postnatal depression measured by MINIAD N Total: 819		PUFA variables: total omega-6; total omega-3; omega-6/omega-3 ratio; DHA; DPA; DPE; EPA+DHA; AA n-3 Measure: Maternal RBC phospholipids at 36 weeks of pregnancy n-3 Units: percentage of total fatty acids in erythrocyte phospholipids	NR N Cases: 87	OR	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Pike, et al., 2012[186] Study name: Southampton Women's Survey Study dates: 2006-2010 Study design: Observational prospective Location: UK Funding source / conflict: Government, Some authors serve on scientific advisory boards for corporations Follow-up: Birth to 6 years	Study Population: Healthy infants Pregnant enrolled Infants enrolled 1485 Infants completers 865 Pregnant age: 30.4 (3.8) Race of Mother: NR (100)	Inclusion Criteria: mothers and children in the Southampton Women's Survey Exclusion Criteria: Infants born = 35 weeks' gestation were excluded to avoid abnormal lung development associated with prematurity	Adjustments: Child's age, maternal asthma, and paternal rhinitis for airway inflammation outcome

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Pike 2012[186]	Airway inflammation N Total: 452	6 years	AA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.108 95% CI(0.014, 0.201)	
	Airway inflammation N Total: 452	6 years	ALA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: -0.05 95% CI(-0.144, 0.044)	
	Airway inflammation N Total: 452	6 years	DHA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.095 95% CI(0.002, 0.189)	
	Airway inflammation N Total: 452	6 years	EPA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: -0.022 95% CI(-0.119, 0.074)	
	Airway inflammation N Total: 452	6 years	Total n-3 PUFAs n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.042 95% CI(-0.052, 0.135)	
	Airway inflammation N Total: 452	6 years	Total n-3:n-6 n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.039 95% CI(-0.053, 0.131)	
	Atopy N Total: 638	6 years	AA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 1.1 95% CI(0.96, 1.26)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Atopy N Total: 638	6 years	ALA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.99 95% CI(0.86, 1.14)	
	Atopy N Total: 638	6 years	DHA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 1 95% CI(0.87, 1.14)	
	Atopy N Total: 638	6 years	EPA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.94 95% CI(0.83, 1.06)	
	Atopy N Total: 638	6 years	Total n-3 PUFAs n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.99 95% CI(0.87, 1.13)	
	Atopy N Total: 638	6 years	Total n-3:n-6 n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 1 95% CI(0.88, 1.14)	
	Lung function N Total: 702	6 years	AA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0 95% CI(-0.014, 0.015)	
	Lung function N Total: 702	6 years	ALA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: -0.009 95% CI(-0.024, 0.005)	
	Lung function N Total: 702	6 years	DHA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.008 95% CI(-0.006, 0.022)	
	Lung function N Total: 702	6 years	EPA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.013 95% CI(-0.001, 0.027)	
	Lung function N Total: 702	6 years	Total n-3 PUFAs n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.01 95% CI(-0.004, 0.024)	
	Lung function N Total: 702	6 years	Total n-3:n-6 n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.01 95% CI(-0.004, 0.024)	
	Persistent/late wheeze with atopy N Total: 861	6 years	AA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 1.06 95% CI(0.82, 1.36)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Persistent/late wheeze with atopy N Total: 861	6 years	ALA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.91 95% CI(0.7, 1.19)	
	Persistent/late wheeze with atopy N Total: 861	6 years	DHA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.74 95% CI(0.55, 1)	
	Persistent/late wheeze with atopy N Total: 861	6 years	EPA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.65 95% CI(0.43, 0.98)	
	Persistent/late wheeze with atopy N Total: 861	6 years	Total n-3 PUFAs n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.72 95% CI(0.54, 0.96)	
	Persistent/late wheeze with atopy N Total: 861	6 years	Total n-3:n-6 n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.73 95% CI(0.54, 0.99)	
	Persistent/late wheeze without atopy N Total: 861	6 years	AA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.76 95% CI(0.6, 0.96)	
	Persistent/late wheeze without atopy N Total: 861	6 years	ALA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 1.17 95% CI(0.87, 1.58)	
	Persistent/late wheeze without atopy N Total: 861	6 years	DHA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.67 95% CI(0.49, 0.93)	
	Persistent/late wheeze without atopy N Total: 861	6 years	EPA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.57 95% CI(0.37, 0.89)	
	Persistent/late wheeze without atopy N Total: 861	6 years	Total n-3 PUFAs n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.69 95% CI(0.51, 0.95)	
	Persistent/late wheeze without atopy N Total: 861	6 years	Total n-3:n-6 n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.73 95% CI(0.53, 0.99)	
	Persistent/late wheeze N Total: 861	6 years	AA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.88 95% CI(0.76, 1.02)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Persistent/late wheeze N Total: 861	6 years	ALA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 1.09 95% CI(0.96, 1.24)	
	Persistent/late wheeze N Total: 861	6 years	DHA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.91 95% CI(0.76, 1.08)	
	Persistent/late wheeze N Total: 861	6 years	EPA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.91 95% CI(0.73, 1.14)	
	Persistent/late wheeze N Total: 861	6 years	Total n-3 PUFAs n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.93 95% CI(0.79, 1.11)	
	Persistent/late wheeze N Total: 861	6 years	Total n-3:n-6 n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.94 95% CI(0.79, 1.12)	
	Transient wheeze N Total: 861	6 years	AA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.94 95% CI(0.88, 1.02)	
	Transient wheeze N Total: 861	6 years	ALA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 1.06 95% CI(0.98, 1.14)	
	Transient wheeze N Total: 861	6 years	DHA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.95 95% CI(0.88, 1.03)	
	Transient wheeze N Total: 861	6 years	EPA% n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.98 95% CI(0.92, 1.06)	
	Transient wheeze N Total: 861	6 years	Total n-3 PUFAs n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.97 95% CI(0.9, 1.04)	
	Transient wheeze N Total: 861	6 years	Total n-3:n-6 n-3 Measure: Maternal plasma phosphatidylcholine at 34 weeks gestation n-3 Units: % total fatty acids	All	RR Estimate: 0.98 95% CI(0.92, 1.05)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Saito, et al., 2010[181] Study name: Osaka maternal and child health study Study dates: Recruitment: November 2001 to March 2003 Follow-up: 3-4 months Study design: Observational prospective Location: Japan Funding source / conflict: Government Follow-up: 3-4 months	Study Population: Healthy infants Healthy pregnant women Pregnant completers 771 Infants completers 771 Pregnant age: 29.9 (4.0) Race of Mother: NR (100%)	Inclusion Criteria: Pregnant women living in Neyagawa City (one of the 43 municipalities in Osaka Prefecture) and a few municipalities other than Neyagawa Exclusion Criteria: Survey completed outside 3-5 month postpartum window	Adjustments: Maternal age, gestation at baseline, family income, maternal and paternal education, maternal and paternal history of asthma, atopic eczema and allergic rhinitis, mite allergen level from maternal bedclothes, vacuuming living room, mold in kitchen, changes in maternal diet in the previous 1 month, season when data at baseline were collected, baby's older siblings, baby's sex, baby's birth weight, breastfeeding and bathing or showering infant.

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Yokoyama 2010[181]	Atopic eczema N Total: 771	3-5 months	ALA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q1 1.3 N Quantile: 192 N Cases: 13	OR	
	Atopic eczema N Total: 771	3-5 months	ALA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q2 1.6 N Quantile: 193 N Cases: 19	OR Estimate: 1.59 95% CI(0.73, 3.57)	
	Atopic eczema N Total: 771	3-5 months	ALA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q3 1.9 N Quantile: 193 N Cases: 23	OR Estimate: 2.26 95% CI(1.06, 5.03)	
	Atopic eczema N Total: 771	3-5 months	ALA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q4 2.3 N Quantile: 193 N Cases: 10	OR Estimate: 0.76 95% CI(0.3, 1.87)	
	Atopic eczema N Total: 771	3-5 months	DHA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q1 0.15 N Quantile: 192 N Cases: 16	OR	
	Atopic eczema N Total: 771	3-5 months	DHA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q2 0.24 N Quantile: 193 N Cases: 14	OR Estimate: 0.96 95% CI(0.43, 2.11)	
	Atopic eczema N Total: 771	3-5 months	DHA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q3 0.31 N Quantile: 193 N Cases: 16	OR Estimate: 0.93 95% CI(0.42, 2.05)	
	Atopic eczema N Total: 771	3-5 months	DHA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q4 0.46 N Quantile: 193 N Cases: 19	OR Estimate: 1.43 95% CI(0.68, 3.07)	
	Atopic eczema N Total: 771	3-5 months	EPA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q1 0.07 N Quantile: 192 N Cases: 13	OR	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Atopic eczema N Total: 771	3-5 months	EPA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q2 0.13 N Quantile: 193 N Cases: 20	OR Estimate: 1.57 95% CI(0.72, 3.53)	
	Atopic eczema N Total: 771	3-5 months	EPA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q3 0.18 N Quantile: 193 N Cases: 13	OR Estimate: 0.98 95% CI(0.41, 2.31)	
	Atopic eczema N Total: 771	3-5 months	EPA n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q4 0.27 N Quantile: 193 N Cases: 19	OR Estimate: 1.84 95% CI(0.84, 4.15)	
	Atopic eczema N Total: 771	3-5 months	n-3 Polyunsaturated fatty acids n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q1 1.71 N Quantile: 192 N Cases: 13	OR	
	Atopic eczema N Total: 771	3-5 months	n-3 Polyunsaturated fatty acids n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q2 2.1 N Quantile: 193 N Cases: 22	OR Estimate: 2.06 95% CI(0.97, 4.55)	
	Atopic eczema N Total: 771	3-5 months	n-3 Polyunsaturated fatty acids n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q3 2.5 N Quantile: 193 N Cases: 14	OR Estimate: 1.33 95% CI(0.57, 3.11)	
	Atopic eczema N Total: 771	3-5 months	n-3 Polyunsaturated fatty acids n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q4 3 N Quantile: 193 N Cases: 16	OR Estimate: 1.45 95% CI(0.64, 3.31)	
	Atopic eczema N Total: 771	3-5 months	n-3/n-6 Polyunsaturated fatty acid ratio n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q1 0.17 N Quantile: 192 N Cases: 15	OR	
	Atopic eczema N Total: 771	3-5 months	n-3/n-6 Polyunsaturated fatty acid ratio n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q2 0.19 N Quantile: 193 N Cases: 16	OR Estimate: 0.95 95% CI(0.43, 2.11)	
	Atopic eczema N Total: 771	3-5 months	n-3/n-6 Polyunsaturated fatty acid ratio n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q3 0.21 N Quantile: 193 N Cases: 19	OR Estimate: 1.27 95% CI(0.59, 2.78)	
	Atopic eczema N Total: 771	3-5 months	n-3/n-6 Polyunsaturated fatty acid ratio n-3 Measure: Intake (FFQ) n-3 Units: g/d	Q4 0.24 N Quantile: 193 N Cases: 15	OR Estimate: 1.17 95% CI(0.52, 2.62)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Sallis, et al., 2014[96] Study name: Avon Longitudinal Study of Parents and Children (ALSPAC) Study dates: 1991-1992 Study design: Observational prospective Location: NR Funding source / conflict: Industry, Government	Study Population: Healthy pregnant women Pregnant enrolled 14,541 Pregnant withdrawals 11,144 Pregnant completers 3,397 Pregnant age: 28.9 (4.5) not reported Race of Mother: White European (100%)	Inclusion Criteria: All women with an expected due date between April 1991 and December 1992 were eligible for the study. Only women with data available on genotype, FA levels and depressive symptoms during pregnancy or at 8 weeks postnatally and women with a self-reported ethnicity of White European were included in this analysis. Exclusion Criteria: Mothers who lost a child during the neonatal period and those with a still birth; mothers with multiple births.	Adjustments: Social class (I/II, III or IV/V) and maternal age

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Sallis 2014[96]	Antenatal depression N Total: 2911		EPA n-3 Measure: Maternal red blood cells n-3 Units: % total RBC phospholipid	All N Cases: 441	OR Estimate: 0.97 95% CI(0.91, 1.04)	
	Antenatal depression N Total: 2912		DHA n-3 Measure: Maternal red blood cells n-3 Units: % total RBC phospholipid	All	OR Estimate: 0.99 95% CI(0.91, 1.07)	
	Antenatal depression N Total: 2912		DHA n-3 Measure: Maternal red blood cells n-3 Units: % total RBC phospholipid	All	RD Estimate: 0.05 95% CI(-0.09, 0.19)	
	Perinatal onset depression N Total: 2377		EPA n-3 Measure: Maternal red blood cells n-3 Units: % total RBC phospholipid	All N Cases: 306	OR Estimate: 1.07 95% CI(0.99, 1.15)	
	Perinatal onset depression N Total: 2378		DHA n-3 Measure: Maternal red blood cells n-3 Units: % total RBC phospholipid	All	OR Estimate: 1.08 95% CI(0.98, 1.19)	
	Perinatal onset depression N Total: 2378		DHA n-3 Measure: Maternal red blood cells n-3 Units: % total RBC phospholipid	All	RD Estimate: 0.08 95% CI(-0.05, 0.22)	
	Postnatal depression N Total: 2756		EPA n-3 Measure: Maternal red blood cells n-3 Units: % total RBC phospholipid	All N Cases: 265	OR Estimate: 1.04 95% CI(0.96, 1.13)	
	Postnatal depression N Total: 2757		DHA n-3 Measure: Maternal red blood cells n-3 Units: % total RBC phospholipid	All	OR Estimate: 1.04 95% CI(0.94, 1.15)	
	Postnatal depression N Total: 2757		DHA n-3 Measure: Maternal red blood cells n-3 Units: % total RBC phospholipid	All	RD Estimate: 0.02 95% CI(-0.08, 0.13)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Scholtens, et al., 2009[103] Study name: The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study Study dates: Recruitment: 1996-1997 Follow-up: 1 year Study design: Observational prospective Location: Netherlands Funding source / conflict: Industry, Government, Multiple foundations and Societies, None Follow-up: 1 year Original, same study, or follow-up studies: Study described in Brunekreef, 2002	Study Population: NR Pregnant enrolled 4146 Infants enrolled 276 Infants completers 244 Infant age: Birth Race of Mother: NR (NR)	Inclusion Criteria: Children of mothers recruited from the general population during pregnancy Exclusion Criteria: None reported	Adjustments: Age of child at breast-milk collection and total breast-feeding duration

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Scholtens 2008[103]	Mean BMI gain N Total: 244	1 y	ALA (18 : 3n-3) n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: 0.002 95% CI(0.002, -0.01)	
	Mean BMI gain N Total: 244	1 y	ALA (18 : 3n-3) n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: 0.007 95% CI(0.007, -0.004)	
	Mean BMI gain N Total: 244	1 y	DHA (22 : 6n-3) n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: 0.004 95% CI(0.004, -0.008)	
	Mean BMI gain N Total: 244	1 y	DHA (22 : 6n-3) n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: 0.009 95% CI(0.009, -0.003)	
	Mean BMI gain N Total: 244	1 y	EPA (20 : 5n-3) n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: -0.003 95% CI(-0.003, -0.015)	
	Mean BMI gain N Total: 244	1 y	EPA (20 : 5n-3) n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: -0.004 95% CI(-0.004, -0.015)	
	Mean BMI gain N Total: 244	1 y	Total n-3 LCPUFA n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: -0.009 95% CI(-0.009, -0.021)	
	Mean BMI gain N Total: 244	1 y	Total n-3 LCPUFA n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: -0.01 95% CI(-0.01, -0.021)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Mean BMI gain N Total: 244	1 y	Total n-3 PUFA n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: -0.001 95% CI(-0.001, -0.013)	
	Mean BMI gain N Total: 244	1 y	Total n-3 PUFA n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: 0.008 95% CI(0.008, -0.004)	
	Mean length gain N Total: 244	1 y	ALA (18 : 3n-3) n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: -0.011 95% CI(-0.011, -0.029)	
	Mean length gain N Total: 244	1 y	ALA (18 : 3n-3) n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: -0.01 95% CI(-0.01, -0.028)	
	Mean length gain N Total: 244	1 y	DHA (22 : 6n-3) n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: -0.013 95% CI(-0.013, -0.031)	
	Mean length gain N Total: 244	1 y	DHA (22 : 6n-3) n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: 0.006 95% CI(0.006, 0.024)	
	Mean length gain N Total: 244	1 y	EPA (20 : 5n-3) n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: 0.007 95% CI(0.007, -0.011)	
	Mean length gain N Total: 244	1 y	EPA (20 : 5n-3) n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: 0.01 95% CI(0.01, -0.008)	
	Mean length gain N Total: 244	1 y	Total n-3 LCPUFA n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: 0.009 95% CI(0.009, -0.008)	
	Mean length gain N Total: 244	1 y	Total n-3 LCPUFA n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: 0.016 95% CI(0.016, 0.001)	
	Mean length gain N Total: 244	1 y	Total n-3 PUFA n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: -0.002 95% CI(-0.002, -0.02)	
	Mean length gain N Total: 244	1 y	Total n-3 PUFA n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: -0.004 95% CI(-0.004, -0.022)	
	Mean weight gain N Total: 244	1 y	ALA (18 : 3n-3) n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: -1.64 95% CI(-1.64, -6.596)	
	Mean weight gain N Total: 244	1 y	ALA (18 : 3n-3) n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: 0.697 95% CI(0.697, -4.275)	
	Mean weight gain N Total: 244	1 y	DHA (22 : 6n-3) n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: 0.606 95% CI(0.606, -4.387)	
	Mean weight gain N Total: 244	1 y	DHA (22 : 6n-3) n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: 0.833 95% CI(0.833, -4.124)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Mean weight gain N Total: 244	1 y	EPA (20 : 5n-3) n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: 2.434 95% CI(2.434, -2.516)	
	Mean weight gain N Total: 244	1 y	EPA (20 : 5n-3) n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: 3.187 95% CI(3.187, -1.776)	
	Mean weight gain N Total: 244	1 y	Total n-3 LCPUFA n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: -0.329 95% CI(-0.329, -5.282)	
	Mean weight gain N Total: 244	1 y	Total n-3 LCPUFA n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: -1.574 95% CI(-1.574, 6.532)	
	Mean weight gain N Total: 244	1 y	Total n-3 PUFA n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: -0.253 95% CI(-0.253, -5.216)	
	Mean weight gain N Total: 244	1 y	Total n-3 PUFA n-3 Measure: Breast milk wt% n-3 Units: wt%		Coefficient Estimate: 2.843 95% CI(2.843, -2.17)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Smits, et al., 2013[73] Study name: Amsterdam Born Children and their Development (ABCD) Study dates: Jan 2003- Mar 2004 Study design: Observational prospective Location: Netherlands Funding source / conflict: None	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 1659 Pregnant completers 1659 Infants enrolled 1659 Infants completers 1659 Pregnant age: <25 y, 5.7% 25-34 y, 61.2% >=35 y, 33.1% Infant age: 40.0 weeks (1.2) Race of Mother: White European (88.4)	Inclusion Criteria: NR Exclusion Criteria: primiparous women or delivered preterm	Adjustments: Potential confounding factors were evaluated but none of them was significant confounding defined as changing the odds ratio by 10%

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Smits 2015[73]	Birth weight N Total: 1659		DHA n-3 Measure: Maternal plasma phospholipids at early pregnancy n-3 Units: mg/L	Q1 <3.74 - N Quantile: NR N Cases: NR	-118.2 95% CI(-195.032, -41.368)	
	Birth weight N Total: 1659		DHA n-3 Measure: Maternal plasma phospholipids at early pregnancy n-3 Units: mg/L	Q2 3.74 - 4.35 N Quantile: NR N Cases: NR	-43.8 95% CI(-120.632, 33.032)	
	Birth weight N Total: 1659		DHA n-3 Measure: Maternal plasma phospholipids at early pregnancy n-3 Units: mg/L	Q3 4.35 - 4.86 N Quantile: NR N Cases: NR		
	Birth weight N Total: 1659		DHA n-3 Measure: Maternal plasma phospholipids at early pregnancy n-3 Units: mg/L	Q4 4.88 - 5.54 N Quantile: NR N Cases: NR	-34.4 95% CI(-111.232, 42.432)	
	Birth weight N Total: 1659		DHA n-3 Measure: Maternal plasma phospholipids at early pregnancy n-3 Units: mg/L	Q5 >=5.54 - N Quantile: NR N Cases: NR	-15.4 95% CI(-92.232, 61.432)	
	Birth weight N Total: 1659		EPA n-3 Measure: Maternal plasma phospholipids at early pregnancy n-3 Units: mg/L	Q1 <0.33 - N Quantile: NR N Cases: NR	-182.5 95% CI(-258.94, -106.06)	
	Birth weight N Total: 1659		EPA n-3 Measure: Maternal plasma phospholipids at early pregnancy n-3 Units: mg/L	Q2 0.33 - 0.46 N Quantile: NR N Cases: NR	-66.1 95% CI(-142.54, 10.34)	
	Birth weight N Total: 1659		EPA n-3 Measure: Maternal plasma phospholipids at early pregnancy n-3 Units: mg/L	Q3 0.46 - 0.58 N Quantile: NR N Cases: NR		

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Birth weight N Total: 1659		EPA n-3 Measure: Maternal plasma phospholipids at early pregnancy n-3 Units: mg/L	Q4 0.58 - 0.81 N Quantile: NR N Cases: NR	18.4 95% CI(-57.844, 94.644)	
	Birth weight N Total: 1659		EPA n-3 Measure: Maternal plasma phospholipids at early pregnancy n-3 Units: mg/L	Q5 >=0.81 - N Quantile: NR N Cases: NR	-26.6 95% CI(-103.04, 49.84)	
	SGA N Total: 1659		DHA n-3 Measure: Biomarker n-3 Units: mg/L	Q1 <3.74 - N Quantile: 332 N Cases: 44	OR Estimate: 1.11 95% CI(0.7, 1.75)	
	SGA N Total: 1659		DHA n-3 Measure: Biomarker n-3 Units: mg/L	Q2 3.74 - 4.35 N Quantile: 332 N Cases: 42	OR Estimate: 1.05 95% CI(0.66, 1.67)	
	SGA N Total: 1659		DHA n-3 Measure: Biomarker n-3 Units: mg/L	Q3 4.35 - 4.86 N Quantile: 332 N Cases: 40	OR	
	SGA N Total: 1659		DHA n-3 Measure: Biomarker n-3 Units: mg/L	Q4 4.88 - 5.54 N Quantile: 332 N Cases: 39	OR Estimate: 0.96 95% CI(0.6, 1.54)	
	SGA N Total: 1659		DHA n-3 Measure: Biomarker n-3 Units: mg/L	Q5 >=5.54 - N Quantile: 332 N Cases: 40	OR Estimate: 0.99 95% CI(0.62, 4.59)	
	SGA N Total: 1659		EPA n-3 Measure: Biomarker n-3 Units: mg/L	Q1 <0.33 - N Quantile: 332 N Cases: 42	OR Estimate: 2.09 95% CI(1.32, 3.3)	
	SGA N Total: 1659		EPA n-3 Measure: Biomarker n-3 Units: mg/L	Q2 0.33 - 0.46 N Quantile: 332 N Cases: 44	OR Estimate: 1.42 95% CI(0.88, 2.31)	
	SGA N Total: 1659		EPA n-3 Measure: Biomarker n-3 Units: mg/L	Q3 0.46 - 0.58 N Quantile: 332 N Cases: 32	OR	
	SGA N Total: 1659		EPA n-3 Measure: Biomarker n-3 Units: mg/L	Q4 0.58 - 0.81 N Quantile: 332 N Cases: 32	OR Estimate: 0.98 95% CI(0.59, 1.64)	
	SGA N Total: 1659		EPA n-3 Measure: Biomarker n-3 Units: mg/L	Q5 >=0.81 - N Quantile: 332 N Cases: 36	OR Estimate: 1.13 95% CI(0.68, 1.87)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Standl, et al., 2014[177] Study name: LISAplus Study dates: Recruitment 1997-1999 Study design: Observational prospective Location: Germany Funding source / conflict: Government Follow-up: 10 years	Study Population: Healthy infants Infants enrolled 436 Infants completers 243 Mother age: 32.7 (3.9) NR Infant age: Birth (NR) NR Race of Mother: NR (100)	Inclusion Criteria: NR Exclusion Criteria: Neonates displaying at least one of the following criteria: preterm birth (maturity <37 gestational weeks), low birth weight (<2,500 g), congenital malformation, symptomatic neonatal infection, antibiotic medication, hospitalization or intensive medical care during neonatal period. In addition, newborns from mothers with immune-related diseases (autoimmune disorders, diabetes, hepatitis B), on long-term medication or who abuse drugs and/or alcohol, and newborns from parents with a nationality other than German or who were not born in Germany, were excluded.	Adjustments: Parental education, sex, time of follow-up (2 yr, 6 yr or 10 yr for eczema; 6 yr and 10 yr for asthma, hay fever/allergic rhinitis and aeroallergen sensitization), age, maternal age at birth, parental atopy, total sum of fatty acids

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Standl 2014[177]	Aeroallergen sensitization N Total: 243	10 y	n-3 LC-PUFA n-3 Measure: Cord blood serum fatty acids n-3 Units: percentage of total fatty acids	All N Cases: 43	OR Estimate: 1.03 95% CI(0.87, 1.23)	
	Aeroallergen sensitization N Total: 243	10 y	n-6/n-3 ratio n-3 Measure: Cord blood serum fatty acids n-3 Units: percentage of total fatty acids	All N Cases: 43	OR Estimate: 0.82 95% CI(0.56, 1.22)	
	Aeroallergen sensitization N Total: 277	6 y	n-3 LC-PUFA n-3 Measure: Cord blood serum fatty acids n-3 Units: percentage of total fatty acids	All N Cases: 24	OR Estimate: 1.03 95% CI(0.85, 1.25)	
	Aeroallergen sensitization N Total: 277	6 y	n-6/n-3 ratio n-3 Measure: Cord blood serum fatty acids n-3 Units: percentage of total fatty acids	All N Cases: 24	OR Estimate: 0.94 95% CI(0.61, 1.44)	
	Asthma N Total: 243	10 y	n-3 LC-PUFA n-3 Measure: Cord blood serum fatty acids n-3 Units: percentage of total fatty acids	All N Cases: 5	OR Estimate: 1.18 95% CI(0.79, 1.75)	
	Asthma N Total: 243	10 y	n-6/n-3 ratio n-3 Measure: Cord blood serum fatty acids n-3 Units: percentage of total fatty acids	All N Cases: 5	OR Estimate: 0.77 95% CI(0.29, 2.04)	
	Asthma N Total: 277	6 y	n-3 LC-PUFA n-3 Measure: Cord blood serum fatty acids n-3 Units: percentage of total fatty acids	All N Cases: 3	OR Estimate: 0.83 95% CI(0.48, 1.44)	
	Asthma N Total: 277	6 y	n-6/n-3 ratio n-3 Measure: Cord blood serum fatty acids n-3 Units: percentage of total fatty acids	All N Cases: 3	OR Estimate: 1.75 95% CI(0.73, 4.21)	
	Eczema N Total: 243	10 y	n-3 LC-PUFA n-3 Measure: Cord blood serum fatty acids n-3 Units: percentage of total fatty acids	All N Cases: 7	OR Estimate: 0.76 95% CI(0.52, 1.12)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Eczema N Total: 243	10 y	n-6/n-3 ratio n-3 Measure: Cord blood serum fatty acids n-3 Units: percentage of total fatty acids	All N Cases: 7	OR Estimate: 1.31 95% CI(0.63, 2.71)	
	Eczema N Total: 277	6 y	n-3 LC-PUFA n-3 Measure: Cord blood serum fatty acids n-3 Units: percentage of total fatty acids	All N Cases: 14	OR Estimate: 1.18 95% CI(0.95, 1.48)	
	Eczema N Total: 277	6 y	n-6/n-3 ratio n-3 Measure: Cord blood serum fatty acids n-3 Units: percentage of total fatty acids	All N Cases: 14	OR Estimate: 0.75 95% CI(0.45, 1.25)	
	Eczema N Total: 280	2 y	n-3 LC-PUFA n-3 Measure: Cord blood serum fatty acids n-3 Units: percentage of total fatty acids	All N Cases: 15	OR Estimate: 0.99 95% CI(0.78, 1.25)	
	Eczema N Total: 280	2 y	n-6/n-3 ratio n-3 Measure: Cord blood serum fatty acids n-3 Units: percentage of total fatty acids	All N Cases: 15	OR Estimate: 0.97 95% CI(0.58, 1.63)	
	Hay fever or allergic rhinitis N Total: 243	10 y	n-3 LC-PUFA n-3 Measure: Cord blood serum fatty acids n-3 Units: percentage of total fatty acids	All N Cases: 13	OR Estimate: 1 95% CI(0.77, 1.3)	
	Hay fever or allergic rhinitis N Total: 243	10 y	n-6/n-3 ratio n-3 Measure: Cord blood serum fatty acids n-3 Units: percentage of total fatty acids	All N Cases: 13	OR Estimate: 0.84 95% CI(0.47, 1.51)	
	Hay fever or allergic rhinitis N Total: 277	6 y	n-3 LC-PUFA n-3 Measure: Cord blood serum fatty acids n-3 Units: percentage of total fatty acids	All N Cases: 3	OR Estimate: 0.96 95% CI(0.6, 1.56)	
	Hay fever or allergic rhinitis N Total: 277	6 y	n-6/n-3 ratio n-3 Measure: Cord blood serum fatty acids n-3 Units: percentage of total fatty acids	All N Cases: 3	OR Estimate: 0.75 95% CI(0.27, 2.1)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Steer, et al., 2013[164] Study name: Avon Longitudinal Study of Parents and Children (ALSPAC) Study dates: 1991-2000 Study design: Observational prospective Location: UK Funding source / conflict: Government Follow-up: 8 years	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 14,541 Infants completers 2,839 Mother age: 29.33 (4.48) Infant age: birth Race of Mother: White European (98.8) Black (0.6) Asian (0.6)	Inclusion Criteria: pregnant women with expected delivery date between 4/91 and 12/92 in Bristol UK Exclusion Criteria: Not reported	Adjustments: Maternal age, education, ethnicity, alcohol consumption and smoking; partner status, housing tenure, crowding index, parity, preterm gestation (,37 wk), low birth weight (,2500 g), multiple births, sex, breastfeeding, and measures of adversity (in pregnancy and during the first 2 y after birth) and child stimulation (both from the home environment and maternal interaction with the child)

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Steer 2013[164]	IQ N Total: 2839	7 years	AA n-3 Measure: maternal erythrocyte	Highest to other 3	Coefficient Estimate: -1.18 95% CI(-2.53, 0.18)	
	IQ N Total: 2839	7 years	AA n-3 Measure: maternal erythrocyte	Lowest to other 3	Coefficient Estimate: -1.54 95% CI(-2.91, -0.14)	
	IQ N Total: 2839	7 years	DHA n-3 Measure: maternal erythrocyte	Highest to other 3	Coefficient Estimate: -0.18 95% CI(-1.52, 1.17)	
	IQ N Total: 2839	7 years	DHA n-3 Measure: maternal erythrocyte	Lowest to other 3	Coefficient Estimate: -1.52 95% CI(-2.91, -0.14)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Strom, et al., 2009[92] Study name: Danish National Birth Cohort Study dates: 1996-2002 Study design: Observational prospective Location: Denmark Funding source / conflict: Government, Multiple foundations and Societies, Funding Affiliations trade group, March of Dimes	Study Population: Healthy pregnant women Pregnant enrolled 86,453 Pregnant withdrawals 32,251 Pregnant completers 54,202 Pregnant age: not reported (not reported) not reported Race of Mother: NR (100%)	Inclusion Criteria: All pregnant women living in Denmark between 1996 and 2002, who were fluent in Danish Exclusion Criteria: NR	Adjustments: Total energy intake, pre-pregnant BMI, maternal age, parity, alcohol intake, smoking, occupation, education, homeownership, marital status, social support, and history of previous depression

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Strom 2009[92]	PPD admission		n-3 PUFA intake n-3 Measure: FFQ n-3 Units: mg/d	Q1 9.1 N Cases: 16	OR Estimate: 0.96 95% CI(0.51, 1.78)	
	PPD admission		n-3 PUFA intake n-3 Measure: FFQ n-3 Units: mg/d	Q2 14.1 N Cases: 16	OR Estimate: 1.03 95% CI(0.55, 1.92)	
	PPD admission		n-3 PUFA intake n-3 Measure: FFQ n-3 Units: mg/d	Q3 18.1 N Cases: 11	OR Estimate: 0.73 95% CI(0.36, 1.48)	
	PPD admission		n-3 PUFA intake n-3 Measure: FFQ n-3 Units: mg/d	Q4 22.2 N Cases: 19	OR Estimate: 1.33 95% CI(0.74, 2.39)	
	PPD admission		n-3 PUFA intake n-3 Measure: FFQ n-3 Units: mg/d	Q5 27 N Cases: 17	OR Estimate: 1.21 95% CI(0.66, 2.21)	
	PPD admission		n-3 PUFA intake n-3 Measure: FFQ n-3 Units: mg/d	Q6 32.7 N Cases: 23	OR Estimate: 1.65 95% CI(0.95, 2.88)	
	PPD admission		n-3 PUFA intake n-3 Measure: FFQ n-3 Units: mg/d	Q7 39.6 N Cases: 18	OR Estimate: 1.3 95% CI(0.72, 2.36)	
	PPD admission		n-3 PUFA intake n-3 Measure: FFQ n-3 Units: mg/d	Q8 48.4 N Cases: 11	OR Estimate: 0.79 95% CI(0.39, 1.59)	
	PPD admission		n-3 PUFA intake n-3 Measure: FFQ n-3 Units: mg/d	Q9+Q10 72.8 N Cases: 28	OR	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	PPD prescription		n-3 PUFA intake n-3 Measure: FFQ n-3 Units: mg/d	Q1 9.1 N Cases: 110	OR Estimate: 1.24 95% CI(0.96, 1.61)	
	PPD prescription		n-3 PUFA intake n-3 Measure: FFQ n-3 Units: mg/d	Q2 14.1 N Cases: 97	OR Estimate: 1.17 95% CI(0.9, 1.53)	
	PPD prescription		n-3 PUFA intake n-3 Measure: FFQ n-3 Units: mg/d	Q3 18.1 N Cases: 82	OR Estimate: 0.99 95% CI(0.75, 1.31)	
	PPD prescription		n-3 PUFA intake n-3 Measure: FFQ n-3 Units: mg/d	Q4 22.2 N Cases: 102	OR Estimate: 1.29 95% CI(0.99, 1.68)	
	PPD prescription		n-3 PUFA intake n-3 Measure: FFQ n-3 Units: mg/d	Q5 27 N Cases: 83	OR Estimate: 1.09 95% CI(0.83, 1.44)	
	PPD prescription		n-3 PUFA intake n-3 Measure: FFQ n-3 Units: mg/d	Q6 32.7 N Cases: 85	OR Estimate: 1.11 95% CI(0.84, 1.46)	
	PPD prescription		n-3 PUFA intake n-3 Measure: FFQ n-3 Units: mg/d	Q7 39.6 N Cases: 80	OR Estimate: 1.04 95% CI(0.79, 1.38)	
	PPD prescription		n-3 PUFA intake n-3 Measure: FFQ n-3 Units: mg/d	Q8 48.4 N Cases: 70	OR Estimate: 0.89 95% CI(0.67, 1.2)	
	PPD prescription		n-3 PUFA intake n-3 Measure: FFQ n-3 Units: mg/d	Q9+Q10 72.8 N Cases: 157	OR	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Sun, et al., 2010[131] Study name: Danish National Birth Cohort Study dates: Recruitment March 1996 to November 2002 Study design: Observational prospective Location: Denmark Funding source / conflict: Government Follow-up: 10.8 years (median 7.8 years)	Study Population: Healthy infants Infants enrolled 65,754 Infants completers 65754 Infant age: birth Race of Mother: NR (NR)	Inclusion Criteria: live-born singletons whose mothers provided information on fish intake from food frequency questionnaire Exclusion Criteria: children with missing information on maternal smoking and parity, children who died during the neonatal period, and children born to mothers with an unlikely high (>16,700 kJ/day) or low (<4200 kJ/day) intake of energy during pregnancy	Adjustments: Energy intake, sex, gestational age, parity, time breastfeeding, maternal age, SES, pre-pregnancy BMI, smoking status at recruitment, maternal history of epilepsy

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Sun, 2010[131]	Epilepsy	Up to 10.8 years, mean 7.8 years	Total n-3 LCPUFA n-3 Measure: FFQ n-3 Units: mg/day	N Quantile: 12,245 N Cases: 126	Incidence rate ratio (IRR) Estimate: 1.33 95% CI(1.02, 1.74)	
	Epilepsy	Up to 10.8 years, mean 7.8 years	Total n-3 LCPUFA n-3 Measure: FFQ n-3 Units: mg/day	N Quantile: 12,318 N Cases: 97	Incidence rate ratio (IRR)	
	Epilepsy	Up to 10.8 years, mean 7.8 years	Total n-3 LCPUFA n-3 Measure: FFQ n-3 Units: mg/day	N Quantile: 12,332 N Cases: 104	Incidence rate ratio (IRR) Estimate: 1.05 95% CI(0.79, 1.38)	
	Epilepsy	Up to 10.8 years, mean 7.8 years	Total n-3 LCPUFA n-3 Measure: FFQ n-3 Units: mg/day	N Quantile: 12,421 N Cases: 102	Incidence rate ratio (IRR) Estimate: 1.05 95% CI(0.81, 1.41)	
	Epilepsy	Up to 10.8 years, mean 7.8 years	Total n-3 LCPUFA n-3 Measure: FFQ n-3 Units: mg/day	N Quantile: 4,528 N Cases: 34	Incidence rate ratio (IRR) Estimate: 1.01 95% CI(0.68, 1.49)	
	Epilepsy N Total: 65754	Up to 10.8 years, mean 7.8 years	Supplements during pregnancy n-3 Measure: Maternal food frequency questionnaire n-3 Units: mg/day	377 N Quantile: 4,528 N Cases: 34	Incidence rate ratio (IRR) Estimate: 1.01 95% CI(0.68, 1.49)	
	Epilepsy N Total: 65754	Up to 10.8 years, mean 7.8 years	Total n-3 LCPUFA n-3 Measure: FFQ n-3 Units: mg/day	N Quantile: 11,910 N Cases: 128	Incidence rate ratio (IRR) Estimate: 1.28 95% CI(0.98, 1.67)	
	Epilepsy N Total: 65754	Up to 10.8 years, mean 7.8 years	Total n-3 LCPUFA n-3 Measure: Maternal food frequency questionnaire n-3 Units: mg/day	Q1 117 N Quantile: 11,910 N Cases: 128	Incidence rate ratio (IRR) Estimate: 1.28 95% CI(0.98, 1.67)	
	Epilepsy N Total: 65754	Up to 10.8 years, mean 7.8 years	Total n-3 LCPUFA n-3 Measure: Maternal food frequency questionnaire n-3 Units: mg/day	Q2 207 N Quantile: 12,332 N Cases: 104	Incidence rate ratio (IRR) Estimate: 1.05 95% CI(0.79, 1.38)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Epilepsy N Total: 65754	Up to 10.8 years, mean 7.8 years	Total n-3 LCPUFA n-3 Measure: Maternal food frequency questionnaire n-3 Units: mg/day	Q3 308 N Quantile: 12,318 N Cases: 97	Incidence rate ratio (IRR)	
	Epilepsy N Total: 65754	Up to 10.8 years, mean 7.8 years	Total n-3 LCPUFA n-3 Measure: Maternal food frequency questionnaire n-3 Units: mg/day	Q4 451 N Quantile: 12,421 N Cases: 102	Incidence rate ratio (IRR) Estimate: 1.05 95% CI(0.81, 1.41)	
	Epilepsy N Total: 65754	Up to 10.8 years, mean 7.8 years	Total n-3 LCPUFA n-3 Measure: Maternal food frequency questionnaire n-3 Units: mg/day	Q5 817 N Quantile: 12,245 N Cases: 126	Incidence rate ratio (IRR) Estimate: 1.33 95% CI(1.02, 1.74)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Thijs, et al., 2011[178] Study name: KOALA Birth Cohort Study Study dates: 2003 Study design: Observational prospective Location: Netherlands Funding source / conflict: Government, None Follow-up: 2 years	Study Population: Healthy pregnant women Pregnant enrolled 312 Pregnant completers 304 Infants enrolled 312 Infants completers 304 Pregnant age: 33.3 (3.9) NR Race of Mother: NR (100)	Inclusion Criteria: availability of complete baseline data from the 34 weeks pregnancy questionnaire and availability of a breast milk sample. Exclusion Criteria: NR	Adjustments: Recruitment group, maternal age, maternal education, infant's gender, number of older siblings and their atopic history, parental atopic history, maternal smoking during pregnancy and/or smoking in presence of the infant, place of birth, season of breast milk collection, duration and exclusivity of breastfeeding, maternal n-3 fatty acids supplement use, maternal probiotic supplement use, maternal probiotic dairy use, maternal antibiotic use during lactation, infant's antibiotic use, vaccination schedule, dampness of the home, pet animals in the home.

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Thijs 2011[178]	Allergic sensitisation N Total: 204	2 y	Main n-3 LCPs (EPA+DHA+DPA) n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: weight-percentage (wt%, mg/100 mg) of total breast milk fat	Qt1 0.3-0.56 N Quantile: 41 N Cases: 10	OR	
	Allergic sensitisation N Total: 204	2 y	Main n-3 LCPs (EPA+DHA+DPA) n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: weight-percentage (wt%, mg/100 mg) of total breast milk fat	Qt2 0.56-0.65 N Quantile: 44 N Cases: 13	OR Estimate: 1.29 95% CI(0.45, 3.68)	
	Allergic sensitisation N Total: 204	2 y	Main n-3 LCPs (EPA+DHA+DPA) n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: weight-percentage (wt%, mg/100 mg) of total breast milk fat	Qt3 0.65-0.78 N Quantile: 53 N Cases: 15	OR Estimate: 1.32 95% CI(0.47, 3.72)	
	Allergic sensitisation N Total: 204	2 y	Main n-3 LCPs (EPA+DHA+DPA) n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: weight-percentage (wt%, mg/100 mg) of total breast milk fat	Qt4 0.78-2.55 N Quantile: 66 N Cases: 13	OR Estimate: 0.89 95% CI(0.32, 2.5)	
	Allergic sensitisation N Total: 220	1 y	Main n-3 LCPs (EPA+DHA+DPA) n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: weight-percentage (wt%, mg/100 mg) of total breast milk fat	Qt1 0.3-0.56 N Quantile: 49 N Cases: 8	OR	
	Allergic sensitisation N Total: 220	1 y	Main n-3 LCPs (EPA+DHA+DPA) n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: weight-percentage (wt%, mg/100 mg) of total breast milk fat	Qt2 0.56-0.65 N Quantile: 45 N Cases: 6	OR Estimate: 0.8 95% CI(0.21, 3.08)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Allergic sensitisation N Total: 220	1 y	Main n-3 LCPs (EPA+DHA+DPA) n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: weight-percentage (wt%, mg/100 mg) of total breast milk fat	Qt3 0.65-0.78 N Quantile: 58 N Cases: 9	OR Estimate: 0.68 95% CI(0.21, 2.2)	
	Allergic sensitisation N Total: 220	1 y	Main n-3 LCPs (EPA+DHA+DPA) n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: weight-percentage (wt%, mg/100 mg) of total breast milk fat	Qt4 0.78-2.55 N Quantile: 68 N Cases: 5	OR Estimate: 0.17 95% CI(0.04, 0.77)	
	Atopic dermatitis N Total: 207	2 y	Main n-3 LCPs (EPA+DHA+DPA) n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: NR	All N Cases: 31	OR Estimate: 0.33 95% CI(0.13, 0.87)	
	Atopic dermatitis N Total: 207	2 y	Main n-3 LCPs (EPA+DHA+DPA) n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: weight-percentage (wt%, mg/100 mg) of total breast milk fat	Qt1 0.3-0.56 N Quantile: 43 N Cases: 10	OR	
	Atopic dermatitis N Total: 207	2 y	Main n-3 LCPs (EPA+DHA+DPA) n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: weight-percentage (wt%, mg/100 mg) of total breast milk fat	Qt2 0.56-0.65 N Quantile: 44 N Cases: 7	OR Estimate: 0.83 95% CI(0.27, 2.57)	
	Atopic dermatitis N Total: 207	2 y	Main n-3 LCPs (EPA+DHA+DPA) n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: weight-percentage (wt%, mg/100 mg) of total breast milk fat	Qt3 0.65-0.78 N Quantile: 54 N Cases: 8	OR Estimate: 0.46 95% CI(0.13, 1.59)	
	Atopic dermatitis N Total: 207	2 y	Main n-3 LCPs (EPA+DHA+DPA) n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: weight-percentage (wt%, mg/100 mg) of total breast milk fat	Qt4 0.78-2.55 N Quantile: 66 N Cases: 6	OR Estimate: 0.34 95% CI(0.12, 0.97)	
	Eczema N Total: 304	2 y	Main n-3 LCPs (EPA+DHA+DPA) n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: NR	All N Cases: 95	OR Estimate: 0.6 95% CI(0.37, 0.98)	
	Eczema N Total: 304	2 y	Main n-3 LCPs (EPA+DHA+DPA) n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: weight-percentage (wt%, mg/100 mg) of total breast milk fat	Qt1 0.3-0.56 N Quantile: 72 N Cases: 26	OR	
	Eczema N Total: 304	2 y	Main n-3 LCPs (EPA+DHA+DPA) n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: weight-percentage (wt%, mg/100 mg) of total breast milk fat	Qt2 0.56-0.65 N Quantile: 68 N Cases: 21	OR Estimate: 0.8 95% CI(0.37, 1.71)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Eczema N Total: 304	2 y	Main n-3 LCPs (EPA+DHA+DPA) n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: weight-percentage (wt%, mg/100 mg) of total breast milk fat	Qt3 0.65-0.78 N Quantile: 74 N Cases: 24	OR Estimate: 0.89 95% CI(0.43, 1.88)	
	Eczema N Total: 304	2 y	Main n-3 LCPs (EPA+DHA+DPA) n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: weight-percentage (wt%, mg/100 mg) of total breast milk fat	Qt4 0.78-2.55 N Quantile: 90 N Cases: 24	OR Estimate: 0.62 95% CI(0.3, 1.29)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Valent, et al., 2013[132] Study dates: 2007-2011 Study design: Observational prospective Location: Italy Funding source / conflict: Government	Study Population: Healthy infants Healthy pregnant women Pregnant enrolled 900 Pregnant completers 767 Infants enrolled 767 Infants completers 632 Pregnant age: 33.3 (4.3) Infant age: Birth Race of Mother: NR (100)	Inclusion Criteria: Permanent residents of the study areas for at least 2 years, at least 18 years of age, and had no absence from the study area for more than 6 weeks during pregnancy, no history of drug abuse, no serious health problems or complications of pregnancy, and no twin gestation Exclusion Criteria: Preterm births (<37 weeks of gestational age), babies with congenital malformations or severe perinatal problems, and those with severe health problems that presented postnatally and potentially compromised their neurological development	Adjustments: Fish intake, fatty acids in maternal serum and proportion of PUFAs, sex, birth weight, maternal IQ, weight gain during pregnancy, marital status at delivery, SES index, number of children living in home, alcohol intake during pregnancy, breastfeeding history, child intake of fish until age 18 months, and daycare attendance at age 18 months

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Valent 2013[132]	Bayley Scales of Infant Dev., Version 3, Cognitive Scale N Total: 606	18 months	AA n-3 Measure: Maternal prenatal serum n-3 Units: mg/ml	All	Coefficient	P value: P=0.95
	Bayley Scales of Infant Dev., Version 3, Cognitive Scale N Total: 606	18 months	ALA n-3 Measure: Maternal prenatal serum n-3 Units: mg/ml	All	Coefficient	P value: P=0.35
	Bayley Scales of Infant Dev., Version 3, Cognitive Scale N Total: 606	18 months	DHA n-3 Measure: Maternal prenatal serum n-3 Units: mg/ml	All	Coefficient	P value: P=0.49
	Bayley Scales of Infant Dev., Version 3, Cognitive Scale N Total: 606	18 months	DPA n-3 Measure: Maternal prenatal serum n-3 Units: mg/ml	All	Coefficient	P value: P=0.28
	Bayley Scales of Infant Dev., Version 3, Cognitive Scale N Total: 606	18 months	EPA n-3 Measure: Maternal prenatal serum n-3 Units: mg/ml	All	Coefficient	P value: P=0.99
	Bayley Scales of Infant Dev., Version 3, Cognitive Scale N Total: 606	18 months	Total n-3s n-3 Measure: Maternal prenatal serum n-3 Units: mg/ml	All	Coefficient	P value: P=0.66
	Bayley Scales of Infant Dev., Version 3, Cognitive Scale N Total: 606	18 months	n-6/n-3 n-3 Measure: Maternal prenatal serum n-3 Units: mg/ml	All	Coefficient	P value: P=0.82
	Motor function N Total: 606	18 months	AA n-3 Measure: Maternal prenatal serum n-3 Units: mg/ml	All	Coefficient	P value: P=0.79
	Motor function N Total: 606	18 months	ALA n-3 Measure: Maternal prenatal serum n-3 Units: mg/ml	All	Coefficient	P value: P=0.56
	Motor function N Total: 606	18 months	DHA n-3 Measure: Maternal prenatal serum n-3 Units: mg/ml	All	Coefficient	P value: P=0.51

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Motor function N Total: 606	18 months	DPA n-3 Measure: Maternal prenatal serum n-3 Units: mg/ml	All	Coefficient	P value: P=0.22
	Motor function N Total: 606	18 months	EPA n-3 Measure: Maternal prenatal serum n-3 Units: mg/ml	All	Coefficient	P value: P=0.31
	Motor function N Total: 606	18 months	Total n-3s n-3 Measure: Maternal prenatal serum n-3 Units: mg/ml	All	Coefficient	P value: P=0.41
	Motor function N Total: 606	18 months	n-6/n-3 n-3 Measure: Maternal prenatal serum n-3 Units: mg/ml	All	Coefficient	P value: P=0.61

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Wijga, et al., 2006[175] Study name: The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study Study dates: 1995-2000 Study design: Observational prospective Location: Netherlands Funding source / conflict: Industry, Government Follow-up: 4 years	Study Population: NR Pregnant enrolled 276 Pregnant withdrawals 11 Pregnant completers 265 Infants enrolled 276 Infants withdrawals 11 Infants completers 265 Pregnant age: 31.0 (3.9) NR Race of Mother: NR (100)	Inclusion Criteria: Mothers reporting at least 1 of the following: (a history of) asthma, current hay fever, current allergy for pets, or current allergy for house dust or house dust mite were defined as allergic, and mothers reporting that they had none of these were defined as non-allergic. Exclusion Criteria: NR	Adjustments: Sex, number of older siblings, maternal age, maternal smoking during pregnancy, and maternal body mass index before pregnancy

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Wilja 2006[175]	Asthma N Total: 158	4 y	AA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 14	OR Estimate: 0.74 95% CI(0.37, 1.47)	
	Asthma N Total: 158	4 y	ALA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 14	OR Estimate: 0.93 95% CI(0.5, 1.35)	
	Asthma N Total: 158	4 y	All n-3 n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 14	OR Estimate: 0.5 95% CI(0.22, 1.13)	
	Asthma N Total: 158	4 y	DHA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 14	OR Estimate: 0.39 95% CI(0.15, 0.99)	
	Asthma N Total: 158	4 y	EPA/AA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 14	OR Estimate: 0.79 95% CI(0.48, 1.29)	
	Asthma N Total: 158	4 y	EPA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 14	OR Estimate: 0.72 95% CI(0.41, 1.26)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Asthma N Total: 158	4 y	n-3LCP/n-6LCP n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 14	OR Estimate: 0.39 95% CI(0.16, 1)	
	Eczema N Total: 158	1 y	AA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 26	OR Estimate: 0.62 95% CI(0.36, 1.01)	
	Eczema N Total: 158	1 y	ALA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 26	OR Estimate: 0.67 95% CI(0.39, 1.2)	
	Eczema N Total: 158	1 y	All n-3 n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 26	OR Estimate: 0.74 95% CI(0.45, 1.21)	
	Eczema N Total: 158	1 y	DHA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 26	OR Estimate: 0.79 95% CI(0.5, 1.23)	
	Eczema N Total: 158	1 y	EPA/AA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 26	OR Estimate: 1.06 95% CI(0.83, 1.37)	
	Eczema N Total: 158	1 y	EPA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 26	OR Estimate: 0.9 95% CI(0.65, 1.26)	
	Eczema N Total: 158	1 y	n-3LCP/n-6LCP n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 26	OR Estimate: 0.82 95% CI(0.52, 1.27)	
	Eczema N Total: 158	4 y	AA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 27	OR Estimate: 0.82 95% CI(0.48, 1.39)	
	Eczema N Total: 158	4 y	ALA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 27	OR Estimate: 0.82 95% CI(0.5, 1.35)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Eczema N Total: 158	4 y	All n-3 n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 27	OR Estimate: 0.84 95% CI(0.54, 1.3)	
	Eczema N Total: 158	4 y	DHA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 27	OR Estimate: 0.99 95% CI(0.7, 1.41)	
	Eczema N Total: 158	4 y	EPA/AA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 27	OR Estimate: 0.91 95% CI(0.68, 1.23)	
	Eczema N Total: 158	4 y	EPA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 27	OR Estimate: 0.9 95% CI(0.65, 1.26)	
	Eczema N Total: 158	4 y	n-3LCP/n-6LCP n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 27	OR Estimate: 0.81 95% CI(0.52, 1.26)	
	Persistent symptoms (eczema at 1 year as well as eczema and/or asthma at age 4 years) N Total: 158	1 y/4 y	AA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 20	OR Estimate: 0.81 95% CI(0.45, 1.48)	
	Persistent symptoms (eczema at 1 year as well as eczema and/or asthma at age 4 years) N Total: 158	1 y/4 y	ALA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 20	OR Estimate: 0.66 95% CI(0.35, 1.25)	
	Persistent symptoms (eczema at 1 year as well as eczema and/or asthma at age 4 years) N Total: 158	1 y/4 y	All n-3 n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 20	OR Estimate: 0.53 95% CI(0.27, 1.04)	
	Persistent symptoms (eczema at 1 year as well as eczema and/or asthma at age 4 years) N Total: 158	1 y/4 y	DHA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 20	OR Estimate: 0.67 95% CI(0.37, 1.19)	
	Persistent symptoms (eczema at 1 year as well as eczema and/or asthma at age 4 years) N Total: 158	1 y/4 y	EPA/AA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 20	OR Estimate: 0.72 95% CI(0.46, 1.14)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Persistent symptoms (eczema at 1 year as well as eczema and/or asthma at age 4 years) N Total: 158	1 y/4 y	EPA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 20	OR Estimate: 0.67 95% CI(0.41, 1.1)	
	Persistent symptoms (eczema at 1 year as well as eczema and/or asthma at age 4 years) N Total: 158	1 y/4 y	n-3LCP/n-6LCP n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 20	OR Estimate: 0.51 95% CI(0.25, 1.03)	
	Sensitization and symptoms N Total: 81	4 y	AA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 10	OR Estimate: 1.23 95% CI(0.53, 2.82)	
	Sensitization and symptoms N Total: 81	4 y	ALA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 10	OR Estimate: 0.7 95% CI(0.3, 1.63)	
	Sensitization and symptoms N Total: 81	4 y	All n-3 n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 10	OR Estimate: 0.48 95% CI(0.17, 1.31)	
	Sensitization and symptoms N Total: 81	4 y	DHA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 10	OR Estimate: 0.78 95% CI(0.36, 1.69)	
	Sensitization and symptoms N Total: 81	4 y	EPA/AA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 10	OR Estimate: 0.52 95% CI(0.23, 1.18)	
	Sensitization and symptoms N Total: 81	4 y	EPA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 10	OR Estimate: 0.56 95% CI(0.26, 1.22)	
	Sensitization and symptoms N Total: 81	4 y	n-3 LCP/n-6 LCP n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 10	OR Estimate: 0.38 95% CI(0.12, 1.22)	
	Sensitization N Total: 52	4 y	AA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 16	OR Estimate: 0.62 95% CI(0.27, 1.39)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Sensitization N Total: 52	4 y	ALA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 16	OR Estimate: 2.43 95% CI(1.01, 5.88)	
	Sensitization N Total: 52	4 y	All n-3 n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 16	OR Estimate: 1.11 95% CI(0.86, 1.42)	
	Sensitization N Total: 52	4 y	DHA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 16	OR Estimate: 1.1 95% CI(0.9, 1.34)	
	Sensitization N Total: 52	4 y	EPA/AA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 16	OR Estimate: 1.22 95% CI(0.92, 1.62)	
	Sensitization N Total: 52	4 y	EPA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 16	OR Estimate: 1.13 95% CI(0.9, 1.43)	
	Sensitization N Total: 52	4 y	n-3LCP/n-6LCP n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 16	OR Estimate: 1.29 95% CI(0.85, 1.95)	
	Sensitization N Total: 81	4 y	AA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 32	OR Estimate: 0.85 95% CI(0.5, 1.46)	
	Sensitization N Total: 81	4 y	ALA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 32	OR Estimate: 0.81 95% CI(0.49, 1.35)	
	Sensitization N Total: 81	4 y	All n-3 n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 32	OR Estimate: 0.86 95% CI(0.52, 1.41)	
	Sensitization N Total: 81	4 y	DHA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 32	OR Estimate: 0.89 95% CI(0.57, 1.38)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Sensitization N Total: 81	4 y	EPA/AA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 32	OR Estimate: 1.02 95% CI(0.71, 1.46)	
	Sensitization N Total: 81	4 y	EPA n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 32	OR Estimate: 0.85 95% CI(0.55, 1.32)	
	Sensitization N Total: 81	4 y	n-3LCP/n-6LCP n-3 Measure: Breast milk fatty acid content, median wt% (interquartile range) n-3 Units: per interquartile range increase in breast milk FA content (wt%)	All N Cases: 32	OR Estimate: 1.12 95% CI(0.7, 1.77)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Yoshihiro Miyake, et al., 2006[93] Study name: Osaka maternal and child health study Study dates: 2001-2003 Study design: Observational prospective Location: Japan Funding source / conflict: Government, Multiple foundations and Societies, None	Study Population: Healthy pregnant women Pregnant enrolled 1002 Pregnant withdrawals 137 Pregnant completers 865 Pregnant age: age reported in categories Race of Mother: Asian (100%)	Inclusion Criteria: women who became pregnant in Neyagawa City, Osaka Prefecture, Japan Exclusion Criteria: NR	Adjustments: Age, gestation, parity, cigarette smoking, family structure, family income, education, changes in diet in the previous month, season when data at baseline were collected, body mass index, time of delivery before the second survey, medical problems in pregnancy, baby's sex and baby's birthweight

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Miyake 2006[93]			DHA n-3 Measure: FFQ n-3 Units: g/day	Q1 0.16	OR	
			DHA n-3 Measure: FFQ n-3 Units: g/day	Q2 0.26	OR Estimate: 0.76 95% CI(0.44, 1.32)	
			DHA n-3 Measure: FFQ n-3 Units: g/day	Q3 0.34	OR Estimate: 0.62 95% CI(0.34, 1.09)	
			DHA n-3 Measure: FFQ n-3 Units: g/day	Q4 0.5	OR Estimate: 0.85 95% CI(0.49, 1.46)	
			EPA n-3 Measure: FFQ n-3 Units: g/day	Q1 0.08	OR	
			EPA n-3 Measure: FFQ n-3 Units: g/day	Q2 0.15	OR Estimate: 0.93 95% CI(0.54, 1.6)	
			EPA n-3 Measure: FFQ n-3 Units: g/day	Q3 0.21	OR Estimate: 0.81 95% CI(0.46, 1.42)	
			EPA n-3 Measure: FFQ n-3 Units: g/day	Q4 0.32	OR Estimate: 0.89 95% CI(0.51, 1.55)	
			n-3 FA n-3 Measure: FFQ n-3 Units: g/day	Q1 1.6	OR	
			n-3 FA n-3 Measure: FFQ n-3 Units: g/day	Q2 2.1	OR Estimate: 0.68 95% CI(0.39, 1.18)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
			n-3 FA n-3 Measure: FFQ n-3 Units: g/day	Q3 2.4	OR Estimate: 0.58 95% CI(0.33, 1.02)	
			n-3 FA n-3 Measure: FFQ n-3 Units: g/day	Q4 3	OR Estimate: 0.9 95% CI(0.53, 1.53)	

Author, Year, Study, Location, Funding Source, Follow-up	Population and participant information	Inclusion and Exclusion Criteria	Adjustment
Yu, et al., 2015[185] Study dates: Participants recruited between June 2009 and September 2010 Study design: Observational prospective Location: NR Funding source / conflict: Industry, Government	Study Population: Healthy infants Healthy pregnant women Infants enrolled 1162 Infants completers 960 Pregnant age: NR (NR) NR Race of Mother: NR (100%)	Inclusion Criteria: Participants were mother–child pairs in the Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort. Exclusion Criteria: NR	Adjustments: In the models, we adjusted for maternal characteristics including maternal age, ethnicity, gravidity, education level and energy intake. The same was done for infant characteristics including sex, birth weight, gestational age, duration of breast-feeding, family history of allergic diseases (which includes allergic rhinitis, eczema and asthma in first-degree relatives of the children (i.e. father, mother and/or sibling), exposure to environmental tobacco smoking, child day care attendance and having a cat or dog at home up to 18 months of age.

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
Yu 2015[185]	Allergic sensitisation N Total: 728	Up to 18 months	A-linolenic acid n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q1 =1.0 N Quantile: NR N Cases: NR	OR	
	Allergic sensitisation N Total: 728	Up to 18 months	A-linolenic acid n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q2 0.11-0.18 N Quantile: NR N Cases: NR	OR Estimate: 0.8 95% CI(0.43, 1.49)	
	Allergic sensitisation N Total: 728	Up to 18 months	A-linolenic acid n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q3 0.19-0.27 N Quantile: NR N Cases: NR	OR Estimate: 0.92 95% CI(0.51, 1.68)	
	Allergic sensitisation N Total: 728	Up to 18 months	A-linolenic acid n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q4 =0.28 N Quantile: NR N Cases: NR	OR Estimate: 0.85 95% CI(0.46, 1.55)	
	Allergic sensitisation N Total: 728	Up to 18 months	DHA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q1 =3.60 N Quantile: NR N Cases: NR	OR	
	Allergic sensitisation N Total: 728	Up to 18 months	DHA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q2 3.16-4.59 N Quantile: NR N Cases: NR	OR Estimate: 0.9 95% CI(0.48, 1.65)	
	Allergic sensitisation N Total: 728	Up to 18 months	DHA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q3 4.60-5.63 N Quantile: NR N Cases: NR	OR Estimate: 0.73 95% CI(0.38, 1.40)	
	Allergic sensitisation N Total: 728	Up to 18 months	DHA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q4 =5.64 N Quantile: NR N Cases: NR	OR Estimate: 1.24 95% CI(0.69, 2.24)	
	Allergic sensitisation N Total: 728	Up to 18 months	EPA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q1 =0.35 N Quantile: NR N Cases: NR	OR	
	Allergic sensitisation N Total: 728	Up to 18 months	EPA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q2 0.36-0.51 N Quantile: NR N Cases: NR	OR Estimate: 1.12 95% CI(0.57, 2.21)	
	Allergic sensitisation N Total: 728	Up to 18 months	EPA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q3 0.52-0.82 N Quantile: NR N Cases: NR	OR Estimate: 1.26 95% CI(0.65, 2.47)	
	Allergic sensitisation N Total: 728	Up to 18 months	EPA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q4 =0.83 N Quantile: NR N Cases: NR	OR Estimate: 1.82 95% CI(0.94, 3.50)	
	Allergic sensitisation N Total: 728	Up to 18 months	n-3 PUFA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q1 =5.00 N Quantile: NR N Cases: NR	OR	
	Allergic sensitisation N Total: 728	Up to 18 months	n-3 PUFA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q2 5.01-6.18 N Quantile: NR N Cases: NR	OR Estimate: 0.91 95% CI(0.48, 1.72)	
	Allergic sensitisation N Total: 728	Up to 18 months	n-3 PUFA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q3 6.19-7.49 N Quantile: NR N Cases: NR	OR Estimate: 0.83 95% CI(0.43, 1.58)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Allergic sensitisation N Total: 728	Up to 18 months	n-3 PUFA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q4 =7.50 N Quantile: NR N Cases: NR	OR Estimate: 1.41 95% CI(0.77, 2.58)	
	Allergic sensitisation N Total: 728	Up to 18 months	n-6: n-3 PUFA ratio n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q1 =4.52 N Quantile: NR N Cases: NR	OR	
	Allergic sensitisation N Total: 728	Up to 18 months	n-6: n-3 PUFA ratio n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q2 4.53-5.49 N Quantile: NR N Cases: NR	OR Estimate: 0.6 95% CI(0.33, 1.10)	
	Allergic sensitisation N Total: 728	Up to 18 months	n-6: n-3 PUFA ratio n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q3 5.50-6.94 N Quantile: NR N Cases: NR	OR Estimate: 0.67 95% CI(0.37, 1.21)	
	Allergic sensitisation N Total: 728	Up to 18 months	n-6: n-3 PUFA ratio n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q4 =6.95 N Quantile: NR N Cases: NR	OR Estimate: 0.66 95% CI(0.36, 1.22)	
	Eczema N Total: 833	Up to 18 months	A-linolenic acid n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q1 =1.0 N Quantile: NR N Cases: NR	OR	
	Eczema N Total: 833	Up to 18 months	A-linolenic acid n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q2 0.11-0.18 N Quantile: NR N Cases: NR	OR Estimate: 0.87 95% CI(0.50, 1.51)	
	Eczema N Total: 833	Up to 18 months	A-linolenic acid n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q3 0.19-0.27 N Quantile: NR N Cases: NR	OR Estimate: 1.07 95% CI(0.64, 1.81)	
	Eczema N Total: 833	Up to 18 months	A-linolenic acid n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q4 =0.28 N Quantile: NR N Cases: NR	OR Estimate: 0.87 95% CI(0.51, 1.47)	
	Eczema N Total: 833	Up to 18 months	DHA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q1 =3.60 N Quantile: NR N Cases: NR	OR	
	Eczema N Total: 833	Up to 18 months	DHA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q2 3.16-4.59 N Quantile: NR N Cases: NR	OR Estimate: 1.02 95% CI(0.61, 1.70)	
	Eczema N Total: 833	Up to 18 months	DHA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q3 4.60-5.63 N Quantile: NR N Cases: NR	OR Estimate: 0.61 95% CI(0.35, 1.07)	
	Eczema N Total: 833	Up to 18 months	DHA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q4 =5.64 N Quantile: NR N Cases: NR	OR Estimate: 0.8 95% CI(0.47, 1.35)	
	Eczema N Total: 833	Up to 18 months	EPA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q1 =0.35 N Quantile: NR N Cases: NR	OR	
	Eczema N Total: 833	Up to 18 months	EPA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q2 0.36-0.51 N Quantile: NR N Cases: NR	OR Estimate: 1.14 95% CI(0.64, 2.04)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Eczema N Total: 833	Up to 18 months	EPA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q3 0.52-0.82 N Quantile: NR N Cases: NR	OR Estimate: 1.07 95% CI(0.60, 1.89)	
	Eczema N Total: 833	Up to 18 months	EPA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q4 =0.83 N Quantile: NR N Cases: NR	OR Estimate: 1.2 95% CI(0.68, 2.13)	
	Eczema N Total: 833	Up to 18 months	n-3 PUFA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q1 =5.00 N Quantile: NR N Cases: NR	OR	
	Eczema N Total: 833	Up to 18 months	n-3 PUFA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q2 5.01-6.18 N Quantile: NR N Cases: NR	OR Estimate: 1.02 95% CI(0.60, 1.74)	
	Eczema N Total: 833	Up to 18 months	n-3 PUFA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q3 6.19-7.49 N Quantile: NR N Cases: NR	OR Estimate: 0.67 95% CI(0.38, 1.18)	
	Eczema N Total: 833	Up to 18 months	n-3 PUFA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q4 =7.50 N Quantile: NR N Cases: NR	OR Estimate: 0.93 95% CI(0.55, 1.60)	
	Eczema N Total: 833	Up to 18 months	n-6: n-3 PUFA ratio n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q1 1.9-4.5 N Quantile: NR N Cases: NR	OR	
	Eczema N Total: 833	Up to 18 months	n-6: n-3 PUFA ratio n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q2 4.6-5.4 N Quantile: NR N Cases: NR	OR Estimate: 0.55 95% CI(0.32, 0.97)	
	Eczema N Total: 833	Up to 18 months	n-6: n-3 PUFA ratio n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q3 5.5-6.9 N Quantile: NR N Cases: NR	OR Estimate: 1.19 95% CI(0.72, 1.97)	
	Eczema N Total: 833	Up to 18 months	n-6: n-3 PUFA ratio n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q4 7.0-16.6 N Quantile: NR N Cases: NR	OR Estimate: 1.21 95% CI(0.71, 2.06)	
	Rhinitis N Total: 808	Up to 18 months	A-linolenic acid n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q1 =1.0 N Quantile: NR N Cases: NR	OR	
	Rhinitis N Total: 808	Up to 18 months	A-linolenic acid n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q2 0.11-0.18 N Quantile: NR N Cases: NR	OR Estimate: 1.18 95% CI(0.74, 1.89)	
	Rhinitis N Total: 808	Up to 18 months	A-linolenic acid n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q3 0.19-0.27 N Quantile: NR N Cases: NR	OR Estimate: 0.95 95% CI(0.59, 1.52)	
	Rhinitis N Total: 808	Up to 18 months	A-linolenic acid n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q4 =0.28 N Quantile: NR N Cases: NR	OR Estimate: 0.86 95% CI(0.54, 1.38)	
	Rhinitis N Total: 808	Up to 18 months	DHA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q1 =3.60 N Quantile: NR N Cases: NR	OR	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Rhinitis N Total: 808	Up to 18 months	DHA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q2 3.16-4.59 N Quantile: NR N Cases: NR	OR Estimate: 1.53 95% CI(0.94, 2.50)	
	Rhinitis N Total: 808	Up to 18 months	DHA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q3 4.60-5.63 N Quantile: NR N Cases: NR	OR Estimate: 1.97 95% CI(1.22, 3.21)	
	Rhinitis N Total: 808	Up to 18 months	DHA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q4 =5.64 N Quantile: NR N Cases: NR	OR Estimate: 1.42 95% CI(0.87, 2.32)	
	Rhinitis N Total: 808	Up to 18 months	EPA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q1 =0.35 N Quantile: NR N Cases: NR	OR	
	Rhinitis N Total: 808	Up to 18 months	EPA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q2 0.36-0.51 N Quantile: NR N Cases: NR	OR Estimate: 1.09 95% CI(0.68, 1.77)	
	Rhinitis N Total: 808	Up to 18 months	EPA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q3 0.52-0.82 N Quantile: NR N Cases: NR	OR Estimate: 1.02 95% CI(0.63, 1.66)	
	Rhinitis N Total: 808	Up to 18 months	EPA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q4 =0.83 N Quantile: NR N Cases: NR	OR Estimate: 1.04 95% CI(0.64, 1.69)	
	Rhinitis N Total: 808	Up to 18 months	n-3 PUFA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q1 =5.00 N Quantile: NR N Cases: NR	OR	
	Rhinitis N Total: 808	Up to 18 months	n-3 PUFA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q2 5.01-6.18 N Quantile: NR N Cases: NR	OR Estimate: 1.56 95% CI(0.96. 2.54)	
	Rhinitis N Total: 808	Up to 18 months	n-3 PUFA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q3 6.19-7.49 N Quantile: NR N Cases: NR	OR Estimate: 1.67 95% CI(1.03, 2.70)	
	Rhinitis N Total: 808	Up to 18 months	n-3 PUFA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q4 =7.50 N Quantile: NR N Cases: NR	OR Estimate: 1.34 95% CI(0.81. 2.21)	
	Rhinitis N Total: 808	Up to 18 months	n-6: n-3 PUFA ratio n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q1 1.9-4.5 N Quantile: NR N Cases: NR	OR	
	Rhinitis N Total: 808	Up to 18 months	n-6: n-3 PUFA ratio n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q2 4.6-5.4 N Quantile: NR N Cases: NR	OR Estimate: 1.11 95% CI(.7, 1.75)	
	Rhinitis N Total: 808	Up to 18 months	n-6: n-3 PUFA ratio n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q3 5.5-6.9 N Quantile: NR N Cases: NR	OR Estimate: 1.34 95% CI(.85, 2.11)	
	Rhinitis N Total: 808	Up to 18 months	n-6: n-3 PUFA ratio n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q4 7.0-16.6 N Quantile: NR N Cases: NR	OR Estimate: 0.66 95% CI(0.40, 1.10)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Wheezing N Total: 859	Up to 18 months	A-linolenic acid n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q1 =1.0 N Quantile: NR N Cases: NR	OR	
	Wheezing N Total: 859	Up to 18 months	A-linolenic acid n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q2 0.11-0.18 N Quantile: NR N Cases: NR	OR Estimate: 1.22 95% CI(0.61, 2.44)	
	Wheezing N Total: 859	Up to 18 months	A-linolenic acid n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q3 0.19-0.27 N Quantile: NR N Cases: NR	OR Estimate: 1.77 95% CI(0.91, 3.46)	
	Wheezing N Total: 859	Up to 18 months	A-linolenic acid n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q4 =0.28 N Quantile: NR N Cases: NR	OR Estimate: 1.12 95% CI(0.56, 2.24)	
	Wheezing N Total: 859	Up to 18 months	DHA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q1 =3.60 N Quantile: NR N Cases: NR	OR	
	Wheezing N Total: 859	Up to 18 months	DHA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q2 3.16-4.59 N Quantile: NR N Cases: NR	OR Estimate: 0.95 95% CI(0.49, 1.86)	
	Wheezing N Total: 859	Up to 18 months	DHA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q3 4.60-5.63 N Quantile: NR N Cases: NR	OR Estimate: 0.98 95% CI(0.49, 1.96)	
	Wheezing N Total: 859	Up to 18 months	DHA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q4 =5.64 N Quantile: NR N Cases: NR	OR Estimate: 1.15 95% CI(0.60, 2.22)	
	Wheezing N Total: 859	Up to 18 months	EPA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q1 =0.35 N Quantile: NR N Cases: NR	OR	
	Wheezing N Total: 859	Up to 18 months	EPA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q2 0.36-0.51 N Quantile: NR N Cases: NR	OR Estimate: 1.07 95% CI(0.52, 2.21)	
	Wheezing N Total: 859	Up to 18 months	EPA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q3 0.52-0.82 N Quantile: NR N Cases: NR	OR Estimate: 1.19 95% CI(0.60, 2.36)	
	Wheezing N Total: 859	Up to 18 months	EPA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q4 =0.83 N Quantile: NR N Cases: NR	OR Estimate: 1.2 95% CI(0.60, 2.39)	
	Wheezing N Total: 859	Up to 18 months	n-3 PUFA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q1 =5.00 N Quantile: NR N Cases: NR	OR	
	Wheezing N Total: 859	Up to 18 months	n-3 PUFA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q2 5.01-6.18 N Quantile: NR N Cases: NR	OR Estimate: 0.9 95% CI(0.45, 1.78)	
	Wheezing N Total: 859	Up to 18 months	n-3 PUFA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q3 6.19-7.49 N Quantile: NR N Cases: NR	OR Estimate: 1.09 95% CI(0.56, 2.13)	

Article	Outcome, Cohort size	Follow up Time	Exposure Intervention, n-3 measure, n-3 units	Quantile	Metric, Estimate and CI	P value
	Wheezing N Total: 859	Up to 18 months	n-3 PUFA n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q4 =7.50 N Quantile: NR N Cases: NR	OR Estimate: 1.12 95% CI(0.57, 2.2)	
	Wheezing N Total: 859	Up to 18 months	n-6: n-3 PUFA ratio n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q1 1.9-4.5 N Quantile: NR N Cases: NR	OR	
	Wheezing N Total: 859	Up to 18 months	n-6: n-3 PUFA ratio n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q2 4.6-5.4 N Quantile: NR N Cases: NR	OR Estimate: 0.7 95% CI(0.38, 1.30)	
	Wheezing N Total: 859	Up to 18 months	n-6: n-3 PUFA ratio n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q3 5.5-6.9 N Quantile: NR N Cases: NR	OR Estimate: 0.64 95% CI(0.34, 1.23)	
	Wheezing N Total: 859	Up to 18 months	n-6: n-3 PUFA ratio n-3 Measure: Maternal blood n-3 Units: % of total plasma fatty acids	Q4 7.0-16.6 N Quantile: NR N Cases: NR	OR Estimate: 0.63 95% CI(0.32, 1.25)	

Appendix E. Data Abstraction Tools

1. **Data Abstraction Tool for RCTs**
2. **Data Abstraction Tool for Observational Studies**
3. **Modified Cochrane Risk of Bias Tool**
4. **Modified Newcastle-Ottawa Quality Assessment Scale**
5. **McHarms Tool**

1. Data Abstraction Tool

Article information

1. What is the name of this study? (e.g. DART, Physician's Health Study) ***Omit if name of study is not provided.***

- [ ] DART
- [ ] Physician's Health Study
- [ ] Maastricht Essential Fatty Acid Birth (MEFAB) Cohort
- [ ] The DIAMOND Study (DHA Intake And Measurement Of Neural Development)
- [ ] data using DIAMOND study
- [ ] POSGRAD
- [ ] NUHEAL
- [ ] Infant Fish Oil Supplementation Study (IFOS)
- [ ] Danish National Birth Cohort
- [ ] Groningen LCPUFA study
- [ ] DINO (Docosahexaenoic acid for the Improvement in Neurodevelopmental Outcome)
- [ ] DOMINO
- [ ] INFAT
- [ ] BeMIM (Belgrade-Munch Infant Milk Trial)
- [ ] GINI
- [ ] The Docosahexaenoic Acid to Optimise Mother Infant Outcome (DOMInO)
- [ ] Childhood Asthma Prevention Study
- [ ] Salmon in Pregnancy Study (SiPS)

Other study names

2. Study Design

- ● Trial: Randomized Parallel (Omega-3 vs. Control; Omega-3 XX vs. X)
- ● Trial: Randomized Cross-over

- Trial: Randomized Factorial Design
- Observational: Prospective, longitudinal, comparative study
- Observational: Nested Case Control

Other

Clear Response

3. Funding source

- [ ] Industry funded
- [ ] Government funded
- [ ] Some authors employed by industry (companies that make the supplements)
- [ ] Funding or affiliations not reported
- [ ] Mulitple foundations and Societies
- [ ] None of the authors had any personal or financial conflicts of interest
- [ ] Trade group funded
- [ ] March of Dimes
- [ ] Manufacturer supplied product
- [ ] Some authors serve on scientific advisory boards for corporations

Other funding source

4. Country in which study conducted (where subjects live) ***Note that this might be different than the countries where the authors are based. Select "NR (not reported)" if it's truly unclear.***

- [ ] US
- [ ] Canada
- [ ] Denmark
- [ ] Finland
- [ ] Germany
- [ ] Greece
- [ ] Italy

- [ ] Japan
- [ ] Netherlands
- [ ] Norway
- [ ] Sweden
- [ ] UK
- [ ] NR (not reported)
- [ ] Mexico
- [ ] Australia
- [ ] Taiwan
- [ ] Spain
- [ ] Hungary
- [ ] Turkey
- [ ] Bangladesh
- [ ] Thailand
- [ ] Serbia
- [ ] Multie-center study in hospitals of 11 countries in Europe

Other

5. Study Population

- [ ] Healthy infants or children
- [ ] Preterm infants
- [ ] Healthy pregnant women
- [ ] Postpartum women
- [ ] Breast-feeding women
- [ ] Low birth weight infants

- [ ] Pregnant mothers with allergies and their offspring
- [ ] Pregnant women whose unborn children were at high risk of developing asthma
- [ ] children with family history of allergy

Other

6. Inclusion criteria as defined in study

7. Exclusion criteria

II. Participant Information

1. Sample size

Pregnant	Lactating mothers	Mothers	Infants
# Enrolled/Randomized	# Enrolled/Randomized	# Enrolled/Randomized	# Enrolled/Randomized
# of withdrawals	# of withdrawals	# of withdrawals	# of withdrawals
# of completers (largest follow-up)	# of completers (largest follow-up)	# of completers (largest follow-up)	# of completers (largest follow-up)

2. Age at baseline

Mean age (Pregnant)	Mean age (Lactating mothers)	Mean age (Mothers)	Mean age (Infants)
Standard Deviation (Pregnant)	**Standard Deviation (Lactating mothers)**	**Standard Deviation (Mothers)**	**Standard Deviation (Infants)**

Age range (Pregnant)	Age range (Lactating mothers)	Age range (Mothers)	Age range (infants)

3. Race/Ethnicity (Mother)

- White/European (specify %)
- Black/African American/etc. (specify %)
- Asian (specify %)
- Hispanic (specify %)
- Inuit/Eskimo (specify %)
- NR (specify %)
- varied by study site and experimental group (specify %)
- Minority (specify %)
- Other
- non black
- Puerto Rican/Latino
- Native Hawaiian or other pacific ethnicity

Other

4. Race/Ethnicity (Infant)

- White/European (specify %)
- Black/African American/etc. (specify %)
- Asian (specify %)

Hispanic (specify %)

Inuit/Eskimo (specify %)

Not reported (specify %)

varied by study site and experimental groups (specify %)

Non-white

Other

5. Is baseline biomarker information reported?

Yes No Clear Response

6. Is baseline Omega-3 intake reported?

Yes No Clear Response

III. Intervention information [if observational study, please stop here]

	Pregnant	Lactating mothers	Mothers	Infants
Start time of intervention				
Length (duration) of intervention				
Longest follow-up time				

V. Arms

How to fill out this section:

For controlled trials, Arm 1 should be the placebo/control group or lowest dose of intervention.

1. How many arms are there?

Arm 1:

Name

Description

RCT: Arm 1 (placebo or other control)

Brand name (if applicable)

Manufacturer (specify)

Purity data (specify)

Presence of other potentially active ingredients (e.g., arachidonic acid, vitamin E) (specify)

☐ Storage conditions or other efforts to preserve product viability) (specify)

☐ n-3 composition (e.g., grams or percent EPA, DHA per capsule) (specify)

☐ Dose per day (e.g., 1 1gm capsule, twice a day) (specify)

☐ If placebo, how was blinding achieved? (specify)

☐ Maternal conditions

☐ Infant conditions

Arm 2:

☐ Name

☐ Description

RCT: Arm 2 (placebo or other control)

☐ Brand name (if applicable)

☐ Manufacturer (specify)

☐ Purity data (specify)

☐ Presence of other potentially active ingredients (e.g., arachidonic acid, vitamin E) (specify)

☐ Storage conditions or other efforts to preserve product viability) (specify)

☐ n-3 composition (e.g., grams or percent EPA, DHA per capsule) (specify)

☐ Dose per day (e.g., 1 1gm capsule, twice a day) (specify)

☐ If placebo, how was blinding achieved? (specify)

☐ Maternal conditions

☐ Infant conditions

Arm 3:

☐ Name

☐ Description

RCT: Arm 3 (placebo or other control)

☐ Brand name (if applicable)

☐ Manufacturer (specify)

- [ ] Purity data (specify)
- [ ] Presence of other potentially active ingredients (e.g., arachidonic acid, vitamin E) (specify)
- [ ] Storage conditions or other efforts to preserve product viability) (specify)
- [ ] n-3 composition (e.g., grams or percent EPA, DHA per capsule) (specify)
- [ ] Dose per day (e.g., 1 1gm capsule, twice a day) (specify)
- [ ] If placebo, how was blinding achieved? (specify)
- [ ] Maternal conditions
- [ ] Infant conditions

Arm 4:

- [ ] Name
- [ ] Description

RCT: Arm 4 (placebo or other control)

- [ ] Brand name (if applicable)
- [ ] Manufacturer (specify)
- [ ] Purity data (specify)
- [ ] Presence of other potentially active ingredients (e.g., arachidonic acid, vitamin E) (specify)
- [ ] Storage conditions or other efforts to preserve product viability) (specify)
- [ ] n-3 composition (e.g., grams or percent EPA, DHA per capsule) (specify)
- [ ] Dose per day (e.g., 1 1gm capsule, twice a day) (specify)
- [ ] If placebo, how was blinding achieved? (specify)
- [ ] Maternal conditions
- [ ] Infant conditions

Arm 5:

- [ ] Name
- [ ] Description

RCT: Arm 5 (placebo or other control)

- [ ] Brand name (if applicable)
- [ ] Manufacturer (specify)
- [ ] Purity data (specify)
- [ ] Presence of other potentially active ingredients (e.g., arachidonic acid, vitamin E) (specify)
- [ ] Storage conditions or other efforts to preserve product viability) (specify)
- [ ] n-3 composition (e.g., grams or percent EPA, DHA per capsule) (specify)
- [ ] Dose per day (e.g., 1 1gm capsule, twice a day) (specify)
- [ ] If placebo, how was blinding achieved? (specify)
- [ ] Maternal conditions
- [ ] Infant conditions

Please indicate if there are any references from the studies reference list that we should pull (indicate the reference number from the article)

Arm 6:

- [ ] Name
- [ ] Description

RCT: Arm 6 (placebo or other control)

- [ ] Brand name (if applicable)
- [ ] Manufacturer (specify)
- [ ] Purity data (specify)
- [ ] Presence of other potentially active ingredients (e.g., arachidonic acid, vitamin E) (specify)
- [ ] Storage conditions or other efforts to preserve product viability) (specify)
- [ ] n-3 composition (e.g., grams or percent EPA, DHA per capsule) (specify)
- [ ] Dose per day (e.g., 1 1gm capsule, twice a day) (specify)
- [ ] If placebo, how was blinding achieved? (specify)

☐ Maternal conditions

☐ Infant conditions

Arm 7:

☐ Name

☐ Description

RCT: Arm 7 (placebo or other control)

☐ Brand name (if applicable)

☐ Manufacturer (specify)

☐ Purity data (specify)

☐ Presence of other potentially active ingredients (e.g., arachidonic acid, vitamin E) (specify)

☐ Storage conditions or other efforts to preserve product viability) (specify)

☐ n-3 composition (e.g., grams or percent EPA, DHA per capsule) (specify)

☐ Dose per day (e.g., 1 1gm capsule, twice a day) (specify)

☐ If placebo, how was blinding achieved? (specify)

☐ Maternal conditions

☐ Infant conditions

2. Data Abstraction Tool for Observational Studies

I. Article information

1. What is the name of this study? (e.g. DART, Physician's Health Study) ***Omit if name of study is not provided.***

- ☐ DART
- ☐ Physician's Health Study
- ☐ Maastricht Essential Fatty Acid Birth (MEFAB) Cohort
- ☐ The DIAMOND Study (DHA Intake And Measurement Of Neural Development)
- ☐ data using DIAMOND study
- ☐ POSGRAD
- ☐ NUHEAL
- ☐ Infant Fish Oil Supplementation Study (IFOS)
- ☐ Danish National Birth Cohort
- ☐ Groningen LCPUFA study
- ☐ DINO (Docosahexaenoic acid for the Improvement in Neurodevelopmental Outcome)
- ☐ DOMINO
- ☐ INFAT
- ☐ BeMIM (Belgrade-Munch Infant Milk Trial)
- ☐ GINI
- ☐ The Docosahexaenoic Acid to Optimise Mother Infant Outcome (DOMInO)
- ☐ Childhood Asthma Prevention Study
- ☐ Salmon in Pregnancy Study (SiPS)
- ☐ Project Viva
- ☐ INMA
- ☐ Avon Longitudinal Study of Parents and Children (ALSPAC)

- [ ] Alberta Pregnancy Outcomes and Nutrition (APrON) study
- [ ] Osaka maternal and child health study
- [ ] Amsterdam Born Children and their Development （ABCD）
- [ ] EDEN
- [ ] LISAplus
- [ ] The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study
- [ ] KOALA Birth Cohort Study
- [ ] Finnish Type 1 Diabetes Prediction and Prevention Nutrition Study
- [ ] The Prevention of Allergy among Children in Trondheim study
- [ ] Norwegian Mother and Child Cohort Study (MoBa)
- [ ] INfancia y Medio Ambiente (INMA) Project
- [ ] Pregnancy, Infection and Nutrition Study
- [ ] Nurses Health Study
- [ ] Kyushu Okinawa Maternal and Child Health Study
- [ ] Southampton Women's Survey

Other study names

2. Study Design

- ● Trial: Randomized Parallel (Omega-3 vs. Control; Omega-3 XX vs. X)
- ● Trial: Randomized Cross-over
- ● Trial: Randomized Factorial Design
- ● Observational: Prospective, longitudinal, comparative study
- ● Observational: Nested Case Control

Other

Clear Response

3. Funding source

- [ ] Industry funded

☐ Government funded

☐ Some authors employed by industry (companies that make the supplements)

☐ Funding or affiliations not reported

☐ Mulitple foundations and Societies

☐ None of the authors had any personal or financial conflicts of interest

☐ Trade group funded

☐ March of Dimes

☐ Manufacturer supplied product

☐ Some authors serve on scientific advisory boards for corporations

☐ Alberta Innovates-Health Solutions

☐ Infant formula manufacturer performed assays

Other funding source

4. Country in which study conducted (where subjects live) ***Note that this might be different than the countries where the authors are based. Select "NR (not reported)" if it's truly unclear.***

☐ US

☐ Canada

☐ Denmark

☐ Finland

☐ Germany

☐ Greece

☐ Italy

☐ Japan

☐ Netherlands

☐ Norway

☐ Sweden

- [ ] UK
- [ ] NR (not reported)
- [ ] Mexico
- [ ] Australia
- [ ] Taiwan
- [ ] Spain
- [ ] Hungary
- [ ] Turkey
- [ ] Bangladesh
- [ ] Thailand
- [ ] Serbia
- [ ] Multie-center study in hospitals of 11 countries in Europe
- [ ] Iceland
- [ ] England
- [ ] France
- [ ] Malaysia
- [ ] India

Other

5. Study Population

- [ ] Healthy infants or children
- [ ] Preterm infants
- [ ] Healthy pregnant women
- [ ] Postpartum women
- [ ] Breast-feeding women

☐ Low birth weight infants

☐ Pregnant mothers with allergies and their offspring

☐ Pregnant women whose unborn children were at high risk of developing asthma

☐ children with family history of allergy

☐ Children with allergies

☐ Infants at risk for Diabetes 1

☐ Pregnant mothers without allergies and their offspring

☐ Children with a family history of asthma

Other

6. Inclusion criteria as defined in study

7. Exclusion criteria

II. Participant Information

1. Sample size

Pregnant		Lactating mothers		Mothers		Infants	
☐ # Enrolled/Randomized		☐ # Enrolled/Randomized		☐ # Enrolled/Randomized		☐ # Enrolled/Randomized	
☐ # of withdrawals		☐ # of withdrawals		☐ # of withdrawals		☐ # of withdrawals	
☐ # of completers (largest follow-up)		☐ # of completers (largest follow-up)		☐ # of completers (largest follow-up)		☐ # of completers (largest follow-up)	

2. Age at baseline

Mean age (Pregnant)	Mean age (Lactating mothers)	Mean age (Mothers)	Mean age (Infants)

Standard Deviation (Pregnant)	**Standard Deviation (Lactating mothers)**	**Standard Deviation (Mothers)**	**Standard Deviation (Infants)**
Age range (Pregnant)	**Age range (Lactating mothers)**	**Age range (Mothers)**	**Age range (infants)**

3. Race/Ethnicity (Mother)

- White/European (specify %)
- Black/African American/etc. (specify %)
- Asian (specify %)
- Hispanic (specify %)
- Inuit/Eskimo (specify %)
- NR (specify %)
- varied by study site and experimental group (specify %)
- Minority (specify %)
- Other
- non black
- Puerto Rican/Latino
- Native Hawaiian or other pacific ethnicity
- non-western

Other

4. Race/Ethnicity (Infant)

- White/European (specify %)
- Black/African American/etc. (specify %)
- Asian (specify %)
- Hispanic (specify %)
- Inuit/Eskimo (specify %)
- Not reported (specify %)
- varied by study site and experimental groups (specify %)
- Non-white
- Not relevant

Other

5. Is baseline biomarker information reported?

Yes No Clear Response

6. Is baseline Omega-3 intake reported?

Yes No Clear Response

7. Dates of study

When was the actual study conducted as opposed to when it was published

8. Medical history

9. Risk Type

10. Exposure Timing

e.g., second and third trimester, birth to age 1..

3. Modified Cochrane Risk of Bias Tool

1. Was the allocation sequence (randomization method) adequately generated

There is a LOW RISK OF BIAS if the investigators describe a random component in the sequence generation process such as: referring to a random number table, using a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots. There is a HIGH RISK OF BIAS if the investigators describe a non-random component in the sequence generation process, such as: sequence generated by odd or even date of birth, date (or day) of admission, hospital or clinic record number; or allocation by judgement of the clinician, preference of the participant, results of a laboratory test or a series of tests, or availability of the intervention. IF HIGH RISK OF BIAS, EXPLAIN IN NOTES.

- Low risk (yes)
- High risk (no)
- Unclear

Clear Response

High risk notes

2. Was ALLOCATION adequately concealed (prior to assignment)?

There is a LOW RISK OF BIAS if the participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomization); sequentially numbered drug containers of identical appearance; or sequentially numbered, opaque, sealed envelopes. There is a HIGH RISK OF BIAS if participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; or other explicitly unconcealed procedures. IF HIGH RISK OF BIAS, EXPLAIN IN NOTES.

- Low risk
- High risk
- Unclear

Clear Response

High risk notes

3. Were PARTICIPANTS adequately BLINDED?

There is a LOW RISK OF BIAS if blinding of participants was ensured and it was unlikely that the blinding could have been broken; or if there was no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.

- Low risk
- High risk
- Unclear

Clear Response

High risk notes

4. Were OUTCOME ASSESSORS adequately BLINDED?

There is LOW RISK OF BIAS if the blinding of the outcome assessment was ensured and it was unlikely that the blinding could have been broken; or if there was no or incomplete blinding, but the outcome is unlikely to be influenced by lack of blinding (ie, lab tests--lipids--inherently low risk of bias, but not blood pressure).

- Low risk
- High risk
- Unclear

Clear Response

High risk notes

5. If outcome assessor blinding risk of bias is different for different outcomes (eg, lipids vs. MI), choose HIGH risk of bias and describe in Notes

- Low risk
- High risk
- Unclear
- Not applicable

Clear Response

High risk notes

6. Incomplete outcome data (ATTRITION BIAS) due to amount, nature or handling of incomplete outcome data

There is a LOW RISK OF BIAS if there were no missing outcome data; reasons for missing outcome data were unlikely to be related to the true outcome; missing outcome data were balanced in numbers, with similar reasons for missing data across groups (****The percentage of withdrawals and drop-outs should not exceed 20% for short-term follow-up [<=1 year] and 30% for long-term follow-up [>1 year]****). IF HIGH RISK OF BIAS, EXPLAIN IN NOTES.

- Low risk
- High risk
- Unclear

Clear Response

High risk notes

7. If attrition risk of bias is different for different outcomes (eg, lipids vs. MI) or different time points (eg, 1 year vs. 5 years), choose HIGH risk of bias and describe in Notes

- Low risk
- High risk
- Unclear
- Not applicable

Clear Response

High risk notes

8. Is there evidence of SELECTIVE OUTCOME REPORTING bias (Yes/No)?

For LIPIDS, are only selected lipids/lipoproteins reported, were lipids measured at baseline and was a blood sample taken at follow-up but follow-up lipids were not reported, were subgroup lipid outcomes omitted? For BLOOD PRESSURE, was BP measured at baseline and was there a follow-up clinical encounter (where follow-up BP would have been measured), but BP is not reported, were subgroup BP outcomes omitted? For CLINICAL OUTCOMES, are all outcomes in the Methods section (all pre-specified outcomes) reported, were all components of composite outcomes reported? DESCRIBE ISSUES IN NOTES.

- Yes
- No
- Unclear

Clear Response

Notes

9. INTENTION-TO-TREAT analysis? (Yes/No)

YES if they state ITT and methods used were actually ITT, or **all** participants were analyzed in the group to which they were allocated by randomization (no cross-over). IF NO ITT, EXPLAIN IN NOTES.

- Yes
- No
- Unclear

Clear Response

Notes

10. Group SIMILARITY AT BASELINE (GENERAL**)**

There is LOW RISK OF BIAS if groups are similar at baseline for demographic and other factors ("Table 1"). Also LOW risk of bias if any baseline differences were adjusted for in all relevant analyses. IF HIGH RISK OF BIAS, EXPLAIN IN NOTES.

- Low risk
- High risk
- Unclear

Clear Response

Notes

11. Group SIMILARITY AT BASELINE (OMEGA-3**)**

There is LOW RISK OF BIAS if groups were similar (or statistical adjustments were made to account for differences) in omega-3 intake or status (biomarkers) at baseline. There is HIGH RISK OF BIAS if groups had different omega-3 intake/status at baseline that was not accounted for. There is UNCLEAR RISK OF BIAS if baseline omega-3 status was not reported.

- Low risk
- High risk
- Unclear

Clear Response

Notes

12. Was there incomplete COMPLIANCE with interventions across groups?

There is LOW RISK OF BIAS if compliance with the interventions was acceptable (>=80% across intervention duration), based on the reported actual compliance compared to protocol or increased biomarker levels were reported during or at the end of the intervention. There is HIGH RISK OF BIAS if compliance was low (<80%) or no change in biomarker levels were found during or at the end of the intervention. There is UNCLEAR RISK OF BIAS if these data were not reported.

- Low risk
- High risk
- Unclear

Clear Response

Notes

13. Additional Bias: Bias due to problems not covered elsewhere in the table.

- Yes
- No

Clear Response

5. Modified Newcastle-Ottawa Quality Assessment Scale

Selection

1) Representativeness of the exposed cohort

☐ a) truly representative of the average pregnant women and children in the community

☐ b) somewhat representative of the average pregnant women and children in the community

☐ c) selected group of users eg nurses, volunteers

☐ d) no description of the derivation of the cohort

2) Selection of the non exposed cohort

☐ a) drawn from the same community as the exposed cohort

☐ b) drawn from a different source

☐ c) no description of the derivation of the non exposed cohort

☐ d) N/A

3) Ascertainment of exposure

☐ a) secure record (eg surgical records)

☐ b) structured interview

☐ c) written self report

☐ d) no description

4) Demonstration that outcome of interest was not present at start of study (if relevant, which will almost never be the case) or author's statement that a valid outcome measure was chosen.

● a) yes

● b) no

Clear Response

Comparability

1) Comparability of cohorts on the basis of the design or analysis

If the authors describe factors for which they adjusted or noted that cohorts were matched on important factors and listed the factors, count that as a "yes."

☐ a) study controls for _____________ (select the most important factor)

☐ b) study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome

☐ a) independent blind assessment

☐ b) record linkage

☐ c) self report

☐ d) no description

2) Was follow-up long enough for outcomes to occur (e.g., 5 years or older for asthma; for other outcomes, if the authors say why they chose a particular followup time, definitely select "yes"; otherwise use your own judgment.

● a) yes (select an adequate follow up period for outcome of interest)

● b) no

Clear Response

3) Adequacy of follow up of cohorts

☐ a) complete follow up - all subjects accounted for

☐ b) subjects lost to follow up unlikely to introduce bias - small number lost - >80% retention for ≤ 1 year followup; >30% retention for 1-5 years followup; >40% retention for 6-10 years followup; >50% retention for 11-18 years followup; or description provided of those lost)

☐ c) follow up rate < 80% (select an adequate %) and no description of those lost

☐ d) no statement

6. McHarms Tool

1. Were the harms PRE-DEFINED using standardized or precise definitions?

Harms can be defined as the totality of adverse consequences of an intervention or therapy. Harms are the opposite of benefits, against which they are directly compared. The balance between the benefit(s) and harm(s) of an intervention (i.e. drug or surgery) is ideally used to determine its efficacy or effectiveness.

Pre-defined indicates that the harms that were expected are explicitly defined prior to the collection of these expected events. For example, if bleeding is listed as a harmful event, the criteria by which they determine the bleeding (i.e. body location, type, or amount of blood loss that counts as an event, etc) should be specified.

Standardized classification of harms can be derived from any of the following:

1) reference to standard terminology or classifications of harms from a recognized external organization(s)(such as government regulatory or health agencies. Examples of standardized terminology for harms includes, WHO-ART, MEDra, HTA report on the Measurement and Monitoring of Surgical Adverse Events)

2) previously explicitly defined classifications of harms in the literature, or

3) based on pre-specified clinical criteria, or

4) pre-specified laboratory test (may not need to have a specific cut-off level specified in all cases)

In some instances only some of the harms identified in a study will be precisely defined. In this case, there must be some judgement.

- Yes
- No
- Unclear

Clear Response

2. Was the mode of harms collection specified as ACTIVE?

Active ascertainment of harms indicates that participants are asked about the occurrence of specific harms in structured questionnaires or interviews or pre-defined laboratory or diagnostic tests and usually performed at pre-specified time intervals.

Passive ascertainment of harms indicates that study participants spontaneously report (on their own initiatives) or are allowed to report harmful events not probed with active ascertainment.

- Yes
- No
- Unclear

Clear Response

3. Was the potential occurrence of harmful events collected at pre-specified intervals; for example, the occurrence of post-operative complications were evaluated on a daily basis within 30 days of the surgery?

- Yes
- No

- Unclear

Clear Response

4. Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?

For example, the study reported 3 types of harmful events (nausea, vomiting, and bleeding); for each of these events the frequency was reported for each study group.

- Yes
- No
- Unclear

Clear Response

5. Was the TOTAL NUMBER of participants affected by harms specified for each study arm?

- Yes
- No
- Unclear

Clear Response

6. If the study reported that there were no serious AE's reported did they define serious AEs?

- Yes
- No
- Unclear
- N/A

Clear Response

Appendix F. Quality of Included Studies

Table F1. Quality assessment of randomized controlled trials

Author, year	Allocation Sequence Generated Adequately	Allocation Treatment Adequately Concealed	Participants Adequately Blinded	Outcome Assessors Blinded	Outcome Assessor Blinding is Different for Different Outcomes	Incomplete outcome data (Attrition bias) due to amount, nature or handling of incomplete outcome data	Attrition risk of bias is different for different outcomes or different time points	Selective Outcome Reporting	Intention-to-treat	Group Similarity at Baseline (general)	Group Similarity at Baseline (Omega-3)	Incomplete Compliance with Interventions Across Groups	Additional bias
Agostoni C, et al, 2009[139]	Low risk	Low risk	Low risk	Low risk	Not applicable	Low risk	Not applicable	No	No	Low risk	Unclear	Low risk	No
Almaas, et al., 2015[126]	Low risk	Low risk	Low risk	Low risk	Not applicable	Low risk	High risk	No	No	Low risk	Low risk	Unclear	No
Atwell K, et al, 2013[119]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Unclear	Low risk	No
Bergmann et al., 2012 [52]	Unclear	Unclear	Low risk	Low risk	Not applicable	Low risk	Not applicable	No	No	Low risk	Unclear	Low risk	No
Birch EE, et al, 2010[121]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Yes	Low risk	Unclear	Unclear	No
Birch EE, et al, 2005[111]	Low risk	Low risk	Low risk	Unclear	Unclear	Low risk	High risk	No	Unclear	Low risk	Unclear	Unclear	No
Birch EE, et al, 2007[146]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No	No	Unclear	Unclear	Low risk	No
Bouwstra H, et al, 2005[63]	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	No	No	Low risk	Unclear	Unclear	No
Bouwstra H, et al, 2003[62]	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	No	No	Low risk	Unclear	Unclear	No
Brew B, et al., 2015[165]	Unclear	Low risk	Low risk	Low risk	Low risk	High risk	Unclear	Unclear	Yes	Low risk	Unclear	Low risk	Yes

Author, year	Allocation Sequence Generated Adequately	Allocation Treatment Adequately Concealed	Participants Adequately Blinded	Outcome Assessors Blinded	Outcome Assessor Blinding is Different for Different Outcomes	Incomplete outcome data (Attrition bias) due to amount, nature or handling of incomplete outcome data	Attrition risk of bias is different for different outcomes or different time points	Selective Outcome Reporting	Intention-to-treat	Group Similarity at Baseline (general)	Group Similarity at Baseline (Omega-3)	Incomplete Compliance with Interventions Across Groups	Additional bias
Campoy C, et al, 2011[141]	Low risk	Unclear	Low risk	Low risk	Not applicable	High risk	Not applicable	No	No	Low risk	Low risk	Unclear	No
Carlson SE, et al, 2013[31]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Low risk	Low risk	No
Carlson SE, et al, 1996[160]	Low risk	Low risk	Low risk	Low risk	Not applicable	High risk	High risk	No	No	Low risk	Unclear	Unclear	No
Cheatham CL, et al, 2011[129]	Unclear	Unclear	Low risk	Low risk	Low risk	High risk	Not applicable	Yes	No	Low risk	Low risk	Low risk	No
Clandinin MT, et al, 2005[108]	Low risk	Low risk	Low risk	Low risk	Unclear	High risk	High risk	No	No	High risk	Unclear	Unclear	No
Collins CT, et al, 2015[120]	Low risk	Low risk	Unclear	Low risk	Not applicable	Low risk	Not applicable	No	Unclear	Low risk	Low risk	Unclear	No
Collins CT, et al, 2011[105]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Low risk	Low risk	No
Colombo J, et al, 2013[124]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Unclear	No	Unclear	Unclear	Unclear	Unclear	No
Courville AB, et al, 2011[38]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Low risk	Low risk	No
Currie LM, et al,	Unclear	Unclear	Low risk	Low risk	Not applicable	High risk	Not applicable	No	No	Low risk	Unclear	Low risk	No

Author, year	Allocation Sequence Generated Adequately	Allocation Treatment Adequately Concealed	Participants Adequately Blinded	Outcome Assessors Blinded	Outcome Assessor Blinding is Different for Different Outcomes	Incomplete outcome data (Attrition bias) due to amount, nature or handling of incomplete outcome data	Attrition risk of bias is different for different outcomes or different time points	Selective Outcome Reporting	Intention-to-treat	Group Similarity at Baseline (general)	Group Similarity at Baseline (Omega-3)	Incomplete Compliance with Interventions Across Groups	Additional bias
2015[115]													
de Jong C, et al, 2012[65]	Low risk	Low risk	Low risk	Low risk	Not applicable	Low risk	Not applicable	Yes	No	Low risk	Unclear	Unclear	Yes
de Jong C, et al, 2010[64]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No	No	Low risk	Unclear	Unclear	No
Doornbos B, et al, 2009[90]	Unclear	Unclear	Unclear	Unclear	Unclear	High risk	High risk	No	No	Low risk	High risk	Low risk	No
Drover JR, et al, 2012[123]	Low risk	Low risk	Low risk	Low risk	Not applicable	High risk	Not applicable	No	No	Unclear	Unclear	Unclear	No
Drover JR, et al, 2011[122]	Low risk	Low risk	Low risk	Low risk	Not applicable	Low risk	High risk	No	No	Low risk	Unclear	Unclear	No
Dunstan JA, et al, 2003[50]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No	No	Low risk	Unclear	Unclear	No
Dunstan JA, et al, 2008[44]	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	No	No	Low risk	Unclear	Unclear	Yes
D'Vaz N, et al, 2012[142]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	No	Yes	Unclear	Low risk	Low risk	No
Escamilla-Nunez MC, et al, 2014[59]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No	No	Low risk	Low risk	Unclear	No
Escolano-	Uncle	Uncle	Low	Low	Not	High risk	Not	No	No	Low risk	Low risk	Low risk	No

Author, year	Allocation Sequence Generated Adequately	Allocation Treatment Adequately Concealed	Participants Adequately Blinded	Outcome Assessors Blinded	Outcome Assessor Blinding is Different for Different Outcomes	Incomplete outcome data (Attrition bias) due to amount, nature or handling of incomplete outcome data	Attrition risk of bias is different for different outcomes or different time points	Selective Outcome Reporting	Intention-to-treat	Group Similarity at Baseline (general)	Group Similarity at Baseline (Omega-3)	Incomplete Compliance with Interventions Across Groups	Additional bias
Margarit MV, et al, 2011[130]	ar	ar	risk	risk	applicable		applicable						
Fang PC, et al, 2005[137]	Unclear	Unclear	Low risk	Low risk	Not applicable	Low risk	Not applicable	No	No	Low risk	Unclear	Unclear	No
Field CJ, et al, 2008[112]	Unclear	Unclear	Low risk	Low risk	Not applicable	Low risk	Not applicable	No	Yes	Low risk	Low risk	Low risk	No
Fleddermann M, et al, 2014[113]	Low risk	Low risk	Low risk	Low risk	Unclear	High risk	Low risk	No	Yes	Low risk	Unclear	Unclear	No
Furuhjelm C, et al, 2011[172]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Unclear	No	No	Low risk	Low risk	Low risk	No
Furuhjelm C, et al, 2009[173]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Unclear	No	Yes	Low risk	Low risk	Low risk	No
Gonzalez-Casanova I, et al, 2015[60]	Unclear	Unclear	Low risk	Low risk	Not applicable	Low risk	Not applicable	No	No	Low risk	Unclear	Low risk	No
Goor SA, et al, 2011[66]	Unclear	Unclear	Unclear	Unclear	Unclear	High risk	Unclear	No	No	Low risk	Unclear	Unclear	No
Groh-Wargo S, et al, 2005[106]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	High risk	Low risk	Low risk	No

Author, year	Allocation Sequence Generated Adequately	Allocation Treatment Adequately Concealed	Participants Adequately Blinded	Outcome Assessors Blinded	Outcome Assessor Blinding is Different for Different Outcomes	Incomplete outcome data (Attrition bias) due to amount, nature or handling of incomplete outcome data	Attrition risk of bias is different for different outcomes or different time points	Selective Outcome Reporting	Intention-to-treat	Group Similarity at Baseline (general)	Group Similarity at Baseline (Omega-3)	Incomplete Compliance with Interventions Across Groups	Additional bias
Gustafson KM, et al, 2013[74]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk	No	Yes	Low risk	Low risk	Low risk	No
Harper M, et al, 2010[29]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Low risk	Low risk	No
Hauner H, et al, 2012[37]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Low risk	Low risk	No
Helland IB, et al, 2008[76]	Unclear	Unclear	Low risk	Low risk	Unclear	High risk	Unclear	No	No	High risk	Unclear	Unclear	Yes
Henriksen C, et al, 2008[107]	Low risk	Low risk	Low risk	Low risk	Not applicable	High risk	High risk	No	No	Low risk	Unclear	Unclear	No
Hoffman D, et al, 2008[114]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Low risk	Low risk	No
Imhoff-Kunsch B, et al, 2011[58]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Unclear	Low risk	No
Innis SM, et al, 2008[145]	Low risk	Low risk	Low risk	Low risk	Not applicable	Unclear	Not applicable	No	Unclear	High risk	Low risk	Unclear	Yes
Isaacs EB, et al, 2011[99]	Low risk	Low risk	Low risk	Low risk	Not applicable	High risk	Not applicable	No	No	Unclear	Unclear	Unclear	Yes
Jensen CL, et al, 2010[135]	Unclear	Unclear	Low risk	Low risk	Not applicable	Low risk	Not applicable	No	No	Low risk	Unclear	Unclear	No

Author, year	Allocation Sequence Generated Adequately	Allocation Treatment Adequately Concealed	Participants Adequately Blinded	Outcome Assessors Blinded	Outcome Assessor Blinding is Different for Different Outcomes	Incomplete outcome data (Attrition bias) due to amount, nature or handling of incomplete outcome data	Attrition risk of bias is different for different outcomes or different time points	Selective Outcome Reporting	Intention-to-treat	Group Similarity at Baseline (general)	Group Similarity at Baseline (Omega-3)	Incomplete Compliance with Interventions Across Groups	Additional bias
Jensen CL, et al, 2005[136]	Low risk	Unclear	Low risk	Low risk	Not applicable	Low risk	High risk	No	No	Low risk	Unclear	Low risk	No
Judge MP, et al, 2014[91]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Not applicable	No	No	Low risk	Unclear	Unclear	No
Judge MP, et al, 2012[40]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Low risk	Low risk	No
Judge MP, et al, 2007[39]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Low risk	Low risk	No
Knudsen VK, et al, 2006[45]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Low risk	Low risk	No
Lagemaat M, et al, 2011[109]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Low risk	Unclear	No
Lauritzen L, et al, 2005[102]	Unclear	Unclear	Low risk	High risk	Low risk	High risk	Low risk	No	No	Low risk	Low risk	Low risk	No
Lauritzen L, et al, 2004[127]	Low risk	Low risk	Low risk	Low risk	Not applicable	Low risk	Not applicable	No	Yes	Low risk	Low risk	Low risk	No
Lauritzen L, et al, 2005[128]	Unclear	Unclear	Low risk	Low risk	Not applicable	Low risk	Not applicable	Yes	No	Low risk	Unclear	Low risk	No
Linnamaa P, et al, 2010[79]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	No	Yes	Low risk	Low risk	Low risk	No
Llorente	Low	Uncle	Low	Low	Not	High risk	High risk	No	No	Low risk	Low risk	Low risk	No

Author, year	Allocation Sequence Generated Adequately	Allocation Treatment Adequately Concealed	Participants Adequately Blinded	Outcome Assessors Blinded	Outcome Assessor Blinding is Different for Different Outcomes	Incomplete outcome data (Attrition bias) due to amount, nature or handling of incomplete outcome data	Attrition risk of bias is different for different outcomes or different time points	Selective Outcome Reporting	Intention-to-treat	Group Similarity at Baseline (general)	Group Similarity at Baseline (Omega-3)	Incomplete Compliance with Interventions Across Groups	Additional bias
AM, et al, 2003[98]	risk	ar	risk	risk	applicable								
Lucia Bergmann R, et al, 2007[41]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Yes	Yes	Low risk	Low risk	Unclear	No
Makrides M, et al, 2009[116]	Low risk	Unclear	Low risk	Low risk	Not applicable	Low risk	Not applicable	No	Yes	Low risk	Unclear	Low risk	No
Makrides M, et al, 2010[35]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Low risk	Low risk	No
Makrides M, et al, 2014[57]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Unclear	Low risk	No
Malcolm CA, et al, 2003[100]	Unclear	Unclear	Low risk	Low risk	Low risk	High risk	Low risk	No	Yes	Low risk	Low risk	Low risk	No
Manley BJ, et al, 2011[118]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Unclear	Low risk	No
Marks GB, et al, 2006[168]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No	No	Low risk	Unclear	Unclear	No
Meldrum SJ, et al, 2015[56]	Unclear	Unclear	Low risk	Low risk	Low risk	High risk	High risk	Unclear	Yes	Low risk	Unclear	Unclear	No
Meldrum SJ, et al, 2012[140]	Low risk	Low risk	Low risk	Low risk	Not applicable	High risk	Not applicable	No	No	High risk	Low risk	High risk	No
Mihrshahi	Low	Low	Low	Low	Low risk	Low risk	Low risk	No	No	Low risk	Unclear	Unclear	No

Author, year	Allocation Sequence Generated Adequately	Allocation Treatment Adequately Concealed	Participants Adequately Blinded	Outcome Assessors Blinded	Outcome Assessor Blinding is Different for Different Outcomes	Incomplete outcome data (Attrition bias) due to amount, nature or handling of incomplete outcome data	Attrition risk of bias is different for different outcomes or different time points	Selective Outcome Reporting	Intention-to-treat	Group Similarity at Baseline (general)	Group Similarity at Baseline (Omega-3)	Incomplete Compliance with Interventions Across Groups	Additional bias
S, et al, 2003[166]	risk	risk	risk	risk									
Miles EA, et al, 2011[78]	Low risk	High risk	High risk	Low risk	Unclear	Low risk	Unclear	No	No	Low risk	Low risk	Low risk	No
Min Y, et al, 2014[43]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Low risk	Low risk	No
Mozurkewich EL, et al, 2013[42]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Low risk	Low risk	No
Mulder KA, et al, 2014[75]	Low risk	Low risk	Low risk	Low risk	Not applicable	High risk	Low risk	No	No	High risk	Low risk	Unclear	No
Noakes PS, et al, 2012[88]	Low risk	Unclear	High risk	Low risk	Low risk	High risk	Not applicable	No	No	Low risk	Unclear	Unclear	No
Olsen SF, et al, 2008[187]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Low risk	Low risk	No
Palmer DJ, et al, 2012[54]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Unclear	Low risk	No
Palmer DJ, et al, 2013[56]	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	No	Yes	Low risk	Low risk	High risk	No
Peat JK, et al, 2004[167]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Unclear	Unclear	No
Pietrantoni E, et al, 2014[30]	Unclear	Unclear	Unclear	Unclear	Not applicable	Low risk	Not applicable	No	Yes	Low risk	Low risk	High risk	No

Author, year	Allocation Sequence Generated Adequately	Allocation Treatment Adequately Concealed	Participants Adequately Blinded	Outcome Assessors Blinded	Outcome Assessor Blinding is Different for Different Outcomes	Incomplete outcome data (Attrition bias) due to amount, nature or handling of incomplete outcome data	Attrition risk of bias is different for different outcomes or different time points	Selective Outcome Reporting	Intention-to-treat	Group Similarity at Baseline (general)	Group Similarity at Baseline (Omega-3)	Incomplete Compliance with Interventions Across Groups	Additional bias
Ramakrishnan U, et al, 2010[32]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Low risk	Low risk	No
Ramakrishnan U, et al, 2015[61]	Low risk	Low risk	Low risk	Low risk	High risk	Unclear	Not applicable	Yes	Yes	Low risk	Unclear	Low risk	No
Sala-Vila A, et al, 2004[110]	High risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Unclear	Low risk	No
Smithers LG, et al, 2010[117]	Low risk	Low risk	Low risk	Low risk	Not applicable	Low risk	Not applicable	No	Unclear	Low risk	Unclear	Unclear	No
Smithers LG, et al, 2011[53]	Low risk	Low risk	Low risk	Low risk	Not applicable	Low risk	Not applicable	No	Yes	Low risk	Unclear	Unclear	No
Smithers LG, et al, 2008[104]	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	No	Yes	Low risk	Unclear	Unclear	No
Stein AD, et al, 2011[34]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Unclear	Low risk	No
Stein AD, et al, 2012[33]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk	No	Yes	Low risk	Low risk	Low risk	No
Toelle BG, et al, 2010[169]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Not applicable	No	No	Low risk	Unclear	Unclear	No
Tofail F, et al, 2006[77]	Unclear	Unclear	Low risk	Low risk	Unclear	High risk	Not applicable	No	Unclear	High risk	Unclear	Low risk	No

Author, year	Allocation Sequence Generated Adequately	Allocation Treatment Adequately Concealed	Participants Adequately Blinded	Outcome Assessors Blinded	Outcome Assessor Blinding is Different for Different Outcomes	Incomplete outcome data (Attrition bias) due to amount, nature or handling of incomplete outcome data	Attrition risk of bias is different for different outcomes or different time points	Selective Outcome Reporting	Intention-to-treat	Group Similarity at Baseline (general)	Group Similarity at Baseline (Omega-3)	Incomplete Compliance with Interventions Across Groups	Additional bias
Unay B, et al, 2004[138]	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	No	No	Low risk	Unclear	Unclear	No
van Goor SA, et al, 2010[36]	Unclear	Unclear	Low risk	Unclear	Not applicable	High risk	Not applicable	Yes	No	Low risk	Unclear	Unclear	No
Werkman SH, et al, 1996[154]	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Not applicable	Yes	No	Low risk	Unclear	Unclear	No
Westerberg AneC, et al, 2011[125]	Low risk	Low risk	Low risk	Low risk	Not applicable	High risk	Not applicable	Yes	Unclear	Low risk	Low risk	Unclear	No
Willatts P, et al, 2013[170]	Low risk	Low risk	Low risk	Low risk	Not applicable	High risk	Not applicable	Unclear	No	Low risk	Unclear	Unclear	Yes
Zhou SJ, et al, 2012[55]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	No	Yes	Low risk	Unclear	Low risk	No

Table F2. Quality assessment of cohort studies

Author, year	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability of cohorts	Assessment of outcome	Follow-up long enough to occur	Adequacy of follow up of cohorts
Badart-Smook A, et al, 1997[47]	Truly representative	Not applicable	Structured interview	Yes	Controls for most important factor and other factors	Record linkage	Yes	Complete follow-up
Bakker EC, et al, 2003[163]	Truly representative	Drawn from same community	Secure record	Yes	Controls for most important factor and other factors	Independent blind assessment	Yes	Subjects lost to follow up unlikely to introduce bias
Bakker EC, et al, 2009[134]	Somewhat representative	Drawn from same community	Secure record	Yes	Controls for most important factor	Independent blind assessment	Yes	Follow up rate < 80% (select an adequate %) and no description of those lost
Bernard JY, et al, 2013[89]	Somewhat representative	Not applicable	Written self report	Yes	Controls for most important factor and other factors	Independent blind assessment	Yes	Follow up rate < 80% (select an adequate %) and no description of those lost
Bouwstra H, et al, 2006[133]	Somewhat representative	Drawn from same community	Secure record	Yes	Controls for most important factor	Independent blind assessment	Yes	Subjects lost to follow up unlikely to introduce bias
Brantsaeter AL, et al, 2012[81]	Somewhat representative	Not applicable	Structured interview	Yes	Controls for most important factor and other factors	Self report	Yes	No statement
Chong MF, et al, 2015[95]	Truly representative	Drawn from same community	Secure record	Yes	Controls for most important factor and other factors	Record linkage	Yes	Subjects lost to follow up unlikely to introduce bias

Author, year	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability of cohorts	Assessment of outcome	Follow-up long enough to occur	Adequacy of follow up of cohorts
Clausen T, et al, 2001[68]	Truly representative	Drawn from same community	Structured interview	Yes	Controls for most important factor and other factors	Independent blind assessment	Yes	Complete follow-up
Dirix CE, et al, 2009[84]	Truly representative	Not applicable	Secure record	Yes	Controls for most important factor and other factors	Record linkage	Yes	Subjects lost to follow up unlikely to introduce bias
Drouillet P, et al, 2009[80]	Truly representative	Not applicable	Structured interview	Yes	Controls for most important factor and other factors	Record linkage	Yes	Subjects lost to follow up unlikely to introduce bias
Guxens M, et al, 2011[144]	Truly representative	Drawn from same community	Secure record	Yes	Controls for most important factor and other factors	Independent blind assessment	Yes	Subjects lost to follow up unlikely to introduce bias
Jordi Julvez, et al, 2014[143]	Truly representative	Not applicable	Secure record	Yes	Controls for most important factor and other factors	Independent blind assessment	Yes	Follow up rate < 80% (select an adequate %) and no description of those lost
Keim SA, et al, 2012[162]	Somewhat representative	Not applicable	Secure record	Yes	Controls for most important factor and other factors	Independent blind assessment	Yes	Follow up rate < 80% (select an adequate %) and no description of those lost
Klebanoff MA, et al, 2011[49]	Truly representative	Drawn from same community	Secure record, Structured interview	Yes	Controls for most important factor and other factors	Record linkage	Yes	Complete follow-up
Leung BM, et	Truly representative	Drawn from	Structured	Yes	Controls for	Self report	No	Subjects lost

Author, year	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability of cohorts	Assessment of outcome	Follow-up long enough to occur	Adequacy of follow up of cohorts
al, 2013[94]		same community	interview		most important factor and other factors			to follow up unlikely to introduce bias
Lim WY, et al, 2015[71]	Somewhat representative	Drawn from same community	Secure record	Yes	Controls for most important factor and other factors	Independent blind assessment	Yes	Follow up rate < 80% (select an adequate %) and no description of those lost
Lumia M, et al, 2011[188]	Truly representative	Drawn from same community	Structured interview	Yes	Controls for most important factor	Record linkage	Yes	Follow up rate < 80% (select an adequate %) and no description of those lost
yall K, et al, 2013[171]	Selected group	Not applicable	Written self report	Yes	Controls for most important factor and other factors	Self report	Yes	Follow up rate < 80% (select an adequate %) and no description of those lost
Miyake Y, et al, 2009[182]	Truly representative	Drawn from same community	Structured interview	Yes	Controls for most important factor and other factors	Self report	No	Subjects lost to follow up unlikely to introduce bias
Miyake Y, et al, 2013[183]	Somewhat representative	Drawn from same community	Structured interview	Yes	Controls for most important factor and other factors	Self report	No	Subjects lost to follow up unlikely to introduce bias
Mohanty AF, et al, 2015[85]	Truly representative	Drawn from same community	Secure record	Yes	Controls for most important factor and other	Record linkage	Yes	Subjects lost to follow up unlikely to

Author, year	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability of cohorts	Assessment of outcome	Follow-up long enough to occur	Adequacy of follow up of cohorts
					factors			introduce bias
Molto-Puigmarti C, et al, 2014[48]	Truly representative	Not applicable	Structured interview	Yes	Controls for most important factor and other factors	Record linkage	Yes	Subjects lost to follow up unlikely to introduce bias
Morales E, et al, 2012[184]	Truly representative	Drawn from same community	Secure record	Yes	Controls for most important factor and other factors	Self report	No	Subjects lost to follow up unlikely to introduce bias
Much D, et al, 2013[101]	No description of the derivation of cohort	Not applicable	No description	Yes	Controls for most important factor	Independent blind assessment	Yes	Subjects lost to follow up unlikely to introduce bias
Much D, et al, 2013[83]	No description of the derivation of cohort	Not applicable	Secure record	Yes	Controls for most important factor and other factors	Independent blind assessment	Yes	Subjects lost to follow up unlikely to introduce bias
Muthayya S, et al, 2009[72]	Truly representative	Not applicable	Secure record	Yes	Controls for most important factor and other factors	Record linkage	Yes	Subjects lost to follow up unlikely to introduce bias
Newson RB, et al, 2004[176]	Truly representative	Drawn from same community	Secure record	Yes	Controls for most important factor	Independent blind assessment and self report	Yes	No statement
Notenboom ML, et al, 2011[179]	Somewhat representative	Not applicable	Secure record	Yes	Controls for most important factor and other factors	Record linkage and self report	Yes	Subjects lost to follow up unlikely to introduce bias
Nwaru BI, et al, 2012[180]	Truly representative	Drawn from same	Structured interview	Yes	Controls for most important	Self report	Yes	No statement

Author, year	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability of cohorts	Assessment of outcome	Follow-up long enough to occur	Adequacy of follow up of cohorts
		community			factor and other factors			
Oken E, et al, 2004[46]	Truly representative	Drawn from same community	Structured interview	Yes	Controls for most important factor and other factors	Record linkage	Yes	No statement
Oken E, et al, 2007[69]	Truly representative	Drawn from same community	Structured interview	Yes	Controls for most important factor and other factors	Record linkage	Yes	Subjects lost to follow up unlikely to introduce bias
Olafsdottir AS, et al, 2005[82]	Truly representative	Drawn from same community	Structured interview	Yes	Controls for most important factor and other factors	Record linkage and self report	Yes	Complete follow-up
Olafsdottir AS, et al, 2006[70]	Somewhat representative	Drawn from same community	Structured interview	Yes	Controls for most important factor and other factors	Record linkage	Yes	Subjects lost to follow up unlikely to introduce bias
Parker G, Hegarty B, et al, 2015[97]	Truly representative	Not applicable	Structured interview	Yes	Controls for most important factor and other factors	Record linkage	Yes	Subjects lost to follow up unlikely to introduce bias
Pike KC, et al, 2012[186]	Truly representative	Drawn from same community	Secure record	Yes	Controls for most important factor	Record linkage and self report	Yes	Subjects lost to follow up unlikely to introduce bias
Saito K, et al, 2010[181]	Somewhat representative	Drawn from same community	Structured interview	Yes	Controls for most important factor and other factors	Self report	Yes	Subjects lost to follow up unlikely to introduce bias
Sallis H, et al, 2014[96]	Truly representative	Drawn from same community	Secure record	Yes	Controls for most important factor and other	Record linkage	Yes	No statement

Author, year	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability of cohorts	Assessment of outcome	Follow-up long enough to occur	Adequacy of follow up of cohorts
					factors			
Scholtens S, et al, 2009[103]	Selected group	Not applicable	Secure record	Yes	Controls for most important factor and other factors	Record linkage	Yes	Follow up rate < 80% (select an adequate %) and no description of those lost
Smits LJ, et al, 2013[73]	Truly representative	Not applicable	Secure record	Yes	Controls for most important factor and other factors	No description	Yes	No statement
Standl M, et al, 2014[177]	Truly representative	Drawn from same community	Secure record	Yes	Controls for most important factor and other factors	Self report	Yes	Subjects lost to follow up unlikely to introduce bias
Steer CD, et al, 2013[164]	Truly representative	Drawn from same community	Secure record	Yes	Controls for most important factor	Record linkage	Yes	No statement
Strom M, et al, 2009[92]	Truly representative	Drawn from same community	Structured interview	Yes	Controls for most important factor and other factors	Record linkage	Yes	No statement
Sun Y, et al, 2010[131]	Truly representative	Not applicable	Written self report	Yes	Controls for most important factor and other factors	Record linkage	Yes	Complete follow-up
Thijs C, et al, 2011[178]	Somewhat representative	Drawn from same community	Secure record	Yes	Controls for most important factor and other factors	Record linkage and self report	Yes	Subjects lost to follow up unlikely to introduce bias
Valent F, et al, 2013[132]	Somewhat representative	Drawn from same community	Secure record	Yes	Controls for most important factor and other factors	No description	Yes	Subjects lost to follow up unlikely to introduce bias

Author, year	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability of cohorts	Assessment of outcome	Follow-up long enough to occur	Adequacy of follow up of cohorts
Wijga AH, et al, 2006[175]	Truly representative	Drawn from same community	Secure record	Yes	Controls for most important factor and other factors	Independent blind assessment and self report	Yes	Subjects lost to follow up unlikely to introduce bias
Yoshihiro Miyake, et al, 2006[93]	Truly representative	Drawn from same community	Structured interview	Yes	Controls for most important factor and other factors	Self report	Yes	Subjects lost to follow up unlikely to introduce bias
Yu YM, et al, 2015[185]	Somewhat representative	Drawn from same community	Secure record	Yes	Controls for most important factor and other factors	Record linkage and self report	Yes	Subjects lost to follow up unlikely to introduce bias

Table F3. Quality assessment of studies reporting harms

Author, year	Were the harms predefined using standardized or precise definitions?	Was the mode of harms collected specified as active?	Was the potential occurrence of harmful events collected at pre-specified intervals?	Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?	Was the TOTAL NUMBER of participants affected by harms specified for each study arm?	If the study reported that there were no serious AE's reported did they define serious AEs?
Agostoni C, et al, 2009[139]	No	No	Yes	Yes	Yes	No
Birch EE, et al, 2005[111]	No	Unclear	Unclear	Yes	Yes	Not applicable
Birch EE, et al, 2010[121]	No	Unclear	Yes	No	Yes	Yes
Carlson SE, et al, 2013[31]	Yes	Yes	Unclear	Yes	Yes	Not applicable
Clandinin MT, et al, 2005[108]	Unclear	No	Unclear	Yes	Yes	Not applicable
Dunstan JA, et al, 2003[50]	No	No	No	Yes	Yes	Not applicable
Escolano-Margarit MV, et al, 2011[130]	Unclear	Unclear	Unclear	No	Yes	Not applicable
Fang PC, et al, 2005[137]	No	No	Yes	No	No	No
Field CJ, et al, 2008[112]	No	No	No	No	No	Not applicable
Fleddermann M, et al, 2014[113]	Yes	Yes	Unclear	Yes	Yes	Not applicable
Furuhjelm C, et al, 2009[173]	No	No	No	Yes	Yes	No
Furuhjelm C, et al, 2011[172]	No	No	No	Yes	No	No
Harper M, et al, 2010[29]	Yes	Yes	Yes	Yes	No	Unclear
Henriksen C, et al, 2008[107]	No	Unclear	Yes	No	No	Not applicable
Hoffman D, et al, 2008[114]	Yes	Unclear	Yes	Yes	No	Not applicable
Imhoff-Kunsch B, et al, 2011[58]	Yes	Yes	Yes	Yes	Yes	Not applicable
Llorente AM, et al, 2003[98]	No	Unclear	Unclear	No	No	No
Makrides M, et al, 2009[116]	Yes	Yes	Unclear	Yes	Yes	Not applicable
Makrides M, et al, 2010[35]	Yes	Yes	Yes	Yes	Yes	Not applicable
Ramakrishnan U, et al, 2010[32]	Yes	Yes	Yes	Yes	Yes	No

Appendix G. Strength of Evidence

Table G1. Strength of evidence for KQ1: maternal outcomes (gestational length, preterm birth, SGA/IUGR, low birth weight, birth weight, antenatal and/or postnatal depression)

Table G2. Strength of evidence for KQ1: maternal outcomes (gestational hypertension/preeclampsia)

Table G3. Strength of evidence for KQ2: infant and child outcomes (growth patterns)

Table G4. Strength of evidence for KQ2: infant and child outcomes (neurological development)

Table G5. Strength of evidence for KQ2: infant and child outcomes (visual function)

Table G6. Strength of evidence for KQ2: infant and child outcomes (cognitive)

Table G7. Strength of evidence for KQ2: infant and child outcomes (autism spectrum disorders)

Table G8. Strength of evidence for KQ2: infant and child outcomes (attention deficit hyperactivity disorder)

Table G9. Strength of evidence for KQ2: infant and child outcomes (atopic dermatitis, allergies, and respiratory illness)

Table G10. Strength of evidence for KQ3: infant and child outcomes (adverse events/serious adverse events)

Table G1. Strength of evidence for KQ1: maternal outcomes (gestational length, preterm birth, SGA/IUGR, low birth weight, birth weight, antenatal and/or postnatal depression)

Outcome	Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Gestational length	n-3 FA supplementation	Healthy pregnant women	Moderate	RCT: 14 (original report); 14 Obs intake: 3 Obs biomarkers: 1	Low	RCT: Consistent Obs intake: Consistent Obs biomarkers: NA All: Consistent	Precise	Large heterogeneity in the meta-analysis	Original report: Mixed findings Meta-analysis of 12 RCTs in update: WMD 0.33 (95% CI 0.04, 0.62) weeks
Gestational length	DHA or DHA-rich fish oil	Healthy pregnant women	Moderate	RCT: 3 (original report); 11 Obs intake: 1 Obs biomarkers: 0	Low	RCT: Inconsistent Obs intake: NA Obs biomarkers: NA All: Inconsistent	Precise	Large heterogeneity in the meta-analysis	Original report: Mixed findings Meta-analysis of 11 RCTs in update: WMD 0.34 (95% CI 0.02, 0.67) weeks
Gestational length	Fish oil or EPA+DHA	Healthy pregnant women	Low	RCT: 11 (original report); 2 Obs intake: 2 Obs biomarkers: 1	Low	RCT: Consistent Obs intake: Consistent Obs biomarkers: NA All: Consistent	Imprecise	A few studies excluded preterm infants	Original report: No effects No effects
Gestational length	DHA+AA	Healthy pregnant women	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers: 0	High	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	Imprecise	Sparse	No effects

Outcome	Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Gestational length	EPA+DHA vs. ALA	Healthy pregnant women	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers: 0	Low	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	Precise	Sparse	No differences between 5 differences doses of fish oil (EPA+DHA 0.1, 0.3, 0.7, 1.4 and 2.8 g/d) and ALA control
Gestational length	n-6/n-3	No studies	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	NA	NA	No data	NA
Gestational length	Other – total n-3 FA	Healthy pregnant women	Insufficient	RCT: 0 Obs intake: 1 Obs biomarkers: 1 (original report); 0	Low	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	Precise	Sparse	No associations
Preterm birth	DHA or DHA-rich fish oil	Healthy pregnant women	Low	RCT: 2 (original report); 5 Obs intake: 0 Obs biomarkers: 0	Low	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: NA	Imprecise	No Obs	Meta-analysis of 7 RCTs: OR 0.87 (95% CI 0.66, 1.15)

Outcome	Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Preterm birth	Fish oil or EPA+DHA	At risk pregnant women	Low	RCT: 8 (original report); 1 Obs intake: 1 Obs biomarkers: 1	Moderate	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: Consistent	Imprecise	NA	Meta-analysis of 9 RCTs: 0.86 (95% CI 0.65, 1.15) Highest and lowest quartiles of maternal DHA+EPA intake: OR 1.1 (95% CI 0.7, 1.9) Erythrocyte DHA+EPA top 3 quartiles vs. lowest quartile: OR 1.41 (95% CI 0.97 – 2.05)
Preterm birth	DHA+AA	No studies	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	NA	NA	No data	NA
Preterm birth	n-6/n-3	No studies	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	NA	NA	No data	NA
SGA/ IUGR	DHA or DHA-rich fish oil	At risk pregnant women	Insufficient	RCT: 2 Obs intake: Obs biomarkers: 0	Low	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: NA	Imprecise	Sparse	No effects

Outcome	Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
SGA/ IUGR	Fish oil or EPA+DHA	At risk pregnant women	Low	RCT: 3 (original report); 1 Obs intake: 1 Obs biomarkers: 0	Low	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: Consistent	Imprecise	NA	Meta-analysis of 4 RCTs: OR 1.00 (95% CI 0.70, 1.43) No association between quartiles of DHA+EPA intake and risk of having an SGA birth outcome
SGA/ IUGR	DHA+AA	No studies	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	NA	NA	No data	NA
SGA/ IUGR	n-6/n-3	No studies	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	NA	NA	No data	NA
SGA/ IUGR	Other – EPA or DHA	Healthy pregnant women	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 1	Low	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	Precise	Sparse	Lowest quintile of plasma EPA concentration (<0.33 mg/L) vs. middle quintile (0.46 -0.58 mg/L): AOR 2.09 (95% CI 1.32, 3.30) No associations for concentrations of plasma DHA

Outcome	Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Low birth weight	DHA or DHA-rich fish oil	Healthy pregnant women	Low	RCT: 4 Obs intake: 0 Obs biomarkers: 0	Low	RCT: Inconsistent Obs intake: NA Obs biomarkers: NA All: NA	Imprecise	Moderate heterogeneity in the meta-analysis;	Meta-analysis of 4 RCTs: OR 0.72 (95% CI 0.43, 1.11)
Low birth weight	Fish oil or EPA+DHA	At risk pregnant women	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers: 0	Low	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	Precise	Sparse	No effects
Low birth weight	DHA+AA	No studies	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	NA	NA	No data	NA
Low birth weight	n-6/n-3	No studies	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	NA	NA	No data	NA
Low birth weight	Other - EPA	Healthy pregnant women	Insufficient	RCT: 0 Obs intake: 1 Obs biomarkers: 0	Low	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	Precise	No RCT	1st tertile of EPA intake vs. the highest tertile: AOR 2.75 (95% CI 1.26, 6.02); and 2nd tertile of EPA vs. the highest tertile: AOR 2.54, (95% CI 1.17. 5.50)

Outcome	Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Birth weight	n-3 FA supplementation	Healthy pregnant women	Moderate	RCT: 14 (original report); 16 Obs intake: 6 Obs biomarkers: 4	Low	RCT: Consistent Obs intake: Consistent Obs biomarkers: NA All: Consistent	Precise	Moderate heterogeneity in the meta-analysis	Original report: Mixed findings Meta-analysis of 16 RCTs in update: WMD 74.8 (95% CI 12.4, 137.17) grams
Birth weight	DHA or DHA-rich fish oil	Healthy Pregnant women	Moderate	RCT: 2 (original report); 11 Obs intake: 0 Obs biomarkers: 3	Low	RCT: Consistent Obs intake: Obs biomarkers: Consistent All: Consistent	Precise	Large heterogeneity in the meta-analysis	Original report: mixed findings Meta-analysis of 12 RCTs: WMD 90.12 (95% CI 2.62, 177.62) grams Higher maternal blood DHA concentrations were associated with higher birth weight.
Birth weight	Fish oil or EPA+DHA	Healthy Pregnant women	Low	RCT: 9 (original report); 5 Obs intake: 2 Obs biomarkers: 0	Low	RCT: Consistent Obs intake: Inconsistent Obs biomarkers: NA All: Inconsistent	Precise	NA	Original report: mostly no effects Meta-analysis of 5 RCTs: WMD 37.89 (95% CI -19.53, 95.31) grams
Birth weight	DHA+AA	No studies	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	NA	NA	No data	NA

Outcome	Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Birth weight	n-6/n-3	No studies	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	NA	NA	No data	NA
Birth weight	Other - ALA	Healthy Pregnant women	Insufficient	RCT: 1 Obs intake: Obs biomarkers: 0	Low	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	Imprecise	Sparse	Black current seed oil (ALA 0.42 g/d; SDA 0.09 g/d) vs. placebo: No effects
Birth weight	Other - total n-3 FA	Healthy Pregnant women	Insufficient	RCT: 0 Obs intake: 2 Obs biomarkers: 0	Low	RCT: NA Obs intake: Consistent Obs biomarkers: NA All: NA	Precise	Sparse; No RCT	No associations
Antenatal and/or Postnatal Depression	DHA or DHA-rich fish oil (prenatal)	Pregnant woman	Low	RCT: 4 Obs intake: 0 Obs biomarkers: 3	Moderate	RCTs: Consistent Obs intake: NA Obs biomarkers: Consistent All: Consistent	Imprecise	Outcome definitions were heterogeneous	Mostly no significant effects/associations on both antenatal and postnatal depression outcomes
Antenatal and/or Postnatal Depression	Fish oil or EPA+DHA (prenatal)	Pregnant woman	Insufficient	RCT: 1 Obs intake: 1 Obs biomarkers: 0	Low	RCT: NA Obs intake: NA Obs biomarkers: NA All: Consistent	Imprecise	Outcome definitions were heterogeneous	No significant effects/associations on both antenatal and postnatal depression outcomes
Antenatal and/or Postnatal Depression	DHA+AA (prenatal)	Pregnant woman	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers: 0	High	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	Imprecise	Sparse	No differences in median EPDS scores at either week 36 of pregnancy or 6 months postpartum

Outcome	Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Antenatal and/or Postnatal Depression	n-6/n-3 (prenatal)	No studies	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	NA	NA	No data	NA
Antenatal and/or Postnatal Depression	Other – total n-3 FA (prenatal)	Pregnant woman	Insufficient	RCT: 0 Obs intake: 2 Obs biomarkers: 0	Low	RCT: NA Obs intake: Consistent Obs biomarkers: NA All: NA	Precise	No RCTs; Outcome definitions were heterogeneous	No associations and no significant dose-response relationship
Postnatal Depression	DHA or DHA-rich fish oil (postnatal)	Lactating women	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers: 0	Moderate	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	Imprecise	Sparse	No significant effects any of the time points (3 weeks, 2 months, 4 months, or 18 months postpartum)
Postnatal Depression	Fish oil or EPA+DHA (postnatal)	No studies	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	NA	NA	No data	NA
Postnatal Depression	DHA+AA (postnatal)	No studies	Insufficient	RCT: Obs intake: 0 Obs biomarkers: 0	NA	NA	NA	No data	NA
Postnatal Depression	n-6/n-3 (postnatal)	No studies	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	NA	NA	No data	NA

Outcome	Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Postnatal Depression	Other – total n-3 FA (postnatal)	No studies	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	NA	NA	No data	NA

Table G2. Strength of evidence for KQ1: maternal outcomes (gestational hypertension/preeclampsia)

Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
DHA	Pregnant women not at risk for poor pregnancy outcomes	Low	RCT: 3 Obs intake: 0 Obs biomarkers: 0	Cochrane 11,12,13/13	RCT: Inconsistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: NA	All interventions had very low levels EPA	RCT: OR 0.94[0.66, 1.34], I^2=0% (n=2,818) Obs intake: NA Obs biomarkers: NA
DHA+EPA	Healthy pregnant women	Insufficient	RCT: 0 Obs intake: 1 Obs biomarkers:	Newcastle-Ottawa Low RoB	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	Only 1 cohort study	RCT: NA Obs intake: nonsignificant decrease in risk Obs biomarkers: NA
Fishoil	Pregnant women at risk for poor pregnancy outcomes	Moderate	RCT: 3 Obs intake: 1 Obs biomarkers:	Cochrane: 13/13 Newcastle-Ottawa: Low RoB	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: NA	At-risk populations	RCT: OR 1.04 [0.76 , 1.42], I^{2}= 0% Obs intake: U-shaped association with risk Obs biomarkers: NA
DHA+AA	No studies	Insufficient	RCT: 0 Obs intake: NA Obs biomarkers: NA	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	NA	RCT: NA Obs intake: NA Obs biomarkers: NA
n-3 FA	Healthy pregnant women	Insufficient	RCT: 0 Obs intake:2 Obs biomarkers: 1	Newcastle-Ottawa: Low RoB	RCT: NA Obs intake: Consistent Obs biomarkers: NA (1 study) All: NA	RCT: NA Obs intake: NA Obs biomarker: precise	NA	RCT: NA Obs intake: No association Obs biomarkers: inverse association

Table G3. Strength of evidence for KQ2: infant and child outcomes (growth patterns)

Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
DHA+EPA	Prenatal maternal intervention	Moderate	RCT: 6 Obs intake: 0 Obs biomarkers: 0	Cochrane: 3-9/13	RCT: Mostly consistent Obs intake: NA Obs biomarkers: NA All: Mostly consistent	RCT: Precise Obs intake: NA Obs biomarker: NA	NA	RCT: No effect, pooled results for weight at 18 months 0.22 [-0.62, 0.19], length 0.01 [-0.52, 0.54], head circumf. -0.01 [-0.28,0.27]
DHA+AA	Prenatal + postnatal maternal intervention	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers: 0	Cochrane: 1/13 (very high ROB)	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	Sparse	RCT: No effect
DHA+EPA	Prenatal + postnatal maternal intervention	Low	RCT: 4 Obs intake: 0 Obs biomarkers: 0	Cochrane: 2-10/13	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: Consistent	RCT: NA Obs intake: NA Obs biomarker: NA	NA	RCT: No effect
n-3 FAs	Prenatal + postnatal maternal intervention	Insufficient	RCT: 0 Obs intake: 2 Obs biomarkers: 0	Observational only; fair quality	RCT: NA Obs intake: Inconsistent Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	No RCTs	Obs intake: 1 study found no effect, 1 found neg. assoc. with n-3s and length at 1y
DHA+EPA	Postnatal maternal intervention	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers: 0	Cochrane: 6/13	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	Sparse	RCT: Greater BMI and head circumf. At 2.5 years in fish oil group
n-3 FAs	Postnatal maternal intervention	Insufficient	RCT: 0 Obs intake: 1 Obs biomarkers: 0	Observational only; fair quality	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	No RCTs	Obs intake: No effect

Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
DHA+EPA	Prenatal maternal + preterm infant intervention	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers: 0	Cochrane 7-9/13	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	Sparse	RCT: Pos. assoc. with n-3s and length at 18 mo.
DHA+AA	Preterm infants	Low	RCT: 3 Obs intake: 0 Obs biomarkers: 0	Cochrane: 4-9/13	RCT: Inconsistent Obs intake: NA Obs biomarkers: NA All: Inconsistent	RCT: Imprecise Obs intake: NA Obs biomarker: NA	Sparse	RCT: No effect, pooled results for weight at 4 months -0.01 [-0.48, 0.47, length -0.03 [-0.91, 0.85]; 1 study found lower fat mass and greater lean mass at 12 mo
DHA+AA+EPA	Preterm infants	Insufficient	RCT: 2 Obs intake: 0 Obs biomarkers: 0	Cochrane: 4-9/13	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: Consistent	RCT: NA Obs intake: NA Obs biomarker: NA	Sparse	RCT: No effect on weight, length, head circumf; 1 study found lower fat mass and greater lean mass at 12 mo

Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
DHA+AA	Term infants	Low	RCT: 6 Obs intake: 0 Obs biomarkers: 0	Cochrane: 5-9/13	RCT: Mostly consistent Obs intake: NA Obs biomarkers: NA All: Mostly consistent	RCT: NA Obs intake: NA Obs biomarker: NA	NA	RCT: No differences in overall weight, length, or head circumf.One study had higher rates of length gain. One had overall higher weight and stature for age percentiles from 2-6 years, but no differences in BMI or BMI-for-age.
Infant n-3 FA biomarkers	Term and preterm infants	Low	RCT: 0 Obs intake: 0 Obs biomarkers: 3	Observational only; good quality	RCT: NA Obs intake: NA Obs biomarkers: Inconsistent All: Inconsistent	RCT: NA Obs intake: NA Obs biomarker: NA	NA	Obs biomarkers: Two studies found pos. assoc. with weight and length gain; one study found pos. assoc. with BMI at 7 yrs.

Table G4. Strength of evidence for KQ2: infant and child outcomes (neurological development)

Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
DHA	Preterm intervention	Low	RCT: 4 Obs intake: Obs biomarkers: 4	Cochrane 9-13/13 NOS: fair-very good	RCT: Slightly inconsistent Obs intake: NA Obs biomarkers: Inconsistent All: Consistently inconsistent	RCT: NA Obs intake: NA Obs biomarker: NA	Outcome measures vary. 1 RCT included trace EPA	RCT: No differences for most outcome measures Obs intake: NA Obs biomarkers: Possible associations with some outcomes
DHA+EPA	Preterm intervention	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake:NA Obs biomarker:NA	No data	RCT: NA Obs intake: Obs biomarkers:
Fish oil	Preterm intervention	Insufficient	RCT: 4 Obs intake:0 Obs biomarkers: 1	Cochrane 6-13/13 NOS: fair	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake:NA Obs biomarker:NA	Sparse	RCT: No differences Obs intake: NA Obs biomarkers: NA
DHA+AA	Preterm intervention	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: Obs biomarker:	No data	RCT: NA Obs intake: Obs biomarkers:
n-6/n-3	Preterm intervention	Insufficient	RCT: 0 Obs intake: 1 Obs biomarkers: 1	NOS fair-good	RCT: NA Obs intake: NA Obs biomarkers: NA All: Consistent	RCT: NA Obs intake: NA Obs biomarker: NA	No RCT	RCT: NA Obs intake: No association Obs biomarkers: No association
n-3 FA	Preterm intervention	Insufficient	RCT: 0 Obs intake:2 Obs biomarkers: 5	NOS fair-very good	RCT: NA Obs intake: Inconsistent Obs biomarkers: All:NA	RCT: NA Obs intake: Obs biomarker:	No RCT	RCT: NA Obs intake: 1 of 5 showed association for one outcome Obs biomarkers: NA
DHA	Pre and postnatal intervention	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers: 0	Cochrane: 4/11 12/13	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	Sparse (1 RCT reported in 2 publications)	RCT: Increase in mildly abnormal movements cf. placebo Obs intake: NA Obs biomarkers: NA All: NA

Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
DHA+EPA	Pre and postnatal intervention	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA
Fish oil	Pre and postnatal intervention		RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA
DHA+AA	Pre and postnatal intervention	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers: 0	Cochrane: 4/11 12/13	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	Sparse	RCT: Decrease in mildly abnormal movements cf. DHA alone and placebo Obs intake: NA Obs biomarkers: NA All: NA
n-6/n-3	Pre and postnatal intervention	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 1	Cochrane 4/11	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	No RCT	RCT: NA Obs intake:NA Obs biomarkers: No association
DHA	Breast Feeding Mothers	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers: 1	Cochrane: 7/11 8/12	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	No RCT	RCT: Inconsistent effects over time and among tests Obs intake: NA Obs biomarkers: No association
DHA+EPA	Breast Feeding Mothers	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
Fishoil	Breast Feeding Mothers	Insufficient	RCT: 0 Obs intake:0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA

Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
DHA+AA	Breast Feeding Mothers	Insufficient	RCT: 0 Obs intake:0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
n-6/n- 3	Breast Feeding Mothers	Insufficient	RCT: 0 Obs intake:0 Obs biomarkers: 0	NA	RCT: NA Obs: NA Obs biomarkers: In All:	RCT: NA Obs intake: NA Obs biomarker: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
DHA	Preterm infants	Insuffiient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake:NA Obs biomarkers: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
DHA+EPA	Preterm infants	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers: 0	7357	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	NA	Sparse DHA-enriched tuna oil	RCT: No differences Obs intake: NA Obs biomarkers: NA
Fish oil	Preterm infants	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers:	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
DHA+AA	Preterm infants	Insufficient	RCT: 2 Obs intake: 0 Obs biomarkers: 0	Cochrane: 12/13 6/13	RCT: Consistent Obs: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers:	Sparse	RCT: Significantly higher PDI scores at 12, 18 months Obs intake: NA Obs biomarkers: NA
n-6/n-3	Preterm infants	Insufficient	RCT: 0 Obs: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake:NA Obs biomarkers: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA

Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
DHA	Term Infants	Insufficient	RCT: 2 Obs intake: 0 Obs biomarkers:	Cochrane: 9/13 9/13	RCT: Inconsistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers: NA	Sparse	RCT: Positive effects on brainstem maturation but mixed effects on gross motor control Obs intake: NA Obs biomarkers: NA
DHA+EPA	Term Infants	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers:NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
Fish oil	Term Infants	Insufficient	RCT:1 Obs intake: 0 Obs biomarkers: 0	9/13	RCT: NA Obs intake: NA Obs biomarkers:NA All:NA	NA	No data	RCT: No effects on 3 indices Obs intake: NA Obs biomarkers: NA
DHA+AA	Term Infants	Insufficient	RCT: 2 Obs intake: 0 Obs biomarkers: 0	Cochrane: 9/13 6/13	RCT: NA Obs intake: In Obs biomarkers: NA All: NA	RCT: NA Obs intake: Obs biomarker: NA	1 RCT in 3 publications	RCT: small but significant effect at 3 months not seen at 18 months or 9 years in one RCT; and no effects on PDI in the other RCT Obs intake: NA Obs biomarkers: NA
n-6/n-3	Term Infants	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: Obs intake: NA Obs biomarker: NA		RCT: No effect Obs intake: NA Obs biomarkers: NA

Table G5. Strength of evidence for KQ2: infant and child outcomes (visual function)

Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
DHA	Preterm intervention	Low	RCT: 4 Obs intake: 0 Obs biomarkers: 2	Cochrane:10/13, 9/11, 7/11,13/13	RCT: Consistent Obs intake: Inconsistent Obs biomarkers: Inconsistent All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	2 RCTs included small amts. EPA; all used different outcome measures and FU times	RCT: no effect on visual acuity Obs intake: NA Obs biomarkers: Inconsistent associations
DHA+EPA		Insufficient	RCT: 0 Obs intake:0 Obs biomarkers :0	NA	RCT: NA Obs intake: Inconsistent Obs biomarkers: NA All: Inconsistent	RCT: NA Obs intake: NA Obs biomarker: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
Fish oil		Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
DHA+AA		Insufficient	RCT: 0 Obs intake:0 Obs biomarkers :0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
n-6/n-3		insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
DHA	Breast Feeding mothers	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers: 1	Cochrane 8/12	RCT: Inconsistent across time points Obs intake: Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	Sparse	RCT: Improvement in one VEP outcome 4 and 8 months but no difference at 5 years Obs intake: NA Obs biomarkers: No association

Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
DHA+EPA	Breast Feeding mothers	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake:NA Obs biomarker: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
Fish oil	Breast Feeding mothers	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers : 1	Cochrane 12/12	RCT: NA Obs intake: NA Obs biomarkers: NA All: divergence between RCT and biomarker results	RCT: NA Obs intake: NA;Obs. biomarker	Sparse data	RCT: no effect observed on visual acuity at 4 months Obs intake: NA Obs biomarkers: significant association of infant RBC DHA and visual acuity at 4 months
DHA+AA	Breast Feeding mothers	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers : 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
n-6/n-3	Breast Feeding mothers	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers:	NA	RCT: NA Obs: NA Obs biomarkers: NA All:	RCT: NA Obs intake: NA Obs biomarker: Precise	No data	RCT: NA Obs intake: NA Obs biomarkers: Unclear
Any n-3 FAs	Preterm infants VEP 4 months	Low	Pooled analysis of 4 RCTs (5 outcomes)	Study quality varied widely (Cochrane 6/11 and 4/11, jadad 3 and 5)	Inconsistent	Precise	Studies differed by intervention	WMD non-significant at 4 months followup WMD -0.06 (−0.12; 0.01)
Any n-3 FAs	Preterm infants VEP 6 months	Low	Pooled analysis of 4 RCTs (5 outcomes)	Study quality varied widely (Cochrane 6/11 and 4/11, jadad 3 and 5)	Inconsistent	Precise	Studies differed by intervention	WMD non-significant at 6 months followup WMD -0.04[-0.09, 0.01

Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
DHA	Preterm infants	Insufficient	RCT: 2 Obs intake: 0 Obs biomarkers: 0	Cochrane 10/13, 8/11	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers: NA	Sparse One study included small amount EPA	RCT: No differences at 2, 4 months CA in one study Obs intake: NA Obs biomarkers: NA
DHA+EPA	Preterm infants	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
Fishoil	Preterm infants	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
DHA+AA	Preterm infants	Low	RCT: 1 Obs intake: 0 Obs biomarkers: 0	Cochrane 7/11	RCT: NA Obs: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers: Unclear	Sparse	RCT: 1 new study and 5 from original report show no consistent effect Obs intake: NA Obs biomarkers: NA
n-6/n-3	Preterm infants	Insufficient	RCT: 0 Obs: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
Any n-3 FA	Term infants 2 month followup Behavioral	Low	RCT:6 Obs: 0 Obs biomarkers: 0	Jadad 3.8	Inconsistent	Precise	Small effect size	Significant effect on BM 2 months WMD 0.07 [0.00, 0.14] six RCTs
Any n-3 FA	Term infants 2 month followup VEP	Low	RCT:6 Obs: 0 Obs biomarkers: 0	Jadad 4.2 Cochrane 9/13	Inconsistent	Precise	Medium heterogeneity	Nonsignificant effect on VEP at 2 months WMD 0.07[-0.03, 0.17], six RCTs

Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Any n-3 FA	Term infants 4 month followup Behavioral	Low	RCT:6 Obs: 0 Obs biomarkers : 0	Jadad 3.8	Inconsistent	Precise	No new studies	Non-significant effect on BM at 4 months WMD -0.05 [-0.08, -0.01], six RCTs
Any n-3 FA	Term infants 4 month followup VEP	Moderate	RCT:8 Obs: 0 Obs biomarkers : 0	Jadad 3.8 Cochrane 7-9/13	Inconsistent	Precise		Significant effect of n-3 FAs on VEP at 4 months WMD -0.10 (-0.14, -0.07), eight RCTs
Any n-3 FA	Term infants 12 month followup Behavioral	Low	RCT:6 Obs: 0 Obs biomarkers : 0	Jadad 3.8	Inconsistent	Precise		Non-significant effect of n-3 FA on BM at 12 months WMD -0.10 (-0.14, -0.07) six RCTs
Any n-3 FA	Term infants 12 month followup VEP	Moderate	RCT:8 Obs: 0 Obs biomarkers : 0	Jadad 4.0 Cochrane 7-9/13	Consistent	Precise		Significant effect of n-3 FA on VEP at 12 months WMD -0.14 (-0.17, -0.12) 8 RCTs
DHA	Term infants	Low	RCT: 1 Obs intake: 0 Obs biomarkers : 1	Cochrane 12/13	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers: NA	Sparse	RCT: 1 new study and 2 RCTs from original report suggest possible lasting benefit but inconsistent Obs intake: NA Obs biomarkers: NA
DHA+EPA	Term infants	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers : 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA

Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Fishoil	Term infants	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers :0	NA	RCT: Obs intake: NA Obs biomarkers: NA All:NA	NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
DHA+AA	Term infants 2 months followup Behavioral	Low	RCT: 4 Obs intake: 0 Obs biomarkers : 0	Jadad 3.8	RCT: Inconsistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: NA	No new studies	No significant effect on BM at 2 months Obs intake: NA Obs biomarkers: NA WMD -0.07 (-0.19, 0.04) six RCTs
DHA+AA	Term infants 2 months followup VEP	Low	RCT: 6	Jadad 4.2 Cochrane 9/13	Inconsistent	Precise	One new study	No significant effect on VEP at 2 months WMD -0.06 (−0.22; 0.10)
DHA+AA	Term infants 4 months followup Behavioral	Low	RCT: 6	Jadad 3.8	Inconsistent	Precise	No new studies	No significant effect on BM at 4 months WMD 0.04 (0.02, 0.10)
DHA+AA	Term infants 4 months followup VEP	Low	RCT: 5	Jadad 4.3 Cochrane 7-9/13	Inconsistent	Precise	Two new studies	Significant effect on VEP at 4 months WMD -0.10 [-0.14, -0.07
DHA+AA	Term infants 12 months followup Behavioral	Moderate	RCT: 4	Jadad 3.75	Consistent	Precise	No new studies	No significant effect on BM at 12 months WMD 0.01 (-0.01, 0.02)

Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
DHA+AA	Term infants 12 months followup VEP	Low	RCT: 6	Jadad 4.0 7-9/13	Inconsistent	Precise	2 new studies	Significant effect on VEP at 12 months WMD -0.14 (-0.17, -0.12)
n-6/n-3	Term infants	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA

Table G6. Strength of evidence for KQ2: infant and child outcomes (cognitive)

Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Any n-3 FA	Preterm infants	Moderate	RCTs: 7	Medium risk of bias	High	Imprecise	Heterogeneous interventions	Significant increase in cognitive development (MDI scores) WMD 2.24; (95% CI 0.05, 4.43)
DHA	Preterm Infants	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	No studies	RCT: NA Obs intake: NA Obs biomarkers: NA
DHA+EPA	Preterm Infants	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers: 0	Low risk of bias	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarker: NA	Sparse	RCT: No effect Obs intake: NA Obs biomarkers: NA
DHA+AA	Preterm Infants	Low	RCT: at 2 Obs intake: 0 Obs biomarkers: 0	1 RCT: Unclear allocation concealment and sequence 1 RCT: Attrition bias	RCT: Inconsistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarker: NA	Sparse	RCT: Mixed Obs intake: NA Obs biomarkers: NA
DHA+EPA +AA	Preterm Infants	Insufficient	RCT: 2 Obs intake: 0 Obs biomarkers: 0	1 RCT: High Risk of Bias 1 RCT: Attrition bias	RCT: Inconsistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarker: NA	Sparse	RCT: Mixed Obs intake: NA Obs biomarkers: NA
DHA	Full Term Infants	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers: 0	Low risk of bias	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarker: NA	Sparse	RCT: No effect Obs intake: NA Obs biomarkers: NA

Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
DHA+EPA	Full Term Infants	Insufficient	RCT: 2 Obs intake: 0 Obs biomarkers: 0	1 RCT: Low risk of bias 1 RCT: High risk of bias	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: Imprecise Obs intake: Unclear Obs biomarker: NA	Sparse	RCT: No effect Obs intake: Lower risk Obs biomarkers: NA
DHA+AA	Full Term Infants	Low	RCT: 3 Obs intake: 0 Obs biomarkers: 0	Low risk of bias	RCT: Inconsistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarker: NA	Sparse, heterogeneous studies	No significant effect on MDI scores at 18-24 months of age WMD 0.75, 95% CI -9.29, 10.79 Obs intake: NA Obs biomarkers: NA
DHA	Pregnant women	Low for no effect	RCT: 1 Obs intake: 2 Obs biomarkers: 4	Low risk of bias	RCT: NA Obs intake: Consistent Obs biomarkers: Consistent All: Consistent	RCT: Precise Obs intake: Precise Obs biomarkers: Imprecise	RCT Outcome was Neonatal Behavior Assessment at age 14 days	RCT: Positive effect Obs intake: No effect Obs biomarkers: No effect
DHA+EPA	Pregnant women	Moderate for no effect	RCT: 5 Obs intake: 2 Obs biomarkers 2:	3 RCTs: Low ROB 2 RCTs: High ROB Observational: Low ROB	RCT: Consistent Obs intake: Consistent Obs biomarkers: Consistent All: Consistent	RCT: Precise Obs intake: Precise Obs biomarkers: Precise	Observational report results for DHA **and** EPA levels separately	RCT: No effect Obs intake: No effect of EPA: Obs biomarkers: No effect
DHA+AA	Pregnant women	Moderate for no effect	RCT: 1 Obs intake: 2 Obs biomarkers: 4	RCT: High ROB Observational: Low ROB	RCT: NA Obs: Consistent Obs biomarkers: Inconsistent All: Consistent with one exception	RCT: Precise Obs intake: Precise Obs biomarkers: Imprecise	Observational report results for DHA **and** AA levels separately	RCT: No effect Obs intake: No effect Obs biomarkers: effect in one study
n-6/n-3	Pregnant women	Insufficient	RCT: 0 Obs intake: 1 Obs biomarkers: 0	Low ROB	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: Imprecise Obs: biomarkers: NA	Effect only in offspring never breastfed	RCT: NA Obs intake: Positive effect Obs biomarkers: NA

Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Other: ALA	Pregnant women	Insufficient	RCT: 0 Obs intake: 2 Obs biomarkers: 1	Low ROB	RCT: NA Obs intake: Consistent Obs biomarkers: NA All: NA	RCT: NA Obs intake: Imprecise Obs biomarkers: Precise	No RCTs	RCT: NA Obs intake: No effect Obs biomarkers: No effect
DHA	Breast feeding women	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT:NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers: NA	No studies	RCT: NA Obs intake: NA Obs biomarkers: NA
DHA+EPA	Breast feeding women	Low for no effect	RCT: 4 Obs intake: 0 Obs biomarkers: 0	1 RCT: Low ROB 2 RCTs: Moderate ROB 1 RCT: High ROB	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: Precise Obs intake: Obs biomarkers:		RCT: No effect Obs intake: Obs biomarkers:
DHA+AA	Breast feeding women	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 1	Moderate ROB	RCT: NA Obs intake: NA Obs biomarkers: NA All: A	RCT: NA Obs intake: NA Obs biomarker: Precise	No RCTs Observational report results for DHA **and** AA levels separately	RCT: NA Obs intake: NA Obs biomarkers: No effect

Table G7. Strength of evidence for KQ2: infant and child outcomes (autism spectrum disorders)

Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
DHA	Preterm Infants (1 RCT) Pregnant women (1 RCT, 1 Obs)	Low for no effect	RCT: 2 Obs intake: 1 Obs biomarkers: 0	2 RCTs: Low ROB Obs: Low ROB	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: NA	Obs study authors advise that the results should be interpreted with caution, given the small number of cases	RCT: No association Obs intake: women with the highest quartile of total PUFA intake were at lower risk of having a child with ASD than women in the lowest quartile Obs biomarkers: NA

Table G8. Strength of evidence for KQ2: infant and child outcomes (attention deficit hyperactivity disorder)

Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
DHA	Preterm Infants (2 RCTs) Pregnant women (1 RCT)	Low for no effect	RCT: 3 Obs intake: 0 Obs biomarkers: 0	2 RCTs: Low ROB 1 RCT: High ROB	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: Precise Obs intake: NA Obs biomarker: NA	The RCT reporting ADHD diagnosis at 10 year follow-up had over 50% attrition	RCT: No association with attention outcomes or diagnosis of ADHD Obs intake: NA Obs biomarkers: NA

Table G9. Strength of evidence for KQ2: infant and child outcomes (atopic dermatitis, allergies, and respiratory illness)

Outcome	Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Atopic Dermatitis	DHA	Prenatal + Postnatal intervention- preterm and term infants	Low	RCT:1 Obs intake: 2 Obs biomarkers: 1	Cochrane: 10/11 NOS: fair	RCT: NA Obs intake: Consistent Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	RCT compared high DHA to standard DHA diet	RCT: No difference in risk Obs intake: No significant association Obs biomarkers: low risk
Atopic Dermatitis	DHA+EPA	Prenatal intervention- preterm and term infants	Low	RCT: 4(2 follow-up) Obs intake: 6 Obs biomarkers:NA	Cochrane: 9/12,5/12, 12/13, ,12/13 NOS: poor-fair	RCT: Inconsistent Obs intake: Consistent Obs biomarkers: All: NA	RCT: NA Obs intake: NA Obs biomarker: NA		RCT: one study reported a significant risk reduction, remaining found no significant difference Obs intake: No association Obs biomarkers: NA
Atopic Dermatitis	DHA+EPA	Postnatal intervention- preterm and term infants	Insufficient	RCT: 1 Obs intake: NA Obs biomarkers:NA	Cochrane: 9/13	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	Sparse	RCT: No significant difference Obs intake: NA Obs biomarkers: NA
Atopic Dermatitis	Fish oil	Prenatal +Postnatal intervention	Low	RCT: 3 (+2 follow-up) Obs intake: 0 Obs biomarkers: 0	Cochrane: 9/12,10/13, 10/13	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker:		RCT: No significant difference Obs intake: NA Obs biomarkers: NA

Outcome	Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Atopic Dermatitis	n-3 FA	Prenatal +Postnatal intervention	Low	RCT: 1 (+2 follow-up) Obs intake: 7 Obs biomarkers:3	RCT:10-11/13 NOS: poor-good	RCT: Consistent Obs intake: Inconsistent Obs biomarkers: Consistent All: NA	RCT: NA Obs intake:NA Obs biomarker: NA		RCT: No significant difference Obs intake: One of the studies found reduced risk, others found no significant association Obs biomarkers: No association
Atopic Dermatitis	n-6/n-3	Prenatal +Postnatal intervention-Term infants	Low	RCT: 0 Obs intake: 5 Obs biomarkers: 3	NOS: poor-good	RCT: NA Obs intake: Consistent Obs biomarkers: Inconsistent All: NA	RCT: NA Obs intake:NA Obs biomarker: NA		RCT: NA Obs intake: No association Obs biomarkers: One of the studies found reduced risk, others found no significant association
Atopic Dermatitis	ALA	Prenatal +Postnatal intervention-Term infants	Low	RCT: 1 Obs intake:1 Obs biomarkers:2	Cochrane: 11/12 NOS: fair-good	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker:NA	Sparse	RCT: Significant risk reduction at 12 month follow-up Obs intake: No significant association Obs biomarkers: No significant association

Outcome	Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Allergies	DHA	Prenatal + Postnatal intervention-preterm and term infants	Low	RCT: 1 Obs intake: 2 Obs biomarkers: 3	Cochrane: 10/11 NOS: fair-good	RCT: NA Obs intake: Consistent Obs biomarkers: Inconsistent All: NA	RCT: NA Obs intake: Obs biomarker: NA	Sparse	RCT: No significant difference Obs intake: No significant association Obs biomarkers: One of the studies reported low risk, others found no significant association
Allergies	DHA+EPA	Prenatal intervention	Low	RCT: 3 (+2 follow-up) Obs intake: 1 Obs biomarkers:0	Cochrane: 12/13, 9/12,11-12/13, NOS: fair	RCT: Inconsistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarker: NA		RCT: Non-significant effect on allergy risk at 12 months OR 0.54 (95% CI 0.05, 6.2) (3 RCTs) Obs intake: no significant association Obs biomarkers: NA
Allergies	DHA+EPA	Postnatal intervention	Insufficient	RCT: 1 Obs intake: NA Obs biomarkers:NA	Cochrane: 9/13	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	Sparse	RCT: No significant association Obs intake: NA Obs biomarkers: NA
Allergies	Fish oil	Prenatal + Postnatal intervention-preterm and term infants	Low	RCT: 3 (+2 follow-up) Obs intake: NA Obs biomarkers: NA	Cochrane: 9/13, 10/13, 9/12	RCT: Inconsistent Obs intake: NA Obs biomarkers: NA All: NA	RCT:NA Obs intake: NA Obs biomarker: NA		RCT: No significant association Obs intake: NA Obs biomarkers: NA

Outcome	Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Allergies	n-3 FA	Prenatal + Postnatal intervention-preterm and term infants	Low	RCT: 0 Obs intake:4 Obs biomarkers: 4	NOS: poor-good	RCT: NA Obs intake: Inconsistent Obs biomarkers: Consistent All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	No data	RCT: NA Obs intake: one study found reduced risk, others found no significant association Obs biomarkers: No association
Allergies	n-6/n-3	Prenatal + Postnatal intervention-preterm and term infants	Low	RCT: 0 Obs intake: 2 Obs biomarkers: 4	NOS: poor-good	RCT: NA Obs intake: Inconsistent Obs biomarkers: Consistent All: NA	RCT: NA Obs intake: NA Obs biomarker:NA		RCT: NA Obs intake: one study found a significant association, the other found no significant association Obs biomarkers: No significant association
Allergies	Other-ALA	Prenatal + Postnatal intervention-preterm and term infants	Low	RCT: 1 Obs intake:2 Obs biomarkers:2	Cochrane: 11/12 NOS: fair-good	RCT: NA Obs intake: Consistent Obs biomarkers: Consistent All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	A study reported positive association with sensitization in infants with no maternal history of allergy	RCT: No significant difference Obs intake: No significant association Obs biomarkers: No significant association

Outcome	Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Respiratory Illness: Wheeze	DHA	Prenatal + Postnatal intervention-preterm and term infants	Low	RCT: 3 Obs intake: 5 Obs biomarkers:4	Cochrane: 11/13, 10/13 NOS: poor-good	RCT: Inconsistent Obs intake: Inconsistent Obs biomarkers: Inconsistent All: Inconsistent	RCT:NA Obs intake: NA Obs biomarkers: NA		RCT: no significant effect on risk for wheeze at 12 months OR 0.95 (95% CI 0.77,1.16) (3 RCTs) Obs intake: one study found a significant risk reduction, others found no significant association Obs biomarkers: one study reported a significant risk reduction, others found no significant association.
Respiratory Illness: Wheeze	DHA+EPA	Prenatal intervention	Low	RCT: 2 Obs intake: 1 Obs biomarkers: NA	Cochrane: 5/12,9/12 NOS: poor	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers: NA		RCT: no significant difference Obs intake: Reduced risk Obs biomarkers: NA
Respiratory Illness: Wheeze	Fish oil	Prenatal + Postnatal intervention	Low	RCT: 3 (+3 follow-up) Obs intake: 0 Obs biomarkers:0	Cochrane: 10/13,9/13 9/12	RCT: Consistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers: NA		RCT: No significant difference Obs intake: NA Obs biomarkers: NA
Respiratory Illness: Wheeze	DHA+AA			RCT: 0 Obs intake: 0 Obs biomarkers: 0		RCT: NA Obs: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers:	No data	RCT: NA Obs intake: NA Obs biomarkers: NA

Outcome	Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Respiratory Illness: Wheeze	n-6/n-3	Prenatal + Postnatal intervention	Low	RCT:0 Obs intake: 2 Obs biomarkers:3	NOS: poor- fair	RCT: NA Obs intake: Consistent Obs biomarkers: Consistent All: NA	RCT: NA Obs intake: NA Obs biomarkers: NA		RCT: NA Obs intake: No significant association Obs biomarkers: No significant association
Respiratory Illness: Wheeze	Total n-3 FA	Prenatal + Postnatal intervention	Low	RCT: 2 Obs intake: 3 Obs biomarkers: 4	Cochrane: 10/13, 5/12 NOS: poor-good	RCT: Inconsistent Obs intake: Consistent Obs biomarkers: Inconsistent All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	One of the RCTs reports increased prevalence of wheeze at 8yr follow up.	RCT: One study reported significant risk reduction while the other found no significant difference Obs intake: No significant association Obs biomarkers: 2 studies found reduced risk, the other two found no significant association
Respiratory Illness: Asthma	DHA	Prenatal + Postnatal intervention	Low	RCT: 3 (+3 follow-up) Obs intake:2 Obs biomarkers: 1	Cochrane: 10/13,9/13,10/13 NOS: fair-good	RCT: Consistent Obs intake: Inconsistent Obs biomarkers: NA All: NA	RCT: Imprecise Obs intake: NA Obs biomarkers: NA		RCT: non-significant summary effect Obs intake: one study reported a significant association risk, other non-significant Obs biomarkers: No significant association

Outcome	Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
Respiratory Illness: Asthma	DHA+EPA	Prenatal intervention	Low	RCT: 4 Obs intake: NA Obs biomarkers:NA	Cochrane: 12/13,9/12,11/13,12/13	RCT: Inconsistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers:NA		RCT: non-significant difference Obs intake: NA Obs biomarkers: NA
Respiratory Illness: Asthma	Fish oil	Prenatal + Postnatal intervention	Low	RCT: 4 (+ 3 follow-up) Obs intake: 0 Obs biomarkers: 0	Cochrane: 10/13,9/13,12/13, 9/12	RCT: Inconsistent Obs intake: NA Obs biomarkers:NA All: NA	RCT: NA Obs intake: NA Obs biomarkers:NA		RCT: No significant difference Obs intake: NA Obs biomarkers: NA
Respiratory Illness: Asthma	DHA+AA			RCT: Obs intake: Obs biomarkers:		RCT: Obs intake: Obs biomarkers: All:	RCT: Obs intake: Obs biomarker:	No data	RCT: Obs intake: Obs biomarkers:
Respiratory Illness: Asthma	n-6/n-3	Prenatal + Postnatal intervention	Low	RCT: 0 Obs intake: 2 Obs biomarkers:2	NOS: fair-good	RCT: NA Obs intake: Inconsistent Obs biomarkers: Consistent All: NA	RCT: NA Obs intake: NA Obs biomarker: NA		RCT: NA Obs intake: One study reported significant risk reduction while the other found no significant association Obs biomarkers: No association

Table G10. Strength of evidence for KQ2: infant and child outcomes (adverse events)

Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
DHA	Pregnant women	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers: 0	Fair McH	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	NA	RCT: No effect Obs intake: NA Obs biomarkers: NA
DHA+EPA	Pregnant women	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers:0	Mcharm 4/6	RCT: NA Obs intake: NA Obs biomarkers: NA	RCT: NA Obs intake: NA Obs biomarker:NA	EPA/DHA>1	RCT: ↑risk GI AEs Obs intake: Obs biomarkers:
Fishoil	Pregnant women	Insufficient	RCT: 0 Obs intake: Obs biomarkers:	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
DHA+AA	Pregnant women	Low	RCT: 2 Obs intake:0 Obs biomarkers: 0	Good-fair McH	RCT: Inconsistent Obs intake: NA Obs biomarkers: NA	RCT: NA Obs intake: NA Obs biomarker: NA	Sparse	RCT: Unclear risk for GI AEs No SAEs Obs intake: Obs biomarkers:
n-6/n-3	Pregnant women	Insufficient	RCT:0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: Obs intake: Obs biomarkers	RCT: NA Obs intake: Obs biomarker:	Sparse	RCT: NA Obs intake: NA Obs biomarkers: NA
No studies	Breast Feeding women: maternal outcomes	Insufficient	RCT:0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers			
DHA	Breastfed term infants	Low	RCT: 2 Obs intake: 0 Obs biomarkers:	Good McH	RCT: Inconsistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: Obs biomarkers: NA	Sparse	RCT: No difference in AEs or lower AEs Obs intake: NA Obs biomarkers: NA

Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
DHA+EPA	Breastfed term infants	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers: 0	McHarm 4/6	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
Fishoil	Breastfed term infants	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 1	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers: Unclear	Sparse	RCT: NA Obs intake: NA Obs biomarkers: Lower risk
DHA+AA	Breastfed term infants	Insufficient	RCT: 1 Obs intake: 0 Obs biomarkers:	Mcharm 4/5	RCT: NA Obs: NA Obs biomarkers: NA	RCT: NA Obs intake: NA Obs biomarkers: NA	Sparse, no obs	RCT: No differences in AEs Obs intake: NA Obs biomarkers:
n-6/n-3	Breastfed term infants	Insufficient	RCT: 0 Obs: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
DHA	Preterm infants formula fed	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 1	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarkers: Imprecise	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
DHA+EPA	Preterm infants formula fed	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers: 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: Consistent	RCT: NA Obs intake: Imprecise Obs biomarkers: Imprecise	No data	RCT: NA Obs intake: No association Obs biomarkers:
Fishoil	Preterm infants formula fed	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All:NA	RCT: NA Obs intake: NA Obs biomarker: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
DHA+AA	Preterm infants formula fed	Insufficient	RCT: 4 Obs intake: 0 Obs biomarkers: 0	Mcharm 1,2,4/5; 3/6	RCT: Inconsistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	No obs; Risks associated with prematurity reported as AEs	RCT: No net effect on AEs Obs intake: Obs biomarkers: NA

Intervention /exposure	Population	SoE Grade	Design No. Studies	Study Limitations	Consistency	Precision	Other Issues	Finding
n-6/n-3	Preterm infants formula fed	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers :0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
DHA	Term infants formula fed	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers : 0	NA	RCT: Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
DHA+EPA	Term infants formula fed	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers : 0	NA	RCT: Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
Fishoil	Term infants formula fed	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers : 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA
DHA+AA	Term infants formula fed	Moderate	RCT: 5 Obs intake: 0 Obs biomarkers : 0	Mcharms 0, 2, 3, 4/5; 3/6	RCT: Inconsistent Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	No obs.	RCT: No difference or fewer AEs in n-3 groups; no SAEs Obs intake: NA Obs biomarkers: NA
n-6/n-3	Term infants formula fed	Insufficient	RCT: 0 Obs intake: 0 Obs biomarkers : 0	NA	RCT: NA Obs intake: NA Obs biomarkers: NA All: NA	RCT: NA Obs intake: NA Obs biomarker: NA	No data	RCT: NA Obs intake: NA Obs biomarkers: NA

Appendix H. List of Included Studies From the Original Report

1. Agostoni C, Marangoni F, Giovannini M, et al. Prolonged breast-feeding (six months or more) and milk fat content at six months are associated with higher developmental scores at one year of age within a breast-fed population. Adv Exp Med Biol. 2001;501:137-41. PMID: 11787675.

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CAUSALITY TABLE

Study	Study years (start date)	Country	Population	(total)	intake	(Baseline)	n-3 type(s)	study_design	Follow-up time	Outcome	Effect size type (OR or SMD)	Reported effect Size	Outcome classification
Miles, 2011	NR	UK	Healthy pregnant women	107			Salmon vs Control	Trial randomized parallel	birth	birth weight	SMD	0.042469915	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	27			DHA+ARA (EF) vs Control	Trial randomized parallel	12 months (corrected age)	head circumference	SMD	0	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	28			DHA+ARA (FF) vs Control	Trial randomized parallel	12 months (corrected age)	head circumference	SMD	-0.133630619	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	35			DHA+ARA (FF) vs Control	Trial randomized parallel	35 weeks (corrected age)	head circumference	SMD	-0.128260076	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	36			DHA+ARA (EF) vs Control	Trial randomized parallel	35 weeks (corrected age)	head circumference	SMD	-0.372677982	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	28			DHA+ARA (EF) vs Control	Trial randomized parallel	4 months (corrected age)	head circumference	SMD	0.075592898	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	30			DHA+ARA (FF) vs Control	Trial randomized parallel	4 months (corrected age)	head circumference	SMD	-0.393858671	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	36			DHA+ARA (FF) vs Control	Trial randomized parallel	40 weeks (corrected age)	head circumference	SMD	5.202124119	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	35			DHA+ARA (EF) vs Control	Trial randomized parallel	40 weeks (corrected age)	head circumference	SMD	7.646153927	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	27			DHA+ARA (EF) vs Control	Trial randomized parallel	12 months (corrected age)	length	SMD	0.763140142	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	28			DHA+ARA (EF) vs Control	Trial randomized parallel	12 months (corrected age)	length	SMD	0.386043996	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	36			DHA+ARA (EF) vs Control	Trial randomized parallel	35 weeks (corrected age)	length	SMD	0.094280906	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	35			DHA+ARA (FF) vs Control	Trial randomized parallel	35 weeks (corrected age)	length	SMD	0.079324059	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	28			DHA+ARA (EF) vs Control	Trial randomized parallel	4 months (corrected age)	length	SMD	0.381801784	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	30			DHA+ARA (FF) vs Control	Trial randomized parallel	4 months (corrected age)	length	SMD	-0.359404892	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	35			DHA+ARA (FF) vs Control	Trial randomized parallel	40 weeks (corrected age)	length	SMD	0.038912445	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	36			DHA+ARA (FF) vs Control	Trial randomized parallel	40 weeks (corrected age)	length	SMD	0.067343503	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	27			DHA+ARA (EF) vs Control	Trial randomized parallel	12 months (corrected age)	weight	SMD	0.157750756	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	28			DHA+ARA (FF) vs Control	Trial randomized parallel	12 months (corrected age)	weight	SMD	-0.325969994	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	36			DHA+ARA (EF) vs Control	Trial randomized parallel	35 weeks (corrected age)	weight	SMD	-0.124950208	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	35			DHA+ARA (FF) vs Control	Trial randomized parallel	35 weeks (corrected age)	weight	SMD	-0.111058012	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	28			DHA+ARA (EF) vs Control	Trial randomized parallel	4 months (corrected age)	weight	SMD	-0.112528399	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	30			DHA+ARA (FF) vs Control	Trial randomized parallel	4 months (corrected age)	weight	SMD	-0.083675906	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	36			DHA+ARA (FF) vs Control	Trial randomized parallel	40 weeks (corrected age)	weight	SMD	-0.220495641	Secondary
Groh-Wargo, 2005	sept 1997 - Sept 1998	US	Preterm infants	35			DHA+ARA (EF) vs Control	Trial randomized parallel	40 weeks (corrected age)	weight	SMD	-0.282478869	Secondary
Sala-Vila, 2004	nr	Spain	Healthy infants	23			(HM)	Trial randomized parallel	3 months	head circumference	SMD	0.027388405	Unspecified
Sala-Vila, 2004	nr	Spain	Healthy infants	23			Milk (HM)	Trial randomized parallel	3 months	head circumference	SMD	0.396647155	Unspecified
Sala-Vila, 2004	nr	Spain	Healthy infants	23			Milk (HM)	Trial randomized parallel	3 months	length	SMD	0.027344823	Unspecified
Sala-Vila, 2004	nr	Spain	Healthy infants	23			(HM)	Trial randomized parallel	3 months	length	SMD	0.029529136	Unspecified
Sala-Vila, 2004	nr	Spain	Healthy infants	23			(HM)	Trial randomized parallel	3 months	weight	SMD	0.076811403	Unspecified
Sala-Vila, 2004	nr	Spain	Healthy infants	23			Milk (HM)	Trial randomized parallel	3 months	weight	SMD	0.011815406	Unspecified
Hoffman, 2008	nr	US	Healthy infants	179			DHA + ARA vs Control	Trial randomized parallel	14-120d	head circumference	SMD	0	Secondary
Hoffman, 2008	nr	US	Healthy infants	179			DHA + ARA vs Control	Trial randomized parallel	14-120d	length	SMD	0	Secondary
Hoffman, 2008	nr	US	Healthy infants	179			DHA + ARA vs Control	Trial randomized parallel	14-120d	weight	SMD	-0.07062757	Secondary
Doornbos, 2009	Not reported	Netherlands	Healthy pregnant women			4.44 (3.00–6.92);	group	Trial randomized parallel	36 weeks pregnant	Depression Scale (EPDS)		NC	Secondary
Doornbos, 2009	Not reported	Netherlands	Healthy pregnant women			4.44 (3.00–6.92);	DHA group vs Control group	Trial randomized parallel	36 weeks pregnant	Depression Scale (EPDS)		NC	Secondary
Doornbos, 2009	Not reported	Netherlands	Healthy pregnant women			4.44 (3.00–6.92);	group	Trial randomized parallel	6 weeks post-partum	Depression Scale (EPDS)		NC	Secondary
Doornbos, 2009	Not reported	Netherlands	Healthy pregnant women			4.44 (3.00–6.92);	DHA group vs Control group	Trial randomized parallel	6 weeks post-partum	Depression Scale (EPDS)		NC	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	78			DHA group vs placebo	Trial randomized parallel	12 weeks	definitely abnormal	OR	0.387387395	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	77			DHA + AA group vs placebo	Trial randomized parallel	12 weeks	definitely abnormal	OR	NC	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	77			DHA + AA group vs placebo	Trial randomized parallel	2 weeks	definitely abnormal	OR	3.405405521	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	78			DHA group vs placebo	Trial randomized parallel	2 weeks	definitely abnormal	OR	3.486486435	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	78			DHA group vs placebo	Trial randomized parallel	12 weeks	mildly abnormal	OR	0.513333321	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	77			DHA + AA group vs placebo	Trial randomized parallel	12 weeks	mildly abnormal	OR	0.894841254	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	77			DHA + AA group vs placebo	Trial randomized parallel	2 weeks	mildly abnormal	OR	0.83518517	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	78			DHA group vs placebo	Trial randomized parallel	2 weeks	mildly abnormal	OR	0.641666651	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	77			DHA + AA group vs placebo	Trial randomized parallel	12 weeks	normal optimal	OR	0.439024389	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	78			DHA group vs placebo	Trial randomized parallel	12 weeks	normal optimal	OR	0.172093019	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	78			DHA group vs placebo	Trial randomized parallel	2 weeks	normal optimal	OR	0.286821693	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	77			DHA + AA group vs placebo	Trial randomized parallel	2 weeks	normal optimal	OR	0.878048778	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	78			DHA group vs placebo	Trial randomized parallel	12 weeks	normal suboptimal	OR	0.596273303	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	77			DHA + AA group vs placebo	Trial randomized parallel	12 weeks	normal suboptimal	OR	0.992576897	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	78			DHA group vs placebo	Trial randomized parallel	2 weeks	normal suboptimal	OR	0.766917288	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	77			DHA + AA group vs placebo	Trial randomized parallel	2 weeks	normal suboptimal	OR	1.016688108	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	78			DHA group vs placebo	Trial randomized parallel	2 weeks	classification: number	OR	NC	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	77			DHA + AA group vs placebo	Trial randomized parallel	2 weeks	classification: number	OR	NC	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	78			DHA group vs placebo	Trial randomized parallel	2 weeks	classification: number mildly	OR	1.361111164	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	77			DHA + AA group vs placebo	Trial randomized parallel	2 weeks	classification: number mildly	OR	0.996527791	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	77			DHA + AA group vs placebo	Trial randomized parallel	2 weeks	classification: number normal	OR	1.034843206	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	78			DHA group vs placebo	Trial randomized parallel	2 weeks	classification: number normal	OR	1.071428537	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	78			DHA group vs placebo	Trial randomized parallel	birth	gestational age birth	SMD	0	Secondary
van Goor, 2010	until December 2006	Netherlands	Breast-feeding women	77			DHA + AA group vs placebo	Trial randomized parallel	birth	gestational age birth	SMD	0	Secondary
Tofail, 2006	enrollment January to March 2000	Bangladesh	pregnant women	249			DHA supplement vs placebo	Trial randomized parallel	birth	birth weight	SMD	0	Unspecified
Tofail, 2006	enrollment January to March 2000	Bangladesh	pregnant women	249			DHA supplement vs placebo	Trial randomized parallel	10 months	Development (Mental	SMD	0.12656565	Unspecified
Tofail, 2006	enrollment January to March 2000	Bangladesh	pregnant women					Trial randomized parallel		Development (Psychomotor			Unspecified
Tofail, 2006	enrollment January to March 2000	Bangladesh	pregnant women	249			DHA supplement vs placebo	Trial randomized parallel	10 months	Development (Psychomotor	SMD	0.114185289	Unspecified
Tofail, 2006	enrollment January to March 2000	Bangladesh	pregnant women	249			DHA supplement vs placebo	Trial randomized parallel	10 months	head circumference	SMD	-0.142857149	Unspecified
Peat, 2004	2000-2003	Australia	unborn children were at	526			Placebo group	design	3 years	any eczema	OR	1.226132035	Secondary
Peat, 2004	2000-2003	Australia	unborn children were at	526			Placebo group	design	3 years	any asthma	OR	1.040522456	Primary
Peat, 2004	2000-2003	Australia	unborn children were at	526			Placebo group	design	3 years	any cough	OR	1.226132035	Primary

Study	Study years (start date)	Country	Population	(total)	intake	(Baseline)	n-3 type(s)	study_design	Follow-up time	Outcome	Effect size type (OR or SMD)	Reported effect Size	Outcome classification
Peat, 2004	2000-2003	Australia	unborn children were at	526			Placebo group	design	3 years	any wheeze	OR	1.040522456	Secondary
Birch, 2007	1993-1999	US	women whose unborn	35			DHA vs Control	Trial randomized parallel	4 years	Primary Scale of Intelligence:	SMD	0.36454019	Secondary
Birch, 2007	1993-1999	US	women whose unborn	51			DHA+ARA vs Control	Trial randomized parallel	4 years	Primary Scale of Intelligence:	SMD	0.418064356	Secondary
Birch, 2007	1993-1999	US	women whose unborn	35			DHA vs Control	Trial randomized parallel	4 years	Primary Scale of Intelligence:	SMD	0.290230393	Secondary
Birch, 2007	1993-1999	US	women whose unborn	51			DHA+ARA vs Control	Trial randomized parallel	4 years	Primary Scale of Intelligence:	SMD	0.267109424	Secondary
Birch, 2007	1993-1999	US	women whose unborn	51			DHA+ARA vs Control	Trial randomized parallel	4 years	Primary Scale of Intelligence:	SMD	0.386548072	Secondary
Birch, 2007	1993-1999	US	women whose unborn	35			DHA vs Control	Trial randomized parallel	4 years	Primary Scale of Intelligence:	SMD	0.281229317	Secondary
Birch, 2007	1993-1999	US	women whose unborn	36			DHA+ARA vs Control	Trial randomized parallel	4 years	Visual acuity Left Eye	SMD	0.371920019	Primary
Birch, 2007	1993-1999	US	women whose unborn	35			DHA vs Control	Trial randomized parallel	4 years	Visual acuity Left Eye	SMD	0.508636236	Primary
Birch, 2007	1993-1999	US	women whose unborn	35			DHA vs Control	Trial randomized parallel	4 years	Visual acuity Right Eye	SMD	0.606300414	Primary
Birch, 2007	1993-1999	US	women whose unborn	36			DHA+ARA vs Control	Trial randomized parallel	4 years	Visual acuity Right Eye	SMD	0.495647401	Primary
Birch, 2005	Not reported	US	Healthy infants					Trial randomized parallel					Primary
Birch, 2005	Not reported	US	Healthy infants					Trial randomized parallel					Secondary
2011	October 2005	Norway	Preterm infants			intervention[64.2		Trial randomized parallel		Index			Secondary
2011	October 2005	Norway	Preterm infants	82		intervention[64.2	DHA + AA group vs Placebo	Trial randomized parallel	20 months	Index (MDI)	SMD	0.049930181	Secondary
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	12 months	average time/look	SMD	1.399999976	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	6.5 months	average time/look	SMD	2.166666746	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	9 months	average time/look	SMD	3.073954344	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	12 months	looks to familiar	SMD	3.625	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	6.5 months	looks to familiar	SMD	3.299999952	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	9 months	looks to familiar	SMD	3.555555582	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	12 months	looks to novel	SMD	3	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	6.5 months	looks to novel	SMD	3.799999952	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	9 months	looks to novel	SMD	3.637486458	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	12 months	novel time	SMD	3.279394627	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	6.5 months	novel time	SMD	0.443887442	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	9 months	novel time	SMD	0	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	12 months	time to familiar	SMD	-3.526503086	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	6.5 months	time to familiar	SMD	0	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	9 months	time to familiar	SMD	-0.105032891	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	12 months	time to novel	SMD	0.583333314	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	6.5 months	time to novel	SMD	-0.400000006	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	9 months	time to novel	SMD	0.230769232	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	12 months	time/familiar look	SMD	-1.199999928	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	6.5 months	time/familiar look	SMD	1.833333373	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	9 months	time/familiar look	SMD	2.350671053	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	12 months	time/novel look	SMD	2.285714388	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	6.5 months	time/novel look	SMD	1.760074019	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	9 months	time/novel look	SMD	2.392242908	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	12 months	total looks	SMD	3.925470352	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	6.5 months	total looks	SMD	4.235293865	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	9 months	total looks	SMD	4.466666698	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	12 months	total time	SMD	-1.642857194	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	6.5 months	total time	SMD	-0.342566878	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	9 months	total time	SMD	0.128901288	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	12 months	number of total looks	SMD	0.303032428	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	6.5 months	number of total looks	SMD	1.803665161	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	9 months	number of total looks	SMD	1.611111164	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	12 months	time/total looks	SMD	-0.833333373	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	6.5 months	time/total looks	SMD	-2.259340525	Unspecified
Werkman, 1996	1987-1990	US	Preterm infants	67			and pre-term infant formulas	Trial randomized parallel	9 months	time/total looks	SMD	-1.378915668	Unspecified
Carlson, 1996	NR (<1995)	US	Preterm infants	27			DHA supplement vs Placebo	Trial randomized parallel	12 months	time/look	SMD	2.011306286	Secondary
Carlson, 1996	NR (<1995)	US	Preterm infants	27			DHA supplement vs Placebo	Trial randomized parallel	12 months	looks to familiar	SMD	2.974162817	Secondary
Carlson, 1996	NR (<1995)	US	Preterm infants	27			DHA supplement vs Placebo	Trial randomized parallel	12 months	looks to novel	SMD	1.541632175	Secondary
Carlson, 1996	NR (<1995)	US	Preterm infants	27			DHA supplement vs Placebo	Trial randomized parallel	12 months	novel time	SMD	2.401223183	Secondary
Carlson, 1996	NR (<1995)	US	Preterm infants	27			DHA supplement vs Placebo	Trial randomized parallel	12 months	time to familiar	SMD	-2.538865328	Secondary
Carlson, 1996	NR (<1995)	US	Preterm infants	27			DHA supplement vs Placebo	Trial randomized parallel	12 months	time to novel	SMD	1.098263025	Secondary
Carlson, 1996	NR (<1995)	US	Preterm infants	27			DHA supplement vs Placebo	Trial randomized parallel	12 months	time/familiar look	SMD	0.953569651	Secondary
Carlson, 1996	NR (<1995)	US	Preterm infants	27			DHA supplement vs Placebo	Trial randomized parallel	12 months	time/novel look	SMD	2.811267614	Secondary
Carlson, 1996	NR (<1995)	US	Preterm infants	27			DHA supplement vs Placebo	Trial randomized parallel	12 months	total looks	SMD	2.370370388	Secondary
Carlson, 1996	NR (<1995)	US	Preterm infants	27			DHA supplement vs Placebo	Trial randomized parallel	12 months	total time	SMD	-0.4828749	Secondary
2015	2005-2012	Mexico	infants	802			DHA (algal) vs Placebo	Trial randomized parallel	5 years	bmi-for-age z score	SMD	0	Primary
2015	2005-2012	Mexico	infants	802			DHA (algal) vs Placebo	Trial randomized parallel	5 years	height	SMD	-0.022471754	Primary
2015	2005-2012	Mexico	infants	802			DHA (algal) vs Placebo	Trial randomized parallel	5 years	height-for-age z-score	SMD	0	Primary
2015	2005-2012	Mexico	infants	802			DHA (algal) vs Placebo	Trial randomized parallel	5 years	weight	SMD	-0.033333335	Primary
2015	2005-2012	Mexico	infants	802			DHA (algal) vs Placebo	Trial randomized parallel	5 years	weight-for-age z-score	SMD	-0.090909086	Primary
Currie, 2015	2003-2011	US	Healthy infants	69			DHA < ARA vs Placebo	Trial randomized parallel	2-6 years	BMI	SMD	0.1107613	Secondary
Currie, 2015	2003-2011	US	Healthy infants	69			DHA < ARA vs Placebo	Trial randomized parallel	2-6 years	BMI-for-age percentile	SMD	0.292358667	Secondary
Currie, 2015	2003-2011	US	Healthy infants	69			DHA < ARA vs Placebo	Trial randomized parallel	2-6 years	Length-for-age percentile	SMD	0.518910348	Secondary
Currie, 2015	2003-2011	US	Healthy infants	69			DHA < ARA vs Placebo	Trial randomized parallel	birth-18 months	Length-for-age percentile	SMD	0.511804104	Secondary
Currie, 2015	2003-2011	US	Healthy infants	69			DHA < ARA vs Placebo	Trial randomized parallel	2-6 years	Weight-for-age percentile	SMD	0.246899456	Secondary
Currie, 2015	2003-2011	US	Healthy infants	69			DHA < ARA vs Placebo	Trial randomized parallel	birth-18 months	Weight-for-age percentile	SMD	0.246220678	Secondary

Study	Study years (start date)	Country	Population	(total)	intake	(Baseline)	n-3 type(s)	study_design	Follow-up time	Outcome	Effect size type (OR or SMD)	Reported effect Size	Outcome classification
Collins, 2015	2001-2013	Australia	Preterm infants	604			High DHA vs standard DHA	Trial randomized parallel	7 years	ADHD t score (total score)	SMD	-0.064502522	Secondary
Collins, 2015	2001-2013	Australia	Preterm infants	583			High DHA vs standard DHA	Trial randomized parallel	7 years	reported)	OR	0.743847847	Secondary
Collins, 2015	2001-2013	Australia	Preterm infants	583			High DHA vs standard DHA	Trial randomized parallel	7 years	disorder	OR	0.860738277	
Collins, 2015	2001-2013	Australia	Preterm infants	604			High DHA vs standard DHA	Trial randomized parallel	7 years	of Intelligence: Full Scale IQ	SMD	-0.013818421	Secondary
Collins, 2015	2001-2013	Australia	Preterm infants	604			High DHA vs standard DHA	Trial randomized parallel	7 years	of Intelligence: Performance	SMD	0	Secondary
Collins, 2015	2001-2013	Australia	Preterm infants	604			High DHA vs standard DHA	Trial randomized parallel	7 years	of Intelligence: Verbal IQ	SMD	-0.053154435	Secondary
Collins, 2015	2001-2013	Australia	Preterm infants	604			High DHA vs standard DHA	Trial randomized parallel	7 years	Test: Delayed recall raw score	SMD	0.030764695	Secondary
Collins, 2015	2001-2013	Australia	Preterm infants	604			High DHA vs standard DHA	Trial randomized parallel	7 years	Test: Delayed recognition	SMD	0.071062736	Secondary
Collins, 2015	2001-2013	Australia	Preterm infants	604			High DHA vs standard DHA	Trial randomized parallel	7 years	Test: Total (trials 1-5) correct	SMD	-0.034950692	Secondary
Collins, 2015	2001-2013	Australia	Preterm infants	604			High DHA vs standard DHA	Trial randomized parallel	7 years	Test: Total intrusions	SMD	-0.106173202	Secondary
Collins, 2015	2001-2013	Australia	Preterm infants	604			High DHA vs standard DHA	Trial randomized parallel	7 years	Test: Total repetitions	SMD	0.069810607	Secondary
Collins, 2015	2001-2013	Australia	Preterm infants	604			High DHA vs standard DHA	Trial randomized parallel	7 years	Test: Trial 1 correct words	SMD	0.050000001	Secondary
Collins, 2015	2001-2013	Australia	Preterm infants	604			High DHA vs standard DHA	Trial randomized parallel	7 years	skills: figure ground standard	SMD	-0.049178504	Secondary
Collins, 2015	2001-2013	Australia	Preterm infants	604			High DHA vs standard DHA	Trial randomized parallel	7 years	skills: visual closure standard	SMD	-0.109523952	Secondary
Collins, 2015	2001-2013	Australia	Preterm infants	604			High DHA vs standard DHA	Trial randomized parallel	7 years	skills: visual discrimination	SMD	0	Secondary
Brew, 2015	September 1997 to 1999-2008	Australia	Healthy infants		fish oil, daily,	(DHA+EPA+DPA+A	omega-placebo	Trial randomized parallel	8-9 years	Program Literacy and	MD	-25.39999962	Secondary
Brew, 2015	September 1997 to 1999-2008	Australia	Healthy infants		fish oil, daily,	(DHA+EPA+DPA+A	omega-placebo	Trial randomized parallel	10-11 years	Program Literacy and	MD	-13.69999981	Secondary
Brew, 2015	September 1997 to 1999-2008	Australia	Healthy infants		fish oil, daily,	(DHA+EPA+DPA+A	omega-placebo	Trial randomized parallel	12-13 years	Program Literacy and	MD	-11.69999981	Secondary
Brew, 2015	September 1997 to 1999-2008	Australia	Healthy infants		fish oil, daily,	(DHA+EPA+DPA+A	omega-placebo	Trial randomized parallel	14-15 years	Program Literacy and	MD	-24.10000038	Secondary
Brew, 2015	September 1997 to 1999-2008	Australia	Healthy infants		fish oil, daily,	(DHA+EPA+DPA+A	omega-placebo	Trial randomized parallel	14-15 years	Program Literacy and	MD	-19.89999962	Secondary
Brew, 2015	September 1997 to 1999-2008	Australia	Healthy infants		fish oil, daily,	(DHA+EPA+DPA+A	omega-placebo	Trial randomized parallel	8-9 years	Program Literacy and	MD	-27.03000069	Secondary
Brew, 2015	September 1997 to 1999-2008	Australia	Healthy infants		fish oil, daily,	(DHA+EPA+DPA+A	omega-placebo	Trial randomized parallel	10-11 years	Program Literacy and	MD	-3.200000048	Secondary
Brew, 2015	September 1997 to 1999-2008	Australia	Healthy infants		fish oil, daily,	(DHA+EPA+DPA+A	omega-placebo	Trial randomized parallel	12-13 years	Program Literacy and	MD	-7	Secondary
Min, 2014	Jan 2008 - Dec 2011	UK	Pregnant women with type 2	59			Placebo, healthy women	Trial randomized parallel	birth	birthweight <1500g	OR	0.392857134	Secondary
Min, 2014	Jan 2008 - Dec 2011	UK	Pregnant women with type 2	59			Placebo, healthy women	Trial randomized parallel	birth	birthweight <2500g	OR	0.888888896	Secondary
Min, 2014	Jan 2008 - Dec 2011	UK	Pregnant women with type 2				Placebo, healthy women	Trial randomized parallel	birth	gestational age birth		NC	Secondary
Min, 2014	Jan 2008 - Dec 2011	UK	Pregnant women with type 2	59			Placebo, healthy women	Trial randomized parallel	birth	preterm birth	OR	1.185185194	Secondary
Judge, 2014		US	Healthy pregnant women	42			DHA group vs Placebo	Trial randomized parallel	2 weeks	Screening Scale (PDSS) total	SMD	0.437067092	Primary
Judge, 2014		US	Healthy pregnant women	42			DHA group vs Placebo	Trial randomized parallel	3 months	Screening Scale (PDSS) total	SMD	-0.243067458	Primary
Judge, 2014		US	Healthy pregnant women	42			DHA group vs Placebo	Trial randomized parallel	6 months	Screening Scale (PDSS) total	SMD	0.184672386	Primary
Judge, 2014		US	Healthy pregnant women	42			DHA group vs Placebo	Trial randomized parallel	6 weeks	Screening Scale (PDSS) total	SMD	-0.01572898	Primary
Almaas, 2015	2003-2014	Norway	weight infants	97			Intervention vs Control	Trial randomized parallel	8 years	of Intelligence: Full Scale IQ	SMD	-0.126807705	Secondary
Almaas, 2015	2003-2014	Norway	weight infants	97			Intervention vs Control	Trial randomized parallel	8 years	of Intelligence: Verbal IQ	SMD	-0.130057693	Secondary
Almaas, 2015	2003-2014	Norway	weight infants	97			Intervention vs Control	Trial randomized parallel	8 years	of Intelligence: performance	SMD	-0.066196062	Secondary
Ramakrishnan, 2015	2005-2009	Mexico	Healthy pregnant women	730	study ref 3364		Intervention vs Control	Trial randomized parallel	18 months	Index	SMD	-0.089780308	Primary
Ramakrishnan, 2015	2005-2009	Mexico	Healthy pregnant women	730	study ref 3364		Intervention vs Control	Trial randomized parallel	birth	IUGR	OR	0.923076928	Secondary
Ramakrishnan, 2015	2005-2009	Mexico	Healthy pregnant women	730	study ref 3364		Intervention vs Control	Trial randomized parallel	18 months	Bayley PDI	SMD	-0.032048468	Primary
Meldrum, 2015	followup	Australia	pregnant women	50			Fish oil vs Placebo	Trial randomized parallel	12 years	for Children IV	SMD	0.090011589	Secondary
Meldrum, 2015	followup	Australia	pregnant women	47			Fish oil vs Placebo	Trial randomized parallel	12 years	Test of Visual-Motor	SMD	0.126974538	Secondary
Willatts, 2013	1992	Italy, UK, Belgium	Healthy infants	147			LC-PUFA	Trial randomized parallel	6 years	Primary Scale of Intelligence-	SMD	-0.186616465	Secondary
Willatts, 2013	1992	Italy, UK, Belgium	Healthy infants	147			LC-PUFA	Trial randomized parallel	6 year	Primary Scale of Intelligence:	SMD	-0.186616465	Secondary
Willatts, 2013	1992	Italy, UK, Belgium	Healthy infants	147			LC-PUFA	Trial randomized parallel	6 year	Primary Scale of Intelligence:	SMD	-0.11632973	Secondary
Willatts, 2013	1992	Italy, UK, Belgium	Healthy infants	147			LC-PUFA	Trial randomized parallel	6 year	Primary Scale of Intelligence:	SMD	-0.171192899	Secondary
Colombo, 2013	09/03/03-09/25/05	US	Healthy infants	39			0.32% vs 0.00%	Trial randomized parallel	18 months	Communicative Development	SMD	-0.208973438	
Colombo, 2013	09/03/03-09/25/05	US	Healthy infants	36			0.64% vs 0.00%	Trial randomized parallel	18 months	Communicative Development	SMD	0.306412935	
Colombo, 2013	09/03/03-09/25/05	US	Healthy infants	42			0.96% vs 0.00%	Trial randomized parallel	18 months	Communicative Development	SMD	0.025472023	
Colombo, 2013	09/03/03-09/25/05	US	Healthy infants	84			0.32-0.96% vs 0.00%	Trial randomized parallel	6 year	Test of Intelligence: Full Scale	SMD	0.365765303	Secondary
Colombo, 2013	09/03/03-09/25/05	US	Healthy infants	36			0.64% vs 0.00%	Trial randomized parallel	18 months	Bayley PDI	SMD	-0.094280906	Secondary
Colombo, 2013	09/03/03-09/25/05	US	Healthy infants	42			0.96% vs 0.00%	Trial randomized parallel	18 months	Bayley PDI	SMD	-0.043183353	Secondary
Colombo, 2013	09/03/03-09/25/05	US	Healthy infants	39			0.32% vs 0.00%	Trial randomized parallel	18 months	Bayley PDI	SMD	-0.090301	Secondary
Colombo, 2013	09/03/03-09/25/05	US	Healthy infants					Trial randomized parallel		Communicative Development			Secondary
Dunstan, 2008	2000-2003	Australia	women with allergies	72		erythrocyte (as %	Fish oil vs Control	Trial randomized parallel	birth	birth weight	SMD	0.202062249	Secondary
Dunstan, 2008	2000-2003	Australia	women with allergies	72		erythrocyte (as %	Fish oil vs Control	Trial randomized parallel	2.5 years	Scales: Eye and hand	SMD	0.554988265	Secondary
Dunstan, 2008	2000-2003	Australia	women with allergies	72		erythrocyte (as %	Fish oil vs Control	Trial randomized parallel	2.5 years	Scales: Performance	SMD	0.384841085	Secondary
Dunstan, 2008	2000-2003	Australia	women with allergies	72		erythrocyte (as %	Fish oil vs Control	Trial randomized parallel	2.5 years	Scales: Practical reasoning	SMD	0.047382046	Secondary
Dunstan, 2008	2000-2003	Australia	women with allergies	72		erythrocyte (as %	Fish oil vs Control	Trial randomized parallel	2.5 years	Scales: Speech and hearing	SMD	0.160580263	Secondary
Dunstan, 2008	2000-2003	Australia	women with allergies	72		erythrocyte (as %	Fish oil vs Control	Trial randomized parallel	2.5 years	Scales: General quotient	SMD	0.361256063	Secondary
Dunstan, 2008	2000-2003	Australia	women with allergies	72		erythrocyte (as %	Fish oil vs Control	Trial randomized parallel	2.5 years	Scales: Personal social	SMD	0.256749153	Secondary
Dunstan, 2008	2000-2003	Australia	women with allergies	72		erythrocyte (as %	Fish oil vs Control	Trial randomized parallel	2.5 years	Scales:Locomotor	SMD	0.370407909	Secondary
Dunstan, 2008	2000-2003	Australia	women with allergies	72		erythrocyte (as %	Fish oil vs Control	Trial randomized parallel	birth	gestational age	SMD	0.1875	Secondary
Dunstan, 2008	2000-2003	Australia	women with allergies	64		erythrocyte (as %	Fish oil vs Control	Trial randomized parallel	30 months	head circumference	SMD	-0.24137193	Secondary
Dunstan, 2008	2000-2003	Australia	women with allergies	64		erythrocyte (as %	Fish oil vs Control	Trial randomized parallel	30 months	length	SMD	0.117093936	Secondary
Dunstan, 2008	2000-2003	Australia	women with allergies	64		erythrocyte (as %	Fish oil vs Control	Trial randomized parallel	30 months	weight	SMD	0.200000003	Secondary
Drover, 2011	2003-2006	US	Healthy infants	57			(Control)	Trial randomized parallel	18 months	Development II (Mental	SMD	0.569579899	Secondary
Drover, 2011	2003-2006	US	Healthy infants	60			(Control)	Trial randomized parallel	18 months	Development II (Mental	SMD	0.506325007	Secondary
Drover, 2011	2003-2006	US	Healthy infants	56			(Control)	Trial randomized parallel	18 months	Development II (Mental	SMD	0.335613608	Secondary
Courville, 2011	nr	US	Healthy pregnant women	47	intake (mg/d),		DHA-FF vs Placebo	Trial randomized parallel	birth	birth weight	SMD	0.3114959	Unspecified
Courville, 2011	nr	US	Healthy pregnant women	47	intake (mg/d),		DHA-FF vs Placebo	Trial randomized parallel	birth	gestational age	SMD	0.433120996	Unspecified
Carlson, 2013	2006.01-2011.10	US	Healthy pregnant women	301	intake from	DHA (placebo group	DHA vs Placebo	Trial randomized parallel	birth	birth weight	SMD	0.305268943	Primary
Carlson, 2013	2006.01-2011.10	US	Healthy pregnant women	301	intake from	DHA (placebo group	DHA vs Placebo	Trial randomized parallel	during pregnancy	preeclampsia	OR	1	Secondary
Carlson, 2013	2006.01-2011.10	US	Healthy pregnant women	301	intake from	DHA (placebo group	DHA vs Placebo	Trial randomized parallel	birth	birthweight <1500g	OR	11.51608086	Secondary
Carlson, 2013	2006.01-2011.10	US	Healthy pregnant women	301	intake from	DHA (placebo group	DHA vs Placebo	Trial randomized parallel	birth	birthweight <2500g	OR	2.307692289	Secondary

Study	Study years (start date)	Country	Population	(total)	intake	(Baseline)	n-3 type(s)	study_design	Follow-up time	Outcome	Effect size type (OR or SMD)	Reported effect Size	Outcome classification
Carlson, 2013	2006.01-2011.10	US	Healthy pregnant women	301	intake from	DHA (placebo group	DHA vs Placebo	Trial randomized parallel	birth	gestational age	SMD	0.202394068	Primary
Carlson, 2013	2006.01-2011.10	US	Healthy pregnant women	301	intake from	DHA (placebo group	DHA vs Placebo	Trial randomized parallel	birth	incidence of premature birth	OR	1.134920597	Secondary
Birch, 2010	2003-2006	US	Healthy infants					Trial randomized parallel					Primary
Isaacs, 2011	through 1997 with 10-year followup	UK	Preterm infants	107			formula vs control	Trial randomized parallel	10 years	Children: Attention scaled	SMD	-0.039157018	Secondary
Isaacs, 2011	through 1997 with 10-year followup	UK	Preterm infants	107			formula vs control	Trial randomized parallel	10 years	Children: Creature counting	SMD	0.166753545	Secondary
Isaacs, 2011	through 1997 with 10-year followup	UK	Preterm infants	107			formula vs control	Trial randomized parallel	10 years	Children: Dual-task	SMD	0.112603858	Secondary
Isaacs, 2011	through 1997 with 10-year followup	UK	Preterm infants	107			formula vs control	Trial randomized parallel	10 years	Children: Opposite Worlds	SMD	0.158926487	Secondary
Isaacs, 2011	through 1997 with 10-year followup	UK	Preterm infants	107			formula vs control	Trial randomized parallel	10 years	Children: Score! Scale scored	SMD	-0.029411763	Secondary
Isaacs, 2011	through 1997 with 10-year followup	UK	Preterm infants	107			formula vs control	Trial randomized parallel	10 years	of Intelligence: FSIQ	SMD	0.188561812	Secondary
Isaacs, 2011	through 1997 with 10-year followup	UK	Preterm infants	107			formula vs control	Trial randomized parallel	10 years	of Intelligence: Performance	SMD	-0.022280326	Secondary
Isaacs, 2011	through 1997 with 10-year followup	UK	Preterm infants	107			formula vs control	Trial randomized parallel	10 years	of Intelligence: VIQ	SMD	0.318237037	Secondary
Agostoni, 2009	2005; 1-year followup	Italy	Healthy infants	958			DHA vs placebo	Trial randomized parallel	varies	hands-and-knees crawling	SMD	0.079347178	Primary
Agostoni, 2009	2005; 1-year followup	Italy	Healthy infants	1093			DHA vs placebo	Trial randomized parallel	varies	sitting without support	SMD	0.357142866	Primary
Agostoni, 2009	2005; 1-year followup	Italy	Healthy infants	1091			DHA vs placebo	Trial randomized parallel	varies	standing alone	SMD	0.114615023	Primary
Agostoni, 2009	2005; 1-year followup	Italy	Healthy infants	1091			DHA vs placebo	Trial randomized parallel	varies	walking alone	SMD	0.133323327	Primary
Pietrantoni, 2014	nr	Italy	Healthy pregnant women	255			DHA group vs Placebo	Trial randomized parallel	birth	membranes	OR	4.095238209	Unspecified
Bergmann, 2012	2000-2009	Germany	Healthy infants	115		see refid 2803	prebiotic	Trial randomized parallel	6 yrs	BMI	SMD	0.145546764	Secondary
Bergmann, 2012	2000-2009	Germany	Healthy infants	115		see refid 2803	prebiotic	Trial randomized parallel	6 yrs	head circumference	SMD	-0.14149338	Secondary
Bergmann, 2012	2000-2009	Germany	Healthy infants	115		see refid 2803	prebiotic	Trial randomized parallel	6 yrs	height	SMD	-0.082315855	Secondary
Bergmann, 2012	2000-2009	Germany	Healthy infants	115		see refid 2803	prebiotic	Trial randomized parallel	6 yrs	weight	SMD	0.033643577	Secondary
Lucia Bergmann, 2007	2000-2002	Germany	pregnant women	117		identified fatty acid	minerals	Trial randomized parallel	birth	birth weight	SMD	-0.252969831	Unspecified
Lucia Bergmann, 2007	2000-2002	Germany	pregnant women	117		identified fatty acid	minerals	Trial randomized parallel	birth	gestational age	SMD	-0.270222873	Unspecified
Lucia Bergmann, 2007	2000-2002	Germany	pregnant women	117		identified fatty acid	minerals	Trial randomized parallel	1 month	bmi	SMD	-0.046814039	Unspecified
Lucia Bergmann, 2007	2000-2002	Germany	pregnant women	117		identified fatty acid	minerals	Trial randomized parallel	21 months	bmi	SMD	-0.290478349	Unspecified
Lucia Bergmann, 2007	2000-2002	Germany	pregnant women	117		identified fatty acid	minerals	Trial randomized parallel	3 months	bmi	SMD	0.178672299	Unspecified
Lucia Bergmann, 2007	2000-2002	Germany	pregnant women	117		identified fatty acid	minerals	Trial randomized parallel	1 month	head circumference	SMD	-0.090714887	Unspecified
Lucia Bergmann, 2007	2000-2002	Germany	pregnant women	117		identified fatty acid	minerals	Trial randomized parallel	21 months	head circumference	SMD	0.238690883	Unspecified
Lucia Bergmann, 2007	2000-2002	Germany	pregnant women	117		identified fatty acid	minerals	Trial randomized parallel	3 months	head circumference	SMD	0	Unspecified
Lucia Bergmann, 2007	2000-2002	Germany	pregnant women	117		identified fatty acid	minerals	Trial randomized parallel	1 month	length	SMD	0.135425761	Unspecified
Lucia Bergmann, 2007	2000-2002	Germany	pregnant women	117		identified fatty acid	minerals	Trial randomized parallel	21 months	length	SMD	0.021943457	Unspecified
Lucia Bergmann, 2007	2000-2002	Germany	pregnant women	117		identified fatty acid	minerals	Trial randomized parallel	3 months	length	SMD	-0.037192132	Unspecified
Lucia Bergmann, 2007	2000-2002	Germany	pregnant women	117		identified fatty acid	minerals	Trial randomized parallel	1 month	weight	SMD	0.035049614	Unspecified
Lucia Bergmann, 2007	2000-2002	Germany	pregnant women	117		identified fatty acid	minerals	Trial randomized parallel	21 months	weight	SMD	-0.3739416	Unspecified
Lucia Bergmann, 2007	2000-2002	Germany	pregnant women	117		identified fatty acid	minerals	Trial randomized parallel	3 months	weight	SMD	0.081977032	Unspecified
Furuhjelm, 2011	2003-2007	Sweden	pregnant women	119			w-3 group vs Placebo	Trial randomized parallel	2 years	any food reactions	OR	2.215384722	Primary
Furuhjelm, 2011	2003-2007	Sweden	pregnant women	119			w-3 group vs Placebo	Trial randomized parallel	2 years	any eczema	OR	1.586014032	Primary
Furuhjelm, 2011	2003-2007	Sweden	pregnant women	119			w-3 group vs Placebo	Trial randomized parallel	2 years	any asthma	OR	0.949450553	Primary
Furuhjelm, 2011	2003-2007	Sweden	pregnant women	119			w-3 group vs Placebo	Trial randomized parallel	2 years	any rhinoconjunctivitis	OR	0.830769241	Primary
Makrides, 2010	2005-2008	Australia	Healthy pregnant women	2399			capsules	Trial randomized parallel	6 months	Depression Scale (EPDS) >	OR	1.180698156	Primary
Makrides, 2010	2005-2008	Australia	Healthy pregnant women	2399			capsules	Trial randomized parallel	6 weeks	Depression Scale (EPDS) >	OR	1.132153988	Primary
Makrides, 2010	2005-2008	Australia	Healthy pregnant women					Trial randomized parallel					Secondary
Makrides, 2010	2005-2008	Australia	Healthy pregnant women	726			capsules	Trial randomized parallel	18 months	Development III (Cognitive	SMD	0.005061553	Primary
Makrides, 2010	2005-2008	Australia	Healthy pregnant women	2399			capsules	Trial randomized parallel	birth	birthweight <2500g	OR	1.530193567	Secondary
Makrides, 2010	2005-2008	Australia	Healthy pregnant women				capsules	Trial randomized parallel	birth	gestational age		NC	Secondary
Makrides, 2010	2005-2008	Australia	Healthy pregnant women	2399			capsules	Trial randomized parallel	birth	incidence of premature birth	OR	1.307969332	Secondary
Llorente, 2003	<2002	US	Breast-feeding women	89		saturated 49.7 ± 2.3	omega 3 capsule vs placebo	Trial randomized parallel	2 months	(BDI)	SMD	-0.258840621	Unspecified
Llorente, 2003	<2002	US	Breast-feeding women	89		saturated 49.7 ± 2.3	omega 3 capsule vs placebo	Trial randomized parallel	3 weeks	(BDI)	SMD	-0.15330784	Unspecified
Llorente, 2003	<2002	US	Breast-feeding women	89		saturated 49.7 ± 2.3	omega 3 capsule vs placebo	Trial randomized parallel	4 months	(BDI)	SMD	-0.179693267	Unspecified
Llorente, 2003	<2002	US	Breast-feeding women	63		saturated 49.7 ± 2.3	omega 3 capsule vs placebo	Trial randomized parallel	18 months	Depression Scale (EPDS)	SMD	0	Unspecified
Llorente, 2003	<2002	US	Breast-feeding women	89		saturated 49.7 ± 2.3	omega 3 capsule vs placebo	Trial randomized parallel	at either 2, 4 or 18 months	responder: BDI<10	OR	0.962025285	Unspecified
Llorente, 2003	<2002	US	Breast-feeding women	89		saturated 49.7 ± 2.3	omega 3 capsule vs placebo	Trial randomized parallel	at either 2, 4 or 18 months	responder: BDI<20	OR	0.953926683	Unspecified
Palmer, 2012	2006-2009	Australia	allergies	706			Placebo	Trial randomized parallel	1 year	food allergy with sensitization	OR	1.088757396	Primary
Palmer, 2012	2006-2009	Australia	allergies	706			Placebo	Trial randomized parallel	1 year	eczema with sensitization	OR	1.633136153	Primary
Palmer, 2012	2006-2009	Australia	allergies	706			Placebo	Trial randomized parallel	1 year	respiratory tract infection	OR	1.105507493	Secondary
Field, 2008	NR	Canada	Healthy infants	30			Formula (unsuppl)	Trial randomized parallel	6 wk	head circumference	SMD	0.25981921	Secondary
Field, 2008	NR	Canada	Healthy infants	30			(unsuppl)	Trial randomized parallel	6 wk	head circumference	SMD	-0.157534748	Secondary
Field, 2008	NR	Canada	Healthy infants	30			(unsuppl)	Trial randomized parallel	6 wk	length	SMD	0	Secondary
Field, 2008	NR	Canada	Healthy infants	30			Formula (unsuppl)	Trial randomized parallel	6 wk	length	SMD	0.773905993	Secondary
Field, 2008	NR	Canada	Healthy infants	30			(unsuppl)	Trial randomized parallel	6 wk	weight	SMD	0.28197214	Secondary
Field, 2008	NR	Canada	Healthy infants	30			Formula (unsuppl)	Trial randomized parallel	6 wk	weight	SMD	0.261061996	Secondary
Hauner, 2012	july 14 2006 - may 22 2009	Germany	Healthy pregnant women	188	records	profile in RBCs at	Intervention vs Control	Trial randomized parallel	birth	birth weight	SMD	0.344324082	Secondary
Hauner, 2012	july 14 2006 - may 22 2009	Germany	Healthy pregnant women	188	records	profile in RBCs at	Intervention vs Control	Trial randomized parallel	birth	incidence of premature birth	OR	1.277777791	Secondary
Hauner, 2012	july 14 2006 - may 22 2009	Germany	Healthy pregnant women	188	records	profile in RBCs at	Intervention vs Control	Trial randomized parallel	birth	gestational age	SMD	0.475911558	Secondary
Hauner, 2012	july 14 2006 - may 22 2009	Germany	Healthy pregnant women	170	records	profile in RBCs at	Intervention vs Control	Trial randomized parallel	12 months	bmi	SMD	0.137736201	Secondary
Hauner, 2012	july 14 2006 - may 22 2009	Germany	Healthy pregnant women	174	records	profile in RBCs at	Intervention vs Control	Trial randomized parallel	4 months	bmi	SMD	0.222069964	Secondary
Hauner, 2012	july 14 2006 - may 22 2009	Germany	Healthy pregnant women	180	records	profile in RBCs at	Intervention vs Control	Trial randomized parallel	6 weeks	bmi	SMD	-0.076762483	Secondary
Hauner, 2012	july 14 2006 - may 22 2009	Germany	Healthy pregnant women	170	records	profile in RBCs at	Intervention vs Control	Trial randomized parallel	12 months	head circumference	SMD	0.257732689	Secondary
Hauner, 2012	july 14 2006 - may 22 2009	Germany	Healthy pregnant women	174	records	profile in RBCs at	Intervention vs Control	Trial randomized parallel	4 months	head circumference	SMD	0.15384616	Secondary
Hauner, 2012	july 14 2006 - may 22 2009	Germany	Healthy pregnant women	179	records	profile in RBCs at	Intervention vs Control	Trial randomized parallel	6 weeks	head circumference	SMD	-0.347412616	Secondary
Hauner, 2012	july 14 2006 - may 22 2009	Germany	Healthy pregnant women	170	records	profile in RBCs at	Intervention vs Control	Trial randomized parallel	12 months	length	SMD	0.230509579	Secondary
Hauner, 2012	july 14 2006 - may 22 2009	Germany	Healthy pregnant women	175	records	profile in RBCs at	Intervention vs Control	Trial randomized parallel	4 months	length	SMD	0.095156431	Secondary
Hauner, 2012	july 14 2006 - may 22 2009	Germany	Healthy pregnant women	180	records	profile in RBCs at	Intervention vs Control	Trial randomized parallel	6 weeks	length	SMD	0.172204271	Secondary

Study	Study years (start date)	Country	Population	(total)	intake	(Baseline)	n-3 type(s)	study_design	Follow-up time	Outcome	Effect size type (OR or SMD)	Reported effect Size	Outcome classification
Hauner, 2012	july 14 2006 - may 22 2009	Germany	Healthy pregnant women	170	records	profile in RBCs at	Intervention vs Control	Trial randomized parallel	12 months	weight	SMD	0.263134122	Secondary
Hauner, 2012	july 14 2006 - may 22 2009	Germany	Healthy pregnant women	174	records	profile in RBCs at	Intervention vs Control	Trial randomized parallel	4 months	weight	SMD	0.246487647	Secondary
Hauner, 2012	july 14 2006 - may 22 2009	Germany	Healthy pregnant women	180	records	profile in RBCs at	Intervention vs Control	Trial randomized parallel	6 weeks	weight	SMD	0.092580557	Secondary
Fang, 2005	NR	Taiwan	Preterm infants	27			Neoangelac Plus vs placebo	Trial randomized parallel	1 year	Index	SMD	1.081910968	Primary
Fang, 2005	NR	Taiwan	Preterm infants	27			Neoangelac Plus vs placebo	Trial randomized parallel	6 months	Index	SMD	0.470003933	Primary
Fang, 2005	NR	Taiwan	Preterm infants	27			Neoangelac Plus vs placebo	Trial randomized parallel	12 months	development index	SMD	1.355769992	Primary
Fang, 2005	NR	Taiwan	Preterm infants	27			Neoangelac Plus vs placebo	Trial randomized parallel	6 months	development index	SMD	0.583425582	Primary
Fang, 2005	NR	Taiwan	Preterm infants	27			Neoangelac Plus vs placebo	Trial randomized parallel	4 months	Hiding Heidi Analysis <100%	OR	1.71875	Primary
Fang, 2005	NR	Taiwan	Preterm infants	27			Neoangelac Plus vs placebo	Trial randomized parallel	6 months	Hiding Heidi Analysis <100%	OR	1.109243751	Primary
Fang, 2005	NR	Taiwan	Preterm infants	27			Neoangelac Plus vs placebo	Trial randomized parallel	4 months	cycles per degree	OR	1.370242238	Primary
Fang, 2005	NR	Taiwan	Preterm infants	27			Neoangelac Plus vs placebo	Trial randomized parallel	6 months	cycles per degree	OR	1.2890625	Primary
Fang, 2005	NR	Taiwan	Preterm infants	24			Neoangelac Plus vs placebo	Trial randomized parallel	4 months	Visual evoked potential	SMD	0.565511107	Primary
Fang, 2005	NR	Taiwan	Preterm infants	23			Neoangelac Plus vs placebo	Trial randomized parallel	6 months	Visual evoked potential	SMD	0.155423433	Primary
Helland, 2008	1994-2003	Norway	pregnant women Breast-	143	cod n147 corn	cod(n148) corn	corn oil vs Cod oil	Trial randomized parallel	birth	birth weight	SMD	0.188516736	Primary
Helland, 2008	1994-2003	Norway	pregnant women Breast-		cod n147 corn	cod(n148) corn	corn oil vs Cod oil	Trial randomized parallel	4 years	for Children (K-ABC): mental		NC	Secondary
Helland, 2008	1994-2003	Norway	pregnant women Breast-		cod n147 corn	cod(n148) corn	corn oil vs Cod oil	Trial randomized parallel	7 years	for Children (K-ABC): mental		NC	Secondary
Helland, 2008	1994-2003	Norway	pregnant women Breast-		cod n147 corn	cod(n148) corn	corn oil vs Cod oil	Trial randomized parallel	4 years	for Children (K-ABC): non-		NC	Secondary
Helland, 2008	1994-2003	Norway	pregnant women Breast-		cod n147 corn	cod(n148) corn	corn oil vs Cod oil	Trial randomized parallel	7 years	for Children (K-ABC): non-		NC	Secondary
Helland, 2008	1994-2003	Norway	pregnant women Breast-		cod n147 corn	cod(n148) corn	corn oil vs Cod oil	Trial randomized parallel	4 years	for Children (K-ABC):		NC	Secondary
Helland, 2008	1994-2003	Norway	pregnant women Breast-		cod n147 corn	cod(n148) corn	corn oil vs Cod oil	Trial randomized parallel	7 years	for Children (K-ABC):		NC	Secondary
Helland, 2008	1994-2003	Norway	pregnant women Breast-		cod n147 corn	cod(n148) corn	corn oil vs Cod oil	Trial randomized parallel	4 years	for Children (K-ABC):		NC	Secondary
Helland, 2008	1994-2003	Norway	pregnant women Breast-		cod n147 corn	cod(n148) corn	corn oil vs Cod oil	Trial randomized parallel	7 years	for Children (K-ABC):		NC	Secondary
Helland, 2008	1994-2003	Norway	pregnant women Breast-	143	cod n147 corn	cod(n148) corn	corn oil vs Cod oil	Trial randomized parallel	7 years	bmi	SMD	0.058823526	Secondary
Helland, 2008	1994-2003	Norway	pregnant women Breast-	143	cod n147 corn	cod(n148) corn	corn oil vs Cod oil	Trial randomized parallel	7 years	length	SMD	-0.20782125	Secondary
Helland, 2008	1994-2003	Norway	pregnant women Breast-	143	cod n147 corn	cod(n148) corn	corn oil vs Cod oil	Trial randomized parallel	7 years	weight	SMD	-0.04878049	Secondary
Gustafson, 2013	may 2009 - july 2011	US	pregnant women	46		TFA) placebo group:	DHA vs Placebo	Trial randomized parallel	birth	birth weight	SMD	-0.038860865	Secondary
Gustafson, 2013	may 2009 - july 2011	US	pregnant women	27		TFA) placebo group:	DHA vs Placebo	Trial randomized parallel	1-14 days post-partum	Assessment: state	SMD	0.148237228	Primary
Gustafson, 2013	may 2009 - july 2011	US	pregnant women	27		TFA) placebo group:	DHA vs Placebo	Trial randomized parallel	1-14 days post-partum	Assessment: autonomic	SMD	0.211658597	Primary
Gustafson, 2013	may 2009 - july 2011	US	pregnant women	27		TFA) placebo group:	DHA vs Placebo	Trial randomized parallel	1-14 days post-partum	Assessment: motor	SMD	0.192501962	Primary
Gustafson, 2013	may 2009 - july 2011	US	pregnant women	27		TFA) placebo group:	DHA vs Placebo	Trial randomized parallel	1-14 days post-partum	Assessment: reflexes	SMD	0.047278289	Primary
Gustafson, 2013	may 2009 - july 2011	US	pregnant women	27		TFA) placebo group:	DHA vs Placebo	Trial randomized parallel	1-14 days post-partum	Assessment: state regulation	SMD	0.025446042	Primary
Gustafson, 2013	may 2009 - july 2011	US	pregnant women	27		TFA) placebo group:	DHA vs Placebo	Trial randomized parallel	1-14 days post-partum	Assessment:habituation	SMD	-0.156438708	Primary
Gustafson, 2013	may 2009 - july 2011	US	pregnant women	27		TFA) placebo group:	DHA vs Placebo	Trial randomized parallel	1-14 days post-partum	Assessment:orienting	SMD	0.21324341	Primary
Ramakrishnan, 2010	feb 2005 - feb 2007	Mexico	Healthy pregnant women	973	LA: 17,846 in		DHA vs Controls	Trial randomized parallel	birth	birth weight	SMD	0.011284063	Primary
Ramakrishnan, 2010	feb 2005 - feb 2007	Mexico	Healthy pregnant women	973	LA: 17,846 in		DHA vs Controls	Trial randomized parallel	birth	birthweight <2500g	OR	1.002057672	Secondary
Ramakrishnan, 2010	feb 2005 - feb 2007	Mexico	Healthy pregnant women	973	LA: 17,846 in		DHA vs Controls	Trial randomized parallel	birth	gestational age	SMD	-0.055466857	Primary
Ramakrishnan, 2010	feb 2005 - feb 2007	Mexico	Healthy pregnant women	973	LA: 17,846 in		DHA vs Controls	Trial randomized parallel	birth	incidence of premature birth	OR	0.818006218	Secondary
Jensen, 2010	NR (<2010)	US	Breast-feeding women	117			omega 3 capsule vs placebo	Trial randomized parallel	5 years	Preschool Scale of	SMD	-0.229631856	Secondary
Jensen, 2010	NR (<2010)	US	Breast-feeding women	117			omega 3 capsule vs placebo	Trial randomized parallel	5 years	Preschool Scale of	SMD	-0.046969224	Secondary
Jensen, 2010	NR (<2010)	US	Breast-feeding women	117			omega 3 capsule vs placebo	Trial randomized parallel	5 years	Preschool Scale of	SMD	0.093054555	Secondary
Jensen, 2010	NR (<2010)	US	Breast-feeding women	117			omega 3 capsule vs placebo	Trial randomized parallel	5 years	Preschool Scale of	SMD	-0.15384616	Secondary
Jensen, 2010	NR (<2010)	US	Breast-feeding women	113			omega 3 capsule vs placebo	Trial randomized parallel	5 years	Motor Integration	SMD	-0.108042359	Secondary
Jensen, 2010	NR (<2010)	US	Breast-feeding women	115			omega 3 capsule vs placebo	Trial randomized parallel	5 years	for Children: hand movement	SMD	-0.233761802	Secondary
Jensen, 2010	NR (<2010)	US	Breast-feeding women	115			omega 3 capsule vs placebo	Trial randomized parallel	5 years	McCarthy (leg coordination)	SMD	-0.058601439	Secondary
Jensen, 2010	NR (<2010)	US	Breast-feeding women	116			omega 3 capsule vs placebo	Trial randomized parallel	5 years	(dominant hand)	SMD	-0.088986464	Secondary
Jensen, 2010	NR (<2010)	US	Breast-feeding women	116			omega 3 capsule vs placebo	Trial randomized parallel	5 years	dominant hand)	SMD	0	Secondary
Jensen, 2010	NR (<2010)	US	Breast-feeding women					Trial randomized parallel		(number of letters correct)			Secondary
Jensen, 2010	NR (<2010)	US	Breast-feeding women					Trial randomized parallel		(number of letters correct)			Secondary
Jensen, 2010	NR (<2010)	US	Breast-feeding women					Trial randomized parallel		Sweep VEP acuity			Secondary
Jensen, 2010	NR (<2010)	US	Breast-feeding women					Trial randomized parallel		VEP Amplitude			Secondary
Jensen, 2010	NR (<2010)	US	Breast-feeding women					Trial randomized parallel		sizes)			Secondary
Meldrum, 2012	through October 2008	Australia	allergies	287	food	Fish oil group LA,	fish oil capsul vs placebo	Trial randomized parallel	18 months	Toddler Development (BSID-	SMD	0.144145399	Primary
Meldrum, 2012	through October 2008	Australia	allergies	287	food	Fish oil group LA,	fish oil capsul vs placebo	Trial randomized parallel	18 months	Toddler Development (BSID-	SMD	0.05327452	Primary
Meldrum, 2012	through October 2008	Australia	allergies	128	food	Fish oil group LA,	fish oil capsul vs placebo	Trial randomized parallel	12 months	Communicative Development	SMD	0.219934821	Primary
Meldrum, 2012	through October 2008	Australia	allergies	161	food	Fish oil group LA,	fish oil capsul vs placebo	Trial randomized parallel	18 months	Communicative Development	SMD	0.081229486	Primary
Meldrum, 2012	through October 2008	Australia	allergies	128	food	Fish oil group LA,	fish oil capsul vs placebo	Trial randomized parallel	12 months	Communicative Development	SMD	0.493831664	Primary
Meldrum, 2012	through October 2008	Australia	allergies	161	food	Fish oil group LA,	fish oil capsul vs placebo	Trial randomized parallel	18 months	Communicative Development	SMD	0.356752485	Primary
Meldrum, 2012	through October 2008	Australia	allergies	128	food	Fish oil group LA,	fish oil capsul vs placebo	Trial randomized parallel	12 months	Communicative Development	SMD	-0.041587263	Primary
Meldrum, 2012	through October 2008	Australia	allergies	161	food	Fish oil group LA,	fish oil capsul vs placebo	Trial randomized parallel	18 months	Communicative Development	SMD	0.113986336	Primary
Meldrum, 2012	through October 2008	Australia	allergies	128	food	Fish oil group LA,	fish oil capsul vs placebo	Trial randomized parallel	12 months	Communicative Development	SMD	0.448788583	Primary
Meldrum, 2012	through October 2008	Australia	allergies	161	food	Fish oil group LA,	fish oil capsul vs placebo	Trial randomized parallel	18 months	Communicative Development	SMD	0.357071489	Primary
Meldrum, 2012	through October 2008	Australia	allergies	128	food	Fish oil group LA,	fish oil capsul vs placebo	Trial randomized parallel	12 months	Communicative Development	SMD	0.072471201	Primary
Meldrum, 2012	through October 2008	Australia	allergies	161	food	Fish oil group LA,	fish oil capsul vs placebo	Trial randomized parallel	18 months	Communicative Development	SMD	-0.155814633	Primary
Meldrum, 2012	through October 2008	Australia	allergies	128	food	Fish oil group LA,	fish oil capsul vs placebo	Trial randomized parallel	12 months	Communicative Development	SMD	0.137528867	Primary
Meldrum, 2012	through October 2008	Australia	allergies	161	food	Fish oil group LA,	fish oil capsul vs placebo	Trial randomized parallel	18 months	Communicative Development	SMD	0.096759267	Primary
Meldrum, 2012	through October 2008	Australia	allergies	269	food	Fish oil group LA,	fish oil capsul vs placebo	Trial randomized parallel	18 months	Checklist: Sleep problems -	OR	0.896551728	Primary
de Jong, 2012	through October 1999, follow-up 9	Netherlands	Healthy infants					Trial randomized parallel					Secondary
Jensen, 2005	<2004	US	Breast-feeding women	133			(DHASCO) vs placebo	Trial randomized parallel	30 months	Developmental Index	SMD	0.577999294	Primary
Jensen, 2005	<2004	US	Breast-feeding women	147			(DHASCO) vs placebo	Trial randomized parallel	30 months	Auditory Milestone Scale	SMD	0.013285638	Secondary
Jensen, 2005	<2004	US	Breast-feeding women	162			(DHASCO) vs placebo	Trial randomized parallel	12 months	Auditory Milestone Scale	SMD	-0.136091054	Secondary
Jensen, 2005	<2004	US	Breast-feeding women	147			(DHASCO) vs placebo	Trial randomized parallel	30 months	development quotient (CAT	SMD	-0.022587707	Secondary
Jensen, 2005	<2004	US	Breast-feeding women	162			(DHASCO) vs placebo	Trial randomized parallel	12 months	development quotient (CAT	SMD	-0.096314266	Secondary

Study	Study years (start date)	Country	Population	(total)	intake	(Baseline)	n-3 type(s)	study_design	Follow-up time	Outcome	Effect size type (OR or SMD)	Reported effect Size	Outcome classification
Jensen, 2005	<2004	US	Breast-feeding women	147			(DHASCO) vs placebo	Trial randomized parallel	30 months	development quotient (DQ)	SMD	-0.147750855	Secondary
Jensen, 2005	<2004	US	Breast-feeding women	162			(DHASCO) vs placebo	Trial randomized parallel	12 months	development quotient (DQ)	SMD	0.169517517	Secondary
Jensen, 2005	<2004	US	Breast-feeding women	160			(DHASCO) vs placebo	Trial randomized parallel	4 months	Sweep VEP	SMD	0	Secondary
Jensen, 2005	<2004	US	Breast-feeding women	147			(DHASCO) vs placebo	Trial randomized parallel	4 months	Teller Acuity Card procedure	SMD	0.47184062	Secondary
Jensen, 2005	<2004	US	Breast-feeding women	147			(DHASCO) vs placebo	Trial randomized parallel	8 months	Teller Acuity Card procedure	SMD	-2.180923462	Secondary
Jensen, 2005	<2004	US	Breast-feeding women	168			(DHASCO) vs placebo	Trial randomized parallel	4 months	amplitude	SMD	-0.359262765	Secondary
Jensen, 2005	<2004	US	Breast-feeding women	153			(DHASCO) vs placebo	Trial randomized parallel	8 months	amplitude	SMD	-0.361061066	Secondary
Jensen, 2005	<2004	US	Breast-feeding women	168			(DHASCO) vs placebo	Trial randomized parallel	4 months	latency	SMD	-0.080524042	Secondary
Jensen, 2005	<2004	US	Breast-feeding women	153			(DHASCO) vs placebo	Trial randomized parallel	8 months	latency	SMD	0.021418762	Secondary
Campoy, 2011	NR, <2011	Germany, Spain, Hungary	Healthy pregnant women			mean DHA Placebo	fish oil vs placebo	design	6.5 years	Battery for Children: Mental		NC	Secondary
Campoy, 2011	NR, <2011	Germany, Spain, Hungary	Healthy pregnant women			mean DHA Placebo	placebo	design	6.5 years	Battery for Children: Mental		NC	Secondary
Campoy, 2011	NR, <2011	Germany, Spain, Hungary	Healthy pregnant women			mean DHA Placebo	folic acid vs placebo	design	6.5 years	Battery for Children: Mental		NC	Secondary
Campoy, 2011	NR, <2011	Germany, Spain, Hungary	Healthy pregnant women			mean DHA Placebo	fish oil vs placebo	design	6.5 years	Battery for Children:		NC	Secondary
Campoy, 2011	NR, <2011	Germany, Spain, Hungary	Healthy pregnant women			mean DHA Placebo	placebo	design	6.5 years	Battery for Children:		NC	Secondary
Campoy, 2011	NR, <2011	Germany, Spain, Hungary	Healthy pregnant women			mean DHA Placebo	folic acid vs placebo	design	6.5 years	Battery for Children:		NC	Secondary
Campoy, 2011	NR, <2011	Germany, Spain, Hungary	Healthy pregnant women			mean DHA Placebo	fish oil vs placebo	design	6.5 years	Battery for Children:		NC	Secondary
Campoy, 2011	NR, <2011	Germany, Spain, Hungary	Healthy pregnant women			mean DHA Placebo	placebo	design	6.5 years	Battery for Children:		NC	Secondary
Campoy, 2011	NR, <2011	Germany, Spain, Hungary	Healthy pregnant women			mean DHA Placebo	folic acid vs placebo	design	6.5 years	Battery for Children:		NC	Secondary
Mihrshahi, 2003	1997-2002	Australia	allergies	554			control or intervention vs Diet	Trial randomized parallel	18 months	eczema or dermatitis	OR	1	Primary
Mihrshahi, 2003	1997-2002	Australia	allergies	554			control or intervention vs Diet	Trial randomized parallel	18 months	asthma	OR	1	Primary
Mihrshahi, 2003	1997-2002	Australia	allergies	554			control or intervention vs Diet	Trial randomized parallel	18 months	wheeze ever	OR	1	Primary
Toelle, 2010	1997-2008	Australia	Healthy infants	450			vs Control	Trial randomized parallel	8 yrs	atopy	OR	0.995192289	Primary
Toelle, 2010	1997-2008	Australia	Healthy infants	450			vs Control	Trial randomized parallel	8 yrs	rhinitis	OR	0.97077924	Secondary
Toelle, 2010	1997-2008	Australia	Healthy infants	450			vs Control	Trial randomized parallel	8 yrs	eczema	OR	0.925974011	Secondary
Toelle, 2010	1997-2008	Australia	Healthy infants	450			vs Control	Trial randomized parallel	8 yrs	asthma	OR	0.807017565	Primary
Toelle, 2010	1997-2008	Australia	Healthy infants	450			vs Control	Trial randomized parallel	8 yrs	wheeze	OR	0.730386078	Primary
Innis, 2008	NR, <2008	Canada	Healthy pregnant women	135	assignment:	baseline values for	DHA supplement vs placebo	Trial randomized parallel	60 days	(visual acuity)	SMD	0.316226661	Secondary
Smithers, 2010	2003	Australia	Preterm infants	127			DHA vs Placebo	Trial randomized parallel	26 months CA	Development Inventory	SMD	-0.043016009	Secondary
Knudsen, 2006	2001-	Denmark	Healthy pregnant women	972	EPA+DHA,	and AA in	03 vs CG	Trial randomized parallel	birth	gestational age	SMD	-0.076467894	Primary
Knudsen, 2006	2001-	Denmark	Healthy pregnant women	977	EPA+DHA,	and AA in	01 vs CG	Trial randomized parallel	birth	gestational age	SMD	0.075525202	Primary
Knudsen, 2006	2001-	Denmark	Healthy pregnant women	960	EPA+DHA,	and AA in	14 vs CG	Trial randomized parallel	birth	gestational age	SMD	0	Primary
Knudsen, 2006	2001-	Denmark	Healthy pregnant women	935	EPA+DHA,	and AA in	28 vs CG	Trial randomized parallel	birth	gestational age	SMD	-0.080774717	Primary
Knudsen, 2006	2001-	Denmark	Healthy pregnant women	970	EPA+DHA,	and AA in	07 vs CG	Trial randomized parallel	birth	gestational age	SMD	-0.008395271	Primary
Knudsen, 2006	2001-	Denmark	Healthy pregnant women	924	EPA+DHA,	and AA in	c18 vs CG	Trial randomized parallel	birth	gestational age	SMD	0.008391659	Primary
Olsen, 2008	1989-2006	Denmark	Healthy pregnant women	399			Fish oil vs Control	Trial randomized parallel	16 years	asthma (all types)	OR	2.659007311	Secondary
Olsen, 2008	1989-2006	Denmark	Healthy pregnant women	265			No oil vs Control	Trial randomized parallel	16 years	asthma (all types)	OR	3.477941275	Secondary
Olsen, 2008	1989-2006	Denmark	Healthy pregnant women	399			Fish oil vs Control	Trial randomized parallel	16 years	asthma (allergic)	OR	7.735294342	Secondary
Olsen, 2008	1989-2006	Denmark	Healthy pregnant women	265			No oil vs Control	Trial randomized parallel	16 years	asthma (allergic)	OR	16.13138771	Secondary
Cheatham, 2011	1998-2007	Denmark	Healthy infants	63			Olive oil vs Fish oil	Observational prospective	7.5 years	Stroop scores	SMD	-0.161422551	Secondary
Cheatham, 2011	1998-2007	Denmark	Healthy infants	63			Olive oil vs Fish oil	Observational prospective	7.5 years	Standardized speed of	SMD	-0.230769232	Secondary
Furuhjelm, 2009	2003-2006	Sweden	pregnant women	117	0.2g/day EPA-	mean(sd) mol %	w3 group vs Placebo	Trial randomized parallel	12 months	Food Allergy	OR	8	Primary
Furuhjelm, 2009	2003-2006	Sweden	pregnant women	115	0.2g/day EPA-	mean(sd) mol %	w3 group vs Placebo	Trial randomized parallel	12 months	IgE associated eczema	OR	3.095238209	Primary
Furuhjelm, 2009	2003-2006	Sweden	pregnant women	117	0.2g/day EPA-	mean(sd) mol %	w3 group vs Placebo	Trial randomized parallel	6 months	IgE associated eczema	OR	2.599999905	Primary
Dunstan, 2003	1999-2001	Australia	pregnant women	83			group	Trial randomized parallel	1 year	food allergy	OR	1.550387621	Secondary
Dunstan, 2003	1999-2001	Australia	pregnant women	83			group	Trial randomized parallel	1 year	atopic dermatitis	OR	0.671834648	Secondary
Dunstan, 2003	1999-2001	Australia	pregnant women	83			group	Trial randomized parallel	1 year	asthma	OR	2.790697575	Secondary
Dunstan, 2003	1999-2001	Australia	pregnant women	83			group	Trial randomized parallel	1 year	chronic cough	OR	2.04651165	Secondary
Dunstan, 2003	1999-2001	Australia	pregnant women	83			group	Trial randomized parallel	1 year	recurrent wheeze	OR	1.116279125	Secondary
Zhou, 2012	10. 2005 - 01. 2008	Australia	Healthy pregnant women	2399			DHA vs control	Trial randomized parallel	birth	birth weight	SMD	0.119289018	Secondary
Zhou, 2012	10. 2005 - 01. 2008	Australia	Healthy pregnant women	2399			DHA vs control	Trial randomized parallel	during pregnancy	preeclampsia	OR	0.96264559	Secondary
Zhou, 2012	10. 2005 - 01. 2008	Australia	Healthy pregnant women	2399			DHA vs control	Trial randomized parallel	during pregnancy	hypertension	OR	1.087294936	Secondary
Zhou, 2012	10. 2005 - 01. 2008	Australia	Healthy pregnant women	2399			DHA vs control	Trial randomized parallel	birth	SGA for weight	OR	1.11861515	Secondary
Zhou, 2012	10. 2005 - 01. 2008	Australia	Healthy pregnant women	2399			DHA vs control	Trial randomized parallel	birth	birthweight <2500g	OR	1.530193567	Secondary
Makrides, 2014	25, 2012	Australia	Healthy pregnant women	646			DHA supplement vs Placebo	Trial randomized parallel	4 years	hyperactivity disorder	OR	NC	
Makrides, 2014	25, 2012	Australia	Healthy pregnant women	646			DHA supplement vs Placebo	Trial randomized parallel	4 years	diagnosis of autism	OR	0.531948865	
Makrides, 2014	25, 2012	Australia	Healthy pregnant women				DHA supplement vs Placebo	Trial randomized parallel	4 years	Executive Function-		NC	Secondary
Makrides, 2014	25, 2012	Australia	Healthy pregnant women				DHA supplement vs Placebo	Trial randomized parallel	4 years	Executive Function-		NC	Secondary
Makrides, 2014	25, 2012	Australia	Healthy pregnant women				DHA supplement vs Placebo	Trial randomized parallel	4 years	Executive Function-		NC	Secondary
Makrides, 2014	25, 2012	Australia	Healthy pregnant women				DHA supplement vs Placebo	Trial randomized parallel	4 years	Executive Function-		NC	Secondary
Makrides, 2014	25, 2012	Australia	Healthy pregnant women				DHA supplement vs Placebo	Trial randomized parallel	4 years	Executive Function-		NC	Secondary
Makrides, 2014	25, 2012	Australia	Healthy pregnant women				DHA supplement vs Placebo	Trial randomized parallel	4 years	Executive Function-		NC	Secondary
Makrides, 2014	25, 2012	Australia	Healthy pregnant women				DHA supplement vs Placebo	Trial randomized parallel	4 years	Executive Function-		NC	Secondary
Makrides, 2014	25, 2012	Australia	Healthy pregnant women				DHA supplement vs Placebo	Trial randomized parallel	4 years	Executive Function-		NC	Secondary
Makrides, 2014	25, 2012	Australia	Healthy pregnant women				DHA supplement vs Placebo	Trial randomized parallel	4 years	Executive Function-		NC	Secondary
Makrides, 2014	25, 2012	Australia	Healthy pregnant women				DHA supplement vs Placebo	Trial randomized parallel	4 years	Score		NC	Secondary
Makrides, 2014	25, 2012	Australia	Healthy pregnant women				DHA supplement vs Placebo	Trial randomized parallel	4 years	efficiency)		NC	Secondary
Makrides, 2014	25, 2012	Australia	Healthy pregnant women				DHA supplement vs Placebo	Trial randomized parallel	4 years	second edition (DAS II) score:		NC	Secondary
Makrides, 2014	25, 2012	Australia	Healthy pregnant women				DHA supplement vs Placebo	Trial randomized parallel	4 years	second edition (DAS II) score:		NC	Secondary
Makrides, 2014	25, 2012	Australia	Healthy pregnant women				DHA supplement vs Placebo	Trial randomized parallel	4 years	second edition (DAS II) score:		NC	Secondary
Makrides, 2014	25, 2012	Australia	Healthy pregnant women				DHA supplement vs Placebo	Trial randomized parallel	4 years	second edition (DAS II) score:		NC	Secondary
Makrides, 2014	25, 2012	Australia	Healthy pregnant women				DHA supplement vs Placebo	Trial randomized parallel	4 years	second edition (DAS II) score:		NC	Secondary
Makrides, 2014	25, 2012	Australia	Healthy pregnant women				DHA supplement vs Placebo	Trial randomized parallel	4 years	second edition (DAS II) score:		NC	Secondary

Study	Study years (start date)	Country	Population	(total)	intake	(Baseline)	n-3 type(s)	study_design	Follow-up time	Outcome	Effect size type (OR or SMD)	Reported effect Size	Outcome classification
de Jong, 2010	1997-2008	Netherlands	Healthy infants	214			group	Trial randomized parallel	9 years	neurologically normal	OR	1.062009454	Unspecified
Clandinin, 2005	NR	Canada	Preterm infants	114			Fish-DHA vs Control	Trial randomized parallel	118 weeks	Development II (Mental	SMD	0.661334515	Unspecified
Clandinin, 2005	NR	Canada	Preterm infants	112			Reference vs Control	Trial randomized parallel	118 weeks	Development II (Mental	SMD	1.402211308	Unspecified
Clandinin, 2005	NR	Canada	Preterm infants	98			Algal-DHA vs Control	Trial randomized parallel	118 weeks	Development II (Mental	SMD	0.426311731	Unspecified
Clandinin, 2005	NR	Canada	Preterm infants	113			Fish-DHA vs Control	Trial randomized parallel	118 weeks	Development II (Physical	SMD	0.332264096	Unspecified
Clandinin, 2005	NR	Canada	Preterm infants	113			Reference vs Control	Trial randomized parallel	118 weeks	Development II (Physical	SMD	0.996792257	Unspecified
Clandinin, 2005	NR	Canada	Preterm infants	100			Algal-DHA vs Control	Trial randomized parallel	118 weeks	Development II (Physical	SMD	0.352404565	Unspecified
Clandinin, 2005	NR	Canada	Preterm infants					Trial randomized parallel					Unspecified
Stein, 2011	02. 2005- 02.2007	Mexico	Healthy infants	739			DHA vs Placebo	Trial randomized parallel	birth	birth weight	SMD	0.047999464	Primary
Stein, 2011	02. 2005- 02.2007	Mexico	Healthy infants	737			DHA vs Placebo	Trial randomized parallel	birth	retardation); birth weight for	OR	0.977006674	Secondary
Stein, 2011	02. 2005- 02.2007	Mexico	Healthy infants	739			DHA vs Placebo	Trial randomized parallel	birth	birthweight <2500g	OR	1.255813956	Secondary
Stein, 2011	02. 2005- 02.2007	Mexico	Healthy infants	737			DHA vs Placebo	Trial randomized parallel	birth	gestational age	SMD	0	Primary
Stein, 2011	02. 2005- 02.2007	Mexico	Healthy infants	737			DHA vs Placebo	Trial randomized parallel	birth	incidence of premature birth	OR	0.911561251	Secondary
Stein, 2011	02. 2005- 02.2007	Mexico	Healthy infants	739			DHA vs Placebo	Trial randomized parallel	18 months	head circumference	SMD	0	Primary
Stein, 2011	02. 2005- 02.2007	Mexico	Healthy infants	739			DHA vs Placebo	Trial randomized parallel	18 months	length	SMD	0.035714287	Primary
Stein, 2011	02. 2005- 02.2007	Mexico	Healthy infants	739			DHA vs Placebo	Trial randomized parallel	18 months	weight	SMD	0	Primary
Manley, 2011	2001-2007	Australia	feeding women	481			diet	Trial randomized parallel	12 months	hay fever	OR	2.422489882	Secondary
Manley, 2011	2001-2007	Australia	feeding women	475			diet	Trial randomized parallel	12 or 18 months	hay fever	OR	2.485143423	Secondary
Manley, 2011	2001-2007	Australia	feeding women	603			diet	Trial randomized parallel	18 months	hay fever	OR	1.341295362	Secondary
Manley, 2011	2001-2007	Australia	feeding women	481			diet	Trial randomized parallel	12 months	eczema	OR	1.285140514	Secondary
Manley, 2011	2001-2007	Australia	feeding women	484			diet	Trial randomized parallel	12 or 18 months	eczema	OR	1.045214176	Secondary
Manley, 2011	2001-2007	Australia	feeding women	603			diet	Trial randomized parallel	18 months	eczema	OR	0.997588396	Secondary
Manley, 2011	2001-2007	Australia	feeding women	481			diet	Trial randomized parallel	12 months	asthma	OR	1.294065118	Secondary
Manley, 2011	2001-2007	Australia	feeding women	489			diet	Trial randomized parallel	12 or 18 months	asthma	OR	1.060536981	Secondary
Manley, 2011	2001-2007	Australia	feeding women	603			diet	Trial randomized parallel	18 months	asthma	OR	1.05340755	Secondary
Smithers, 2008	2001-2004	Australia	Preterm infants	115	begun at birth:		Treatment vs Control group	Trial randomized parallel	2 months (corrected age)	Visual evoked potential acuity	SMD	0	Primary
Smithers, 2008	2001-2004	Australia	Preterm infants	95	begun at birth:		Treatment vs Control group	Trial randomized parallel	4 months (corrected age)	Visual evoked potential acuity	SMD	0.492770821	Primary
Smithers, 2008	2001-2004	Australia	Preterm infants	125	begun at birth:		Treatment vs Control group	Trial randomized parallel	4 months (corrected age)	latency: 48 min of arc	SMD	0.130434781	Secondary
Smithers, 2008	2001-2004	Australia	Preterm infants	124	begun at birth:		Treatment vs Control group	Trial randomized parallel	2 months (corrected age)	latency: 69 min of arc	SMD	0.249258399	Secondary
Smithers, 2008	2001-2004	Australia	Preterm infants	125	begun at birth:		Treatment vs Control group	Trial randomized parallel	4 months (corrected age)	latency: 69 min of arc	SMD	0.09735848	Secondary
Smithers, 2008	2001-2004	Australia	Preterm infants	124	begun at birth:		Treatment vs Control group	Trial randomized parallel	2 months (corrected age)	latency: 96 min of arc	SMD	0.233990356	Secondary
Smithers, 2008	2001-2004	Australia	Preterm infants		begun at birth:			Trial randomized parallel					Secondary
Henriksen, 2008	2003-2006	Norway	Preterm infants					Trial randomized parallel		Ages and Stages			Primary
Henriksen, 2008	2003-2006	Norway	Preterm infants	105			Intervention vs Control	Trial randomized parallel	6 months	Communication	SMD	-0.14034833	
Henriksen, 2008	2003-2006	Norway	Preterm infants	105			Intervention vs Control	Trial randomized parallel	6 months	Ages and Stages: Fine motor	SMD	-0.047187887	
Henriksen, 2008	2003-2006	Norway	Preterm infants	105			Intervention vs Control	Trial randomized parallel	6 months	motor	SMD	0.212538749	
Henriksen, 2008	2003-2006	Norway	Preterm infants	105			Intervention vs Control	Trial randomized parallel	6 months	social	SMD	0.079742588	
Henriksen, 2008	2003-2006	Norway	Preterm infants	105			Intervention vs Control	Trial randomized parallel	6 months	solving	SMD	0.464068025	
Henriksen, 2008	2003-2006	Norway	Preterm infants	105			Intervention vs Control	Trial randomized parallel	6 months	Ages and Stages: Total	SMD	0.167406961	
Henriksen, 2008	2003-2006	Norway	Preterm infants	100			Intervention vs Control	Trial randomized parallel	day 65	head circumference	SMD	0.350823224	Secondary
Noakes, 2012	Not reported	UK	Healthy pregnant women	86			group	Trial randomized parallel	6 months	atopic dermatitis	OR	1.357142806	Primary
Noakes, 2012	Not reported	UK	Healthy pregnant women	83			group	Trial randomized parallel	6 months	chest infection	OR	0.268115938	Secondary
Noakes, 2012	Not reported	UK	Healthy pregnant women	83			group	Trial randomized parallel	6 months	pneumonia/bronchiolitis	OR	0.804347813	Secondary
Noakes, 2012	Not reported	UK	Healthy pregnant women	83			group	Trial randomized parallel	6 months	wheeze	OR	1.263975143	Secondary
Fleddermann, 2014	Jan 2010 to May 2011	Serbia	Healthy infants	164			Control Formula (CF)	Trial randomized parallel	days	head circumference gain	SMD	0	Secondary
Fleddermann, 2014	Jan 2010 to May 2011	Serbia	Healthy infants	164			Control Formula (CF)	Trial randomized parallel	days	length gain	SMD	0.5	Secondary
Fleddermann, 2014	Jan 2010 to May 2011	Serbia	Healthy infants	164			Control Formula (CF)	Trial randomized parallel	days	weight gain	SMD	0.29683876	Primary
Goor, 2011	2004-2009	Netherlands	Healthy infants	75			DHA vs placebo	Trial randomized parallel	birth	birth weight	SMD	0.031639852	Unspecified
Goor, 2011	2004-2009	Netherlands	Healthy infants	73			DHA+AA vs placebo	Trial randomized parallel	birth	birth weight	SMD	0.163081348	Unspecified
Goor, 2011	2004-2009	Netherlands	Healthy infants	75			DHA vs placebo	Trial randomized parallel	18 months	Development (Mental	SMD	-0.121097274	Unspecified
Goor, 2011	2004-2009	Netherlands	Healthy infants	75			DHA vs placebo	Trial randomized parallel	18 months	development index	SMD	0.405259818	Unspecified
Goor, 2011	2004-2009	Netherlands	Healthy infants	73			DHA+AA vs placebo	Trial randomized parallel	18 months	development index	SMD	0.081668519	Unspecified
Goor, 2011	2004-2009	Netherlands	Healthy infants				DHA vs placebo	Trial randomized parallel	18 months	fluency score		NC	Unspecified
Goor, 2011	2004-2009	Netherlands	Healthy infants				DHA+AA vs placebo	Trial randomized parallel	18 months	fluency score		NC	Unspecified
Goor, 2011	2004-2009	Netherlands	Healthy infants				DHA+AA vs placebo	Trial randomized parallel	18 months	neurological optimality score		NC	Unspecified
Goor, 2011	2004-2009	Netherlands	Healthy infants				DHA vs placebo	Trial randomized parallel	18 months	neurological optimality score		NC	Unspecified
Goor, 2011	2004-2009	Netherlands	Healthy infants	73			DHA+AA vs placebo	Trial randomized parallel	18 months	neurological dysfunction	OR	1.147058845	Unspecified
Goor, 2011	2004-2009	Netherlands	Healthy infants	75			DHA vs placebo	Trial randomized parallel	18 months	neurological dysfunction	OR	2.00980401	Unspecified
Goor, 2011	2004-2009	Netherlands	Healthy infants	75			DHA vs placebo	Trial randomized parallel	18 months	neurological condition	OR	0.995121956	Unspecified
Goor, 2011	2004-2009	Netherlands	Healthy infants	73			DHA+AA vs placebo	Trial randomized parallel	18 months	neurological condition	OR	1.220512867	Unspecified
Goor, 2011	2004-2009	Netherlands	Healthy infants	75			DHA vs placebo	Trial randomized parallel	18 months	neurological dysfunction	OR	0.775210083	Unspecified
Goor, 2011	2004-2009	Netherlands	Healthy infants	73			DHA+AA vs placebo	Trial randomized parallel	18 months	neurological dysfunction	OR	1.720588207	Unspecified
Goor, 2011	2004-2009	Netherlands	Healthy infants	73			DHA+AA vs placebo	Trial randomized parallel	18 months	head circumference	SMD	-0.207277015	Unspecified
Goor, 2011	2004-2009	Netherlands	Healthy infants	75			DHA vs placebo	Trial randomized parallel	18 months	head circumference	SMD	-0.154297054	Unspecified
Goor, 2011	2004-2009	Netherlands	Healthy infants	75			DHA vs placebo	Trial randomized parallel	18 months	length	SMD	-0.278005928	Unspecified
Goor, 2011	2004-2009	Netherlands	Healthy infants	73			DHA+AA vs placebo	Trial randomized parallel	18 months	length	SMD	-0.119455278	Unspecified
Goor, 2011	2004-2009	Netherlands	Healthy infants	73			DHA+AA vs placebo	Trial randomized parallel	18 months	weight	SMD	0	Unspecified
Goor, 2011	2004-2009	Netherlands	Healthy infants	75			DHA vs placebo	Trial randomized parallel	18 months	weight	SMD	-0.157088354	Unspecified
Bouwstra, 2005	1997-2002	Netherlands	Healthy infants	290			group	Trial randomized parallel	18 months	Development (Mental	SMD	-0.177778691	Secondary
Bouwstra, 2005	1997-2002	Netherlands	Healthy infants	315			group	Trial randomized parallel	18 months	Bayley PDI	SMD	-0.11104764	Secondary
Bouwstra, 2005	1997-2002	Netherlands	Healthy infants				group	Trial randomized parallel	18 months	neurological optimality score		NC	Secondary
Bouwstra, 2005	1997-2002	Netherlands	Healthy infants	315			group	Trial randomized parallel	18 months	neurological dysfunction	OR	0.69112426	Secondary

Study	Study years (start date)	Country	Population	(total)	intake	(Baseline)	n-3 type(s)	study_design	Follow-up time	Outcome	Effect size type (OR or SMD)	Reported effect Size	Outcome classification
Bouwstra, 2003	1997-1999	Netherlands	Healthy infants	250			formula	Trial randomized parallel	3 months	movements	OR	1.631578922	Primary
Bouwstra, 2003	1997-1999	Netherlands	Healthy infants	250			formula	Trial randomized parallel	3 months	movements	OR	0.857142806	Primary
Judge, 2012	nr	US	Healthy pregnant women	48		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	birth	birth weight	SMD	0.395035178	Secondary
Judge, 2012	nr	US	Healthy pregnant women	46		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	1 day after birth	(AS, %)	SMD	-0.233474881	Secondary
Judge, 2012	nr	US	Healthy pregnant women	39		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	2 days after birth	(AS, %)	SMD	-0.009735975	Secondary
Judge, 2012	nr	US	Healthy pregnant women	46		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	1 day after birth	Sleep Transition (AQST, %)	SMD	0.187375277	Secondary
Judge, 2012	nr	US	Healthy pregnant women	39		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	2 days after birth	Sleep Transition (AQST, %)	SMD	0.207601592	Secondary
Judge, 2012	nr	US	Healthy pregnant women	46		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	1 day after birth	(Ar/AS)	SMD	0.654765487	Secondary
Judge, 2012	nr	US	Healthy pregnant women	39		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	2 days after birth	(Ar/AS)	SMD	0.090548791	Secondary
Judge, 2012	nr	US	Healthy pregnant women	46		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	1 day after birth	(Ar/QS)	SMD	0.733264267	Secondary
Judge, 2012	nr	US	Healthy pregnant women	39		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	2 days after birth	(Ar/QS)	SMD	0.470817834	Secondary
Judge, 2012	nr	US	Healthy pregnant women	46		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	1 day after birth	Period (LSP, min)	SMD	0.442723185	Secondary
Judge, 2012	nr	US	Healthy pregnant women	39		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	2 days after birth	Period (LSP, min)	SMD	-0.10683021	Secondary
Judge, 2012	nr	US	Healthy pregnant women	46		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	1 day after birth	Period (MSP, min)	SMD	0.110412516	Secondary
Judge, 2012	nr	US	Healthy pregnant women	39		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	2 days after birth	Period (MSP, min)	SMD	-0.007233827	Secondary
Judge, 2012	nr	US	Healthy pregnant women	46		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	1 day after birth	(W, %)	SMD	0.155022875	Secondary
Judge, 2012	nr	US	Healthy pregnant women	39		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	2 days after birth	(W, %)	SMD	0.105503738	Secondary
Judge, 2012	nr	US	Healthy pregnant women	46		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	1 day after birth	(QS,%)	SMD	0.154997826	Secondary
Judge, 2012	nr	US	Healthy pregnant women	39		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	2 days after birth	(QS,%)	SMD	-0.183042795	Secondary
Judge, 2012	nr	US	Healthy pregnant women	46		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	1 day after birth	length (ASBL, min)	SMD	-0.008501874	Secondary
Judge, 2012	nr	US	Healthy pregnant women	39		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	2 days after birth	length (ASBL, min)	SMD	-0.063578799	Secondary
Judge, 2012	nr	US	Healthy pregnant women	46		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	1 day after birth	Sleep Ratio(AS:QS)	SMD	0.278755456	Secondary
Judge, 2012	nr	US	Healthy pregnant women	39		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	2 days after birth	Sleep Ratio(AS:QS)	SMD	0.039062161	Secondary
Judge, 2012	nr	US	Healthy pregnant women	46		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	1 day after birth	length (QSBL, min)	SMD	0.171680912	Secondary
Judge, 2012	nr	US	Healthy pregnant women	39		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	2 days after birth	length (QSBL, min)	SMD	-0.296015859	Secondary
Judge, 2012	nr	US	Healthy pregnant women	46		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	1 day after birth	Transition (T, %)	SMD	0.251199126	Secondary
Judge, 2012	nr	US	Healthy pregnant women	39		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	2 days after birth	Transition (T, %)	SMD	0.458189279	Secondary
Judge, 2012	nr	US	Healthy pregnant women	48		phospholipid (PL)	DHA vs Placebo	Trial randomized parallel	birth	gestational age	SMD	0.446485102	Secondary
Judge, 2007		US	Healthy pregnant women	29			DHA vs placebo	Trial randomized parallel	birth	birth weight	SMD	0.632310689	Secondary
Judge, 2007		US	Healthy pregnant women	29			DHA vs placebo	Trial randomized parallel	birth	gestational age	SMD	0.989868045	Secondary
Malcolm, 2003		NR	NR	37		fish oil and placebo	DHA vs Placebo	Trial randomized parallel	50 weeks (corrected age)	components of the transient	SMD	0.179844633	Primary
Malcolm, 2003		NR	NR	47		fish oil and placebo	DHA vs Placebo	Trial randomized parallel	66 weeks (corrected age)	components of the transient	SMD	-0.492338538	Primary
Malcolm, 2003		NR	NR	9		fish oil and placebo	DHA vs Placebo	Trial randomized parallel	birth	components of the transient	SMD	1.108460188	Primary
Malcolm, 2003		NR	NR	52		fish oil and placebo	DHA vs Placebo	Trial randomized parallel	50 weeks (corrected age)	components of the transient	SMD	-0.341469467	Primary
Malcolm, 2003		NR	NR	51		fish oil and placebo	DHA vs Placebo	Trial randomized parallel	66 weeks (corrected age)	components of the transient	SMD	-0.199502796	Primary
Malcolm, 2003		NR	NR	49		fish oil and placebo	DHA vs Placebo	Trial randomized parallel	birth	components of the transient	SMD	-0.126309648	Primary
Malcolm, 2003		NR	NR	34		fish oil and placebo	DHA vs Placebo	Trial randomized parallel	50 weeks (corrected age)	components of the transient	SMD	0.716261685	Primary
Malcolm, 2003		NR	NR	26		fish oil and placebo	DHA vs Placebo	Trial randomized parallel	66 weeks (corrected age)	components of the transient	SMD	-0.424542576	Primary
Malcolm, 2003		NR	NR	53		fish oil and placebo	DHA vs Placebo	Trial randomized parallel	birth	components of the transient	SMD	0.111686088	Primary
Malcolm, 2003		NR	NR	45		fish oil and placebo	DHA vs Placebo	Trial randomized parallel	50 weeks (corrected age)	components of the transient	SMD	0.17894046	Primary
Malcolm, 2003		NR	NR	51		fish oil and placebo	DHA vs Placebo	Trial randomized parallel	66 weeks (corrected age)	components of the transient	SMD	-0.202426881	Primary
Malcolm, 2003		NR	NR	14		fish oil and placebo	DHA vs Placebo	Trial randomized parallel	birth	components of the transient	SMD	0.521966219	Primary
Malcolm, 2003		NR	NR	47		fish oil and placebo	DHA vs Placebo	Trial randomized parallel	50 weeks (corrected age)	components of the transient	SMD	-0.060580112	Primary
Malcolm, 2003		NR	NR	31		fish oil and placebo	DHA vs Placebo	Trial randomized parallel	66 weeks (corrected age)	components of the transient	SMD	0.047604621	Primary
Malcolm, 2003		NR	NR	55		fish oil and placebo	DHA vs Placebo	Trial randomized parallel	birth	components of the transient	SMD	-0.003236139	Primary
Malcolm, 2003		NR	NR	55		fish oil and placebo	DHA vs Placebo	Trial randomized parallel	(postconceptional age)	head circumference	SMD	-0.103399284	Secondary
Malcolm, 2003		NR	NR	55		fish oil and placebo	DHA vs Placebo	Trial randomized parallel	age)	head circumference	SMD	-0.143804684	Secondary
Malcolm, 2003		NR	NR	55		fish oil and placebo	DHA vs Placebo	Trial randomized parallel	(postconceptional age)	length	SMD	-0.18173489	Secondary
Malcolm, 2003		NR	NR	55		fish oil and placebo	DHA vs Placebo	Trial randomized parallel	age)	length	SMD	-0.206196889	Secondary
Malcolm, 2003		NR	NR	55		fish oil and placebo	DHA vs Placebo	Trial randomized parallel	(postconceptional age)	weight	SMD	-0.135403872	Secondary
Malcolm, 2003		NR	NR	55		fish oil and placebo	DHA vs Placebo	Trial randomized parallel	age)	weight	SMD	-0.498577684	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	103			Fish oil vs Olive oil	Trial randomized parallel	2 months	bmi	SMD	-0.145485193	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	101			High fish vs Olive oil	Trial randomized parallel	2 months	bmi	SMD	-0.21977061	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	57			High fish vs Olive oil	Trial randomized parallel	2.5 years	bmi	SMD	0.218214259	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	70			Fish oil vs Olive oil	Trial randomized parallel	2.5 years	bmi	SMD	0.57349366	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	95			High fish vs Olive oil	Trial randomized parallel	4 months	bmi	SMD	-0.279849559	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	98			Fish oil vs Olive oil	Trial randomized parallel	4 months	bmi	SMD	-0.074872986	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	95			High fish vs Olive oil	Trial randomized parallel	9 months	bmi	SMD	-0.25416404	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	100			Fish oil vs Olive oil	Trial randomized parallel	9 months	bmi	SMD	0.195860922	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	107			High fish vs Olive oil	Trial randomized parallel	1 week	head circumference	SMD	0.295087546	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	110			Fish oil vs Olive oil	Trial randomized parallel	1 week	head circumference	SMD	0.278649122	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	97			High fish vs Olive oil	Trial randomized parallel	2 months	head circumference	SMD	0.329351515	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	100			Fish oil vs Olive oil	Trial randomized parallel	2 months	head circumference	SMD	0.352829069	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	59			High fish vs Olive oil	Trial randomized parallel	2.5 years	head circumference	SMD	0.683686197	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	71			Fish oil vs Olive oil	Trial randomized parallel	2.5 years	head circumference	SMD	0.539367497	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	91			Fish oil vs Olive oil	Trial randomized parallel	4 months	head circumference	SMD	0.2894862	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	91			High fish vs Olive oil	Trial randomized parallel	4 months	head circumference	SMD	0.446112722	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	97			Fish oil vs Olive oil	Trial randomized parallel	9 months	head circumference	SMD	0.380636931	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	87			High fish vs Olive oil	Trial randomized parallel	9 months	head circumference	SMD	0.376579493	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	57			High fish vs Olive oil	Trial randomized parallel	2.5 years	length	SMD	0.365219474	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	70			Fish oil vs Olive oil	Trial randomized parallel	2.5 years	length	SMD	-0.022575691	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	98			Fish oil vs Olive oil	Trial randomized parallel	4 months	length	SMD	0.089712508	Secondary

Study	Study years (start date)	Country	Population	(total)	intake	(Baseline)	n-3 type(s)	study_design	Follow-up time	Outcome	Effect size type (OR or SMD)	Reported effect Size	Outcome classification
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	96			High fish vs Olive oil	Trial randomized parallel	4 months	length	SMD	0.350786001	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	100			Fish oil vs Olive oil	Trial randomized parallel	9 months	length	SMD	0.230778441	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	95			High fish vs Olive oil	Trial randomized parallel	9 months	length	SMD	0.296311766	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women				High fish vs Olive oil	Trial randomized parallel	2 months	length		NC	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women				Fish oil vs Olive oil	Trial randomized parallel	2 months	length		NC	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	72			Fish oil vs Olive oil	Trial randomized parallel	2.5 years	weight	SMD	0.357142866	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	59			High fish vs Olive oil	Trial randomized parallel	2.5 years	weight	SMD	0.349132419	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	100			Fish oil vs Olive oil	Trial randomized parallel	4 months	weight	SMD	0	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	96			High fish vs Olive oil	Trial randomized parallel	4 months	weight	SMD	-0.091694273	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	95			High fish vs Olive oil	Trial randomized parallel	9 months	weight	SMD	-0.04347815	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women	100			Fish oil vs Olive oil	Trial randomized parallel	9 months	weight	SMD	0.297872335	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women				Fish oil vs Olive oil	Trial randomized parallel	2 months	weight		NC	Secondary
Lauritzen, 2005	2000 Follow-up 2.5 years	Denmark	Breast-feeding women				High fish vs Olive oil	Trial randomized parallel	2 months	weight		NC	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women	80	LCPUFA/d		placebo group	Trial randomized parallel	9 months	solving)	SMD	-0.058045622	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women	86	LCPUFA/d		fish oil vs placebo group	Trial randomized parallel	9 months	solving)	SMD	-0.060069013	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women	79	LCPUFA/d		placebo group	Trial randomized parallel	1 year	Development Inventory	SMD	0.142857149	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women	89	LCPUFA/d		fish oil vs placebo group	Trial randomized parallel	1 year	Development Inventory	SMD	-0.15545632	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women		LCPUFA/d		placebo group	Trial randomized parallel	2 years	Development Inventory		NC	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women		LCPUFA/d		fish oil vs placebo group	Trial randomized parallel	2 years	Development Inventory		NC	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women		LCPUFA/d		fish oil vs placebo group	Trial randomized parallel	2 years	Development Inventory		NC	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women		LCPUFA/d		placebo group	Trial randomized parallel	2 years	Development Inventory		NC	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women		LCPUFA/d		placebo group	Trial randomized parallel	1 year	Development Inventory		NC	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women		LCPUFA/d		fish oil vs placebo group	Trial randomized parallel	1 year	Development Inventory		NC	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women	89	LCPUFA/d		fish oil vs placebo group	Trial randomized parallel	1 year	Development Inventory	OR	0.75	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women	79	LCPUFA/d		placebo group	Trial randomized parallel	1 year	Development Inventory	OR	1.041666627	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women	89	LCPUFA/d		fish oil vs placebo group	Trial randomized parallel	1 year	Development Inventory	SMD	0	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women	79	LCPUFA/d		placebo group	Trial randomized parallel	1 year	Development Inventory	SMD	0	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women	71	LCPUFA/d		placebo group	Trial randomized parallel	2 years	Development Inventory	OR	1.010638356	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women	71	LCPUFA/d		fish oil vs placebo group	Trial randomized parallel	2 years	Development Inventory	OR	0.797872365	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women	71	LCPUFA/d		fish oil vs placebo group	Trial randomized parallel	2 years	Development Inventory	OR	0.78125	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women	71	LCPUFA/d		placebo group	Trial randomized parallel	2 years	Development Inventory	OR	1.25	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women	89	LCPUFA/d		fish oil vs placebo group	Trial randomized parallel	1 year	Development Inventory	SMD	-0.419727713	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women	79	LCPUFA/d		placebo group	Trial randomized parallel	1 year	Development Inventory	SMD	-0.141472399	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women	71	LCPUFA/d		placebo group	Trial randomized parallel	2 years	Development Inventory	SMD	0.102434091	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women	71	LCPUFA/d		fish oil vs placebo group	Trial randomized parallel	2 years	Development Inventory	SMD	-0.342880517	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women		LCPUFA/d		fish oil vs placebo group	Trial randomized parallel	1 year	Development Inventory		NC	Secondary
Lauritzen, 2005	enrolled in 1999	Denmark	feeding women		LCPUFA/d		placebo group	Trial randomized parallel	1 year	Development Inventory		NC	Secondary
Lauritzen, 2004	1999	Denmark	lower than average fish	88	LCPUFA		FO Intervention vs Placebo	Trial randomized parallel	2 months	(SWEEP-VEP)	SMD	0	Primary
Lauritzen, 2004	1999	Denmark	lower than average fish	97	LCPUFA		FO Intervention vs Placebo	Trial randomized parallel	4 months	(SWEEP-VEP)	SMD	0.235909283	Primary
Smithers, 2011	August 2008	Australia	pregnant women	182			placebo	Trial randomized parallel	4 months	VEP Latency: 20 min of arc	SMD	0	Secondary
Smithers, 2011	August 2008	Australia	pregnant women	182			placebo	Trial randomized parallel	4 months	VEP Latency: 48 min of arc	SMD	0	Secondary
Smithers, 2011	August 2008	Australia	pregnant women	182			placebo	Trial randomized parallel	4 months	VEP Latency: 69 min of arc	SMD	0.117291354	Secondary
Smithers, 2011	August 2008	Australia	pregnant women	182			placebo	Trial randomized parallel	4 months	VEP acuity (adjusted)	SMD	-0.09137056	Primary
Smithers, 2011	August 2008	Australia	pregnant women	182			placebo	Trial randomized parallel	4 months	VEP acuity (unadjusted)	SMD	-0.090627246	Primary
Mozurkewich, 2013	Oct 2008 - may 2011	US	Healthy pregnant women	79		0.29+-0.18; DHA	Control/Placebo	Trial randomized parallel	26-28 weeks	(BDI)	SMD	-0.164675847	Primary
Mozurkewich, 2013	Oct 2008 - may 2011	US	Healthy pregnant women	80		0.29+-0.18; DHA	Control/Placebo	Trial randomized parallel	26-28 weeks	(BDI)	SMD	-0.592749	Primary
Mozurkewich, 2013	Oct 2008 - may 2011	US	Healthy pregnant women	79		0.29+-0.18; DHA	Control/Placebo	Trial randomized parallel	34-36 weeks	(BDI)	SMD	0.084774867	Primary
Mozurkewich, 2013	Oct 2008 - may 2011	US	Healthy pregnant women	80		0.29+-0.18; DHA	Control/Placebo	Trial randomized parallel	34-36 weeks	(BDI)	SMD	-0.142899796	Primary
Mozurkewich, 2013	Oct 2008 - may 2011	US	Healthy pregnant women	80		0.29+-0.18; DHA	Control/Placebo	Trial randomized parallel	6-8 weeks post-partum	(BDI)	SMD	-0.123252839	Primary
Mozurkewich, 2013	Oct 2008 - may 2011	US	Healthy pregnant women	79		0.29+-0.18; DHA	Control/Placebo	Trial randomized parallel	6-8 weeks post-partum	(BDI)	SMD	0.036273193	Primary
Mozurkewich, 2013	Oct 2008 - may 2011	US	Healthy pregnant women	78		0.29+-0.18; DHA	Control/Placebo	Trial randomized parallel	birth	birth weight	SMD	0.92729032	Secondary
Mozurkewich, 2013	Oct 2008 - may 2011	US	Healthy pregnant women	80		0.29+-0.18; DHA	Control/Placebo	Trial randomized parallel	birth	birth weight	SMD	0.168324068	Secondary
Mozurkewich, 2013	Oct 2008 - may 2011	US	Healthy pregnant women	79		0.29+-0.18; DHA	Control/Placebo	Trial randomized parallel	during pregnancy	preeclampsia	OR	2.317073107	Secondary
Mozurkewich, 2013	Oct 2008 - may 2011	US	Healthy pregnant women	80		0.29+-0.18; DHA	Control/Placebo	Trial randomized parallel	during pregnancy	preeclampsia	OR	0.594512224	Secondary
Mozurkewich, 2013	Oct 2008 - may 2011	US	Healthy pregnant women	80		0.29+-0.18; DHA	Control/Placebo	Trial randomized parallel	birth	gestational age	SMD	0	Secondary
Mozurkewich, 2013	Oct 2008 - may 2011	US	Healthy pregnant women	79		0.29+-0.18; DHA	Control/Placebo	Trial randomized parallel	birth	gestational age	SMD	1.041483521	Secondary
Makrides, 2009	2005	Australia	feeding women	657			tuna oil capsules vs Placebo	Trial randomized parallel	18 months	Development (Mental	SMD	0.118830428	Primary
Makrides, 2009	2005	Australia	feeding women	657			tuna oil capsules vs Placebo	Trial randomized parallel	18 months	development index	SMD	0.06171966	Secondary
Unay, 2004	2000-2001	Turkey	Healthy infants	44			Formula A vs Formula B	Trial randomized parallel	16 weeks	potentials: interpeak latency I-	SMD	0.598671079	Unspecified
Unay, 2004	2000-2001	Turkey	Healthy infants	44			Formula A vs Formula B	Trial randomized parallel	16 weeks	potentials: interpeak latency I-	SMD	0.773020685	Unspecified
Unay, 2004	2000-2001	Turkey	Healthy infants	44			Formula A vs Formula B	Trial randomized parallel	16 weeks	potentials: interpeak latency III-	SMD	0.695141316	Unspecified
Unay, 2004	2000-2001	Turkey	Healthy infants	44			Formula A vs Formula B	Trial randomized parallel	16 weeks	potentials: wave I	SMD	0.59218657	Unspecified
Unay, 2004	2000-2001	Turkey	Healthy infants	44			Formula A vs Formula B	Trial randomized parallel	16 weeks	potentials: wave III	SMD	1.096204042	Unspecified
Unay, 2004	2000-2001	Turkey	Healthy infants	44			Formula A vs Formula B	Trial randomized parallel	16 weeks	potentials: wave V	SMD	1.541923404	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	215	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	birth	birth weight	SMD	-0.006778704	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	154	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	18 months	Bayley Scales of Infant	OR	0.9009009	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	154	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	18 months	Bayley Scales of Infant	OR	1.593172073	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	154	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	18 months	Bayley Scales of Infant	OR	1.824324369	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	159	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	14 months	Infant MacArthur	OR	2.076923132	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	134	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	18 months	Infant MacArthur	OR	1.880136967	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	159	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	14 months	Infant MacArthur	OR	2.423076868	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	134	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	18 months	Infant MacArthur	OR	2.051058531	Unspecified

Study	Study years (start date)	Country	Population	(total)	intake	(Baseline)	n-3 type(s)	study_design	Follow-up time	Outcome	Effect size type (OR or SMD)	Reported effect Size	Outcome classification
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	134	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	18 months	Toddler MacArthur	OR	2.172602654	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	154	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	18 months	Bayley Scales of Infant	OR	1.189189196	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	154	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	18 months	Bayley Scales of Infant	OR	1.132561088	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	176	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	12 months	acuity>==13 cycles/degree	OR	1.172839522	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	184	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	2 months	acuity>==3.3 cycles/degree	OR	2.219444513	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	178	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	12 months	length-for-age z score	SMD	-0.303669691	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	158	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	18 months	length-for-age z score	SMD	-0.222088635	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	194	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	2 months	length-for-age z score	SMD	-0.113076374	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	196	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	6 months	length-for-age z score	SMD	-0.076164596	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	183	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	9 months	length-for-age z score	SMD	-0.262741685	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	175	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	12 months	weight-for-age z score	SMD	-0.029014073	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	144	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	18 months	weight-for-age z score	SMD	-0.059054446	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	191	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	2 months	weight-for-age z score	SMD	-0.231481478	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	196	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	6 months	weight-for-age z score	SMD	-0.150995702	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	181	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	9 months	weight-for-age z score	SMD	0.009529548	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	174	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	12 months	weight-for-length z score	SMD	0.173458695	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	144	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	18 months	weight-for-length z score	SMD	0	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	191	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	2 months	weight-for-length z score	SMD	-0.228453875	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	196	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	6 months	weight-for-length z score	SMD	-0.1455805	Unspecified
Mulder, 2014	2004 to 2008	Canada	Healthy pregnant women	181	97.5th	Phusphatidylethanol	DHA supplement vs placebo	Trial randomized parallel	9 months	weight-for-length z score	SMD	0.206030265	Unspecified
Escamilla-Nunez, 2014	2005-2009	Mexico	allergies		(25th, 75th			Trial randomized parallel		breathing difficulty			Primary
Escamilla-Nunez, 2014	2005-2009	Mexico	allergies		(25th, 75th			Trial randomized parallel		cough			Primary
Escamilla-Nunez, 2014	2005-2009	Mexico	allergies	869	(25th, 75th		DHA vs Placebo	Trial randomized parallel	18 months	and/or nasal discharge, fever	OR	1	Primary
Escamilla-Nunez, 2014	2005-2009	Mexico	allergies		(25th, 75th			Trial randomized parallel		wheezing			Primary
Harper, 2010	01. 2005 - 10. 2006	US	At risk for preterm labor				DHA+EPA vs placebo	Trial randomized parallel	birth	birth weight		NC	Secondary
Harper, 2010	01. 2005 - 10. 2006	US	At risk for preterm labor					Trial randomized parallel		birthweight <2500g			Secondary
Harper, 2010	01. 2005 - 10. 2006	US	At risk for preterm labor	852			DHA+EPA vs placebo	Trial randomized parallel	during pregnancy	hypertension	OR	1.043478251	Secondary
Harper, 2010	01. 2005 - 10. 2006	US	At risk for preterm labor	837			DHA+EPA vs placebo	Trial randomized parallel	birth	SGA less than 10th percentile	OR	1.220000029	Secondary
Harper, 2010	01. 2005 - 10. 2006	US	At risk for preterm labor	837			DHA+EPA vs placebo	Trial randomized parallel	birth	birthweight <1500g	OR	1.161632299	Secondary
Harper, 2010	01. 2005 - 10. 2006	US	At risk for preterm labor	837			DHA+EPA vs placebo	Trial randomized parallel	birth	birthweight <2500g	OR	1.240892529	
Harper, 2010	01. 2005 - 10. 2006	US	At risk for preterm labor				DHA+EPA vs placebo	Trial randomized parallel	birth	gestational age		NC	Secondary
Harper, 2010	01. 2005 - 10. 2006	US	At risk for preterm labor	852			DHA+EPA vs placebo	Trial randomized parallel	birth	incidence of premature birth	OR	1.101587057	Primary
Stein, 2012	Feb 2005-Feb 2007	NR	pregnant women	900			DHA vs Placebo	Trial randomized parallel	birth	birthweight <2500g	OR	1.394736886	Primary
Stein, 2012	Feb 2005-Feb 2007	NR	pregnant women	749			DHA vs Placebo	Trial randomized parallel	1 month	latency 1	SMD	0.066548586	Primary
Stein, 2012	Feb 2005-Feb 2007	NR	pregnant women	664			DHA vs Placebo	Trial randomized parallel	3 months	latency 1	SMD	0	Primary
Stein, 2012	Feb 2005-Feb 2007	NR	pregnant women	749			DHA vs Placebo	Trial randomized parallel	1 month	latency 1-3	SMD	0.031397559	Primary
Stein, 2012	Feb 2005-Feb 2007	NR	pregnant women	664			DHA vs Placebo	Trial randomized parallel	3 months	latency 1-3	SMD	-0.035714287	Primary
Stein, 2012	Feb 2005-Feb 2007	NR	pregnant women	749			DHA vs Placebo	Trial randomized parallel	1 month	latency 1-5	SMD	0.05330497	Primary
Stein, 2012	Feb 2005-Feb 2007	NR	pregnant women	664			DHA vs Placebo	Trial randomized parallel	3 months	latency 1-5	SMD	0.07692308	Primary
Stein, 2012	Feb 2005-Feb 2007	NR	pregnant women	749			DHA vs Placebo	Trial randomized parallel	1 month	latency 3	SMD	0.030762423	Primary
Stein, 2012	Feb 2005-Feb 2007	NR	pregnant women	664			DHA vs Placebo	Trial randomized parallel	3 months	latency 3	SMD	-0.03076845	Primary
Stein, 2012	Feb 2005-Feb 2007	NR	pregnant women	749			DHA vs Placebo	Trial randomized parallel	1 month	latency 3-5	SMD	0	Primary
Stein, 2012	Feb 2005-Feb 2007	NR	pregnant women	664			DHA vs Placebo	Trial randomized parallel	3 months	latency 3-5	SMD	0.088181496	Primary
Stein, 2012	Feb 2005-Feb 2007	NR	pregnant women	749			DHA vs Placebo	Trial randomized parallel	1 month	latency 5	SMD	0.066548586	Primary
Stein, 2012	Feb 2005-Feb 2007	NR	pregnant women	664			DHA vs Placebo	Trial randomized parallel	3 months	latency 5	SMD	0.097546339	Primary
Stein, 2012	Feb 2005-Feb 2007	NR	pregnant women	679			DHA vs Placebo	Trial randomized parallel	3 months	Amplitude P	SMD	-0.06494198	Primary
Stein, 2012	Feb 2005-Feb 2007	NR	pregnant women	679			DHA vs Placebo	Trial randomized parallel	6 months	Amplitude P	SMD	-0.014183416	Primary
Stein, 2012	Feb 2005-Feb 2007	NR	pregnant women	679			DHA vs Placebo	Trial randomized parallel	3 months	Latency N1	SMD	-0.017955747	Primary
Stein, 2012	Feb 2005-Feb 2007	NR	pregnant women	679			DHA vs Placebo	Trial randomized parallel	6 months	Latency N1	SMD	0.094251022	Primary
Stein, 2012	Feb 2005-Feb 2007	NR	pregnant women	679			DHA vs Placebo	Trial randomized parallel	3 months	Latency N3	SMD	0.096027076	Primary
Stein, 2012	Feb 2005-Feb 2007	NR	pregnant women	679			DHA vs Placebo	Trial randomized parallel	6 months	Latency N3	SMD	0.034909811	Primary
Stein, 2012	Feb 2005-Feb 2007	NR	pregnant women	679			DHA vs Placebo	Trial randomized parallel	3 months	Latency P1	SMD	0.027921384	Primary
Stein, 2012	Feb 2005-Feb 2007	NR	pregnant women	679			DHA vs Placebo	Trial randomized parallel	6 months	Latency P1	SMD	0.055364583	Primary
Stein, 2012	Feb 2005-Feb 2007	NR	pregnant women					Trial randomized parallel					Primary
Lagemaat, 2011	2003 - 2006	Netherlands	weight infants	87		Mean(SD) AA PDF:	HM vs Term Formula (TF)	Trial randomized parallel	term age	head circumference	SMD	-0.13333334	Unspecified
Lagemaat, 2011	2003 - 2006	Netherlands	weight infants	93		Mean(SD) AA PDF:	PDF vs Term Formula (TF)	Trial randomized parallel	term age	head circumference	SMD	0.074617639	Unspecified
Lagemaat, 2011	2003 - 2006	Netherlands	weight infants	87		Mean(SD) AA PDF:	HM vs Term Formula (TF)	Trial randomized parallel	term age	length	SMD	-0.215482861	Unspecified
Lagemaat, 2011	2003 - 2006	Netherlands	weight infants	93		Mean(SD) AA PDF:	PDF vs Term Formula (TF)	Trial randomized parallel	term age	length	SMD	0	Unspecified
Lagemaat, 2011	2003 - 2006	Netherlands	weight infants	87		Mean(SD) AA PDF:	HM vs Term Formula (TF)	Trial randomized parallel	term age	weight	SMD	-0.109594747	Unspecified
Lagemaat, 2011	2003 - 2006	Netherlands	weight infants	93		Mean(SD) AA PDF:	PDF vs Term Formula (TF)	Trial randomized parallel	term age	weight	SMD	-0.111676455	Unspecified
D'Vaz, 2012	2005-2009	Australia	allergies	323			Fish oil group vs Placebo	Trial randomized parallel	12 months	mediated food allergy,	OR	1.044960976	Primary
D'Vaz, 2012	2005-2009	Australia	allergies	323			Fish oil group vs Placebo	Trial randomized parallel	12 months	food allergy	OR	1.229120731	Primary
D'Vaz, 2012	2005-2009	Australia	allergies	323			Fish oil group vs Placebo	Trial randomized parallel	12 months	eczema	OR	1.041327238	Primary
D'Vaz, 2012	2005-2009	Australia	allergies	323			Fish oil group vs Placebo	Trial randomized parallel	12 months	asthma	OR	NC	Primary
D'Vaz, 2012	2005-2009	Australia	allergies	323			Fish oil group vs Placebo	Trial randomized parallel	12 months	persistent cough	OR	0.845166802	Primary
D'Vaz, 2012	2005-2009	Australia	allergies	323			Fish oil group vs Placebo	Trial randomized parallel	6 months	persistent cough	OR	1.327450395	Primary
D'Vaz, 2012	2005-2009	Australia	allergies	323			Fish oil group vs Placebo	Trial randomized parallel	12 months	recurrent wheeze	OR	0.711719394	Primary
D'Vaz, 2012	2005-2009	Australia	allergies	323			Fish oil group vs Placebo	Trial randomized parallel	6 months	recurrent wheeze	OR	1.096589446	Primary
Collins, 2011	2001-2007	Australia	women Breast-feeding	456			High DHA vs standard DHA	Trial randomized parallel	12 months	head circumference	SMD	-0.055555556	Secondary
Collins, 2011	2001-2007	Australia	women Breast-feeding	587			High DHA vs standard DHA	Trial randomized parallel	18 months	head circumference	SMD	0	Secondary
Collins, 2011	2001-2007	Australia	women Breast-feeding	601			High DHA vs standard DHA	Trial randomized parallel	4 months	head circumference	SMD	-0.117647052	Secondary
Collins, 2011	2001-2007	Australia	women Breast-feeding	465			High DHA vs standard DHA	Trial randomized parallel	12 months	length	SMD	0.054768324	Secondary

Study	Study years (start date)	Country	Population	(total)	intake	(Baseline)	n-3 type(s)	study_design	Follow-up time	Outcome	Effect size type (OR or SMD)	Reported effect Size	Outcome classification
Collins, 2011	2001-2007	Australia	women Breast-feeding	592			High DHA vs standard DHA	Trial randomized parallel	18 months	length	SMD	0.177277058	Secondary
Collins, 2011	2001-2007	Australia	women Breast-feeding	605			High DHA vs standard DHA	Trial randomized parallel	4 months	length	SMD	0.030263307	Secondary
Collins, 2011	2001-2007	Australia	women Breast-feeding	471			High DHA vs standard DHA	Trial randomized parallel	12 months	weight	SMD	0.085180961	Secondary
Collins, 2011	2001-2007	Australia	women Breast-feeding	598			High DHA vs standard DHA	Trial randomized parallel	18 months	weight	SMD	0.154532641	Secondary
Collins, 2011	2001-2007	Australia	women Breast-feeding	615			High DHA vs standard DHA	Trial randomized parallel	4 months	weight	SMD	0.014466298	Secondary
Escolano-Margarit, 2011	2001-2008	Germany, Spain, Hungary	Healthy pregnant women	167		plasma DHA	fish oil vs placebo	Trial randomized parallel	5.5 years	Hempel exam	OR	0.993518531	Secondary
Escolano-Margarit, 2011	2001-2008	Germany, Spain, Hungary	Healthy pregnant women	148		plasma DHA	fish oil vs placebo	Trial randomized parallel	5.5 years	Towen exam	OR	1.000791192	Secondary
Imhoff-Kunsch, 2011	February 2005 - February 2007	Mexico	Healthy pregnant women	849			DHA vs Placebo	Trial randomized parallel	1 month (preceding 15 days)	nasal congestion, nasal	OR	1.18617022	Secondary
Imhoff-Kunsch, 2011	February 2005 - February 2007	Mexico	Healthy pregnant women	834			DHA vs Placebo	Trial randomized parallel	3 months	nasal congestion, nasal	OR	1.166666746	Secondary
Imhoff-Kunsch, 2011	February 2005 - February 2007	Mexico	Healthy pregnant women	834			DHA vs Placebo	Trial randomized parallel	6 months (preceding 15 days)	nasal congestion, nasal	OR	1.008658051	Secondary
Imhoff-Kunsch, 2011	February 2005 - February 2007	Mexico	Healthy pregnant women	849			DHA vs Placebo	Trial randomized parallel	1 month (preceding 15 days)	cough	OR	1.157894731	Secondary
Imhoff-Kunsch, 2011	February 2005 - February 2007	Mexico	Healthy pregnant women	834			DHA vs Placebo	Trial randomized parallel	3 months	cough	OR	1.238341928	Secondary
Imhoff-Kunsch, 2011	February 2005 - February 2007	Mexico	Healthy pregnant women	834			DHA vs Placebo	Trial randomized parallel	6 months (preceding 15 days)	cough	OR	0.993957698	Secondary
Imhoff-Kunsch, 2011	February 2005 - February 2007	Mexico	Healthy pregnant women	849			DHA vs Placebo	Trial randomized parallel	1 month (preceding 15 days)	difficulty breathing	OR	0.958333373	Secondary
Imhoff-Kunsch, 2011	February 2005 - February 2007	Mexico	Healthy pregnant women	834			DHA vs Placebo	Trial randomized parallel	3 months	difficulty breathing	OR	0.827586174	Secondary
Imhoff-Kunsch, 2011	February 2005 - February 2007	Mexico	Healthy pregnant women	834			DHA vs Placebo	Trial randomized parallel	6 months (preceding 15 days)	difficulty breathing	OR	1.214285731	Secondary
Imhoff-Kunsch, 2011	February 2005 - February 2007	Mexico	Healthy pregnant women	849			DHA vs Placebo	Trial randomized parallel	1 month (preceding 15 days)	nasal congestion	OR	1.163120627	Secondary
Imhoff-Kunsch, 2011	February 2005 - February 2007	Mexico	Healthy pregnant women	834			DHA vs Placebo	Trial randomized parallel	3 months	nasal congestion	OR	1.131474137	Secondary
Imhoff-Kunsch, 2011	February 2005 - February 2007	Mexico	Healthy pregnant women	834			DHA vs Placebo	Trial randomized parallel	6 months (preceding 15 days)	nasal congestion	OR	0.945945978	Secondary
Imhoff-Kunsch, 2011	February 2005 - February 2007	Mexico	Healthy pregnant women	849			DHA vs Placebo	Trial randomized parallel	1 month (preceding 15 days)	nasal secretion	OR	1.521126747	Secondary
Imhoff-Kunsch, 2011	February 2005 - February 2007	Mexico	Healthy pregnant women	834			DHA vs Placebo	Trial randomized parallel	3 months	nasal secretion	OR	1.15436244	Secondary
Imhoff-Kunsch, 2011	February 2005 - February 2007	Mexico	Healthy pregnant women	834			DHA vs Placebo	Trial randomized parallel	6 months (preceding 15 days)	nasal secretion	OR	1.046099305	Secondary
Imhoff-Kunsch, 2011	February 2005 - February 2007	Mexico	Healthy pregnant women	849			DHA vs Placebo	Trial randomized parallel	1 month (preceding 15 days)	phlegm	OR	1.142857194	Secondary
Imhoff-Kunsch, 2011	February 2005 - February 2007	Mexico	Healthy pregnant women	834			DHA vs Placebo	Trial randomized parallel	3 months	phlegm	OR	0.953846157	Secondary
Imhoff-Kunsch, 2011	February 2005 - February 2007	Mexico	Healthy pregnant women	834			DHA vs Placebo	Trial randomized parallel	6 months (preceding 15 days)	phlegm	OR	1.012552261	Secondary
Imhoff-Kunsch, 2011	February 2005 - February 2007	Mexico	Healthy pregnant women	849			DHA vs Placebo	Trial randomized parallel	1 month (preceding 15 days)	wheezing	OR	0.843373537	Secondary
Imhoff-Kunsch, 2011	February 2005 - February 2007	Mexico	Healthy pregnant women	834			DHA vs Placebo	Trial randomized parallel	3 months	wheezing	OR	1.157142878	Secondary
Imhoff-Kunsch, 2011	February 2005 - February 2007	Mexico	Healthy pregnant women	834			DHA vs Placebo	Trial randomized parallel	6 months (preceding 15 days)	wheezing	OR	0.915966392	Secondary
Marks, 2006	1997-2004	Australia	allergies	516			Active vs Diet control	Trial randomized parallel	5 years	test)	OR	1.062451601	Secondary
Marks, 2006	1997-2004	Australia	allergies	516			Active vs Diet control	Trial randomized parallel	5 years	rhinitis	OR	0.985346794	Secondary
Marks, 2006	1997-2004	Australia	allergies	516			Active vs Diet control	Trial randomized parallel	5 years	current eczema	OR	1.171575189	Secondary
Marks, 2006	1997-2004	Australia	allergies	516			Active vs Diet control	Trial randomized parallel	5 years	cough without cold	OR	0.701861978	Secondary
Marks, 2006	1997-2004	Australia	allergies	516			Active vs Diet control	Trial randomized parallel	5 years	frequent wheeze	OR	0.857831299	Secondary
Marks, 2006	1997-2004	Australia	allergies	516			Active vs Diet control	Trial randomized parallel	5 years	probable current asthma	OR	0.882044315	Primary
Palmer, 2013	Domino study)	Australia	of allergy	706			Fish oil vs Control	Trial randomized parallel	3 years	allergic rhinitis	OR	1.209730387	Primary
Palmer, 2013	Domino study)	Australia	of allergy	706			Fish oil vs Control	Trial randomized parallel	3 years	food allergy	OR	0.846811295	Primary
Palmer, 2013	Domino study)	Australia	of allergy	706			Fish oil vs Control	Trial randomized parallel	3 years	eczema	OR	4.645364761	Primary
Palmer, 2013	Domino study)	Australia	of allergy	706			Fish oil vs Control	Trial randomized parallel	3 years	asthma	OR	0.90729785	Primary
Drover, 2012	NR	US	Healthy infants	42			Control group	Trial randomized parallel	2.5 years	(SRC)	SMD	0.236179456	Secondary
Drover, 2012	NR	US	Healthy infants	46			Control group	Trial randomized parallel	2.5 years	(SRC)	SMD	0.320607185	Secondary
Drover, 2012	NR	US	Healthy infants	43			Control group	Trial randomized parallel	2.5 years	(SRC)	SMD	0.394611269	Secondary
Atwell, 2013	2001-2005	Australia	Preterm infants	657			High DHA vs Standard DHA	Trial randomized parallel	18 months	for lower respiratory	OR	1.094693184	Secondary
Linnamaa, 2010	2004-2008	Finland	pregnant women	241			Intervention vs Controls	Trial randomized parallel	birth	birth weight	SMD	-0.008606554	Secondary
Linnamaa, 2010	2004-2008	Finland	pregnant women	202			Intervention vs Controls	Trial randomized parallel	12 months	positive egg skin test	OR	1.211538434	Secondary
Linnamaa, 2010	2004-2008	Finland	pregnant women	166			Intervention vs Controls	Trial randomized parallel	24 months	positive egg skin test	OR	1.589080453	Secondary
Linnamaa, 2010	2004-2008	Finland	pregnant women	238			Intervention vs Controls	Trial randomized parallel	3 months	positive egg skin test	OR	0.888888896	Secondary
Linnamaa, 2010	2004-2008	Finland	pregnant women	210			Intervention vs Controls	Trial randomized parallel	12 months	atopic dermatitis	OR	1.432506919	Primary
Linnamaa, 2010	2004-2008	Finland	pregnant women	177			Intervention vs Controls	Trial randomized parallel	24 months	atopic dermatitis	OR	1	Primary
Linnamaa, 2010	2004-2008	Finland	pregnant women	241			Intervention vs Controls	Trial randomized parallel	3 months	atopic dermatitis	OR	1	Primary