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Original Research Article

Early-Life Cumulative Intake of Ultra-Processed Foods and Subcortical Brain Volume at Age Six Years: A Prospective Cohort Study

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A B S T R A C T

Background: Diet quality during early life may influence neurodevelopmental trajectories, but the associations between ultra-processed food (UPF) intake and neurocognitive outcomes has not been broadly examined.

Objective: To examine whether cumulative UPF intake from infancy through early childhood is associated with cognitive performance at 24 and 72 months and with subcortical brain volumes at 72 months.

Methods: In this prospective birth cohort study, multiple 24-hour dietary assessments were used to calculate the percentage of UPF-calorie intake, using the Nova classification system. Cumulative UPF intake from 6 to 24 and from 6 to 72 months was summarized as the area under the curve. Cognitive performance was assessed at 24 and 72 months, and subcortical brain volumes were derived from T1-weighted MRI scans at 72 months. Associations were examined using multiple univariate linear regressions with false discovery rate (FDR) correction.

Results: Cumulative UPF intake was not associated with cognitive performance at either 24 months (n=144, 57% girls) or 72 months (n=93, 59% girls). In contrast, cumulative UPF intake from 6 to 72 months (n=79, 58% girls) was inversely associated with the volumes of the bilateral accumbens, left amygdala, bilateral pallidum, left putamen, and bilateral thalamus (all FDR-adjusted $p < 0.05$). On average, a 10% higher proportion of cumulative UPF intake was associated with a 1.92% lower subcortical volume (CI95% -3.29, -0.58). Associations were consistent across exposure windows (6–24 months compared with 72 months) and UPF subtypes (e.g., snacks, fast food).

Conclusions: Greater cumulative UPF intake from infancy through early childhood was associated with differences in neurodevelopment at age six years. These findings highlight this period as a potentially relevant window for nutrition-focused prevention efforts. Future studies are needed to clarify specific windows, neurobiological mechanisms, identify specific nutritional factors, and define long-term implications.

Keywords: Neurodevelopment, Brain, Cognition, Nutrition, Ultra-processed foods, Cohort, Infancy, Childhood, Early-life

Introduction

Ultra-processed foods (UPFs) are industrial formulations designed to enhance food palatability, convenience, and shelf life [1]. In the US, they account for more than half of total energy intake among children aged 1–5 years [2]. Infancy and early childhood represent a period of heightened neuroplasticity [3], during which diet quality may influence neurodevelopment [4]. Early dietary patterns, including higher UPF consumption, tend to persist across development [5], suggesting that exposure initiated during this sensitive period may be sustained over time. Observational studies have reported associations between higher UPF exposure and poorer physical [6] and mental health [7], though causality remains unestablished, and it is unclear whether these associations reflect nutritional composition or food processing per se. As neurodevelopment may represent a pathway linking early diet to later health outcomes, these gaps support examining whether early-life UPF exposure is associated with neurodevelopment.

Higher UPF intake has been associated with adverse cognitive [8–10] and brain-related outcomes [11,12]. In adults, higher intake has been linked to cognitive impairment [9] and dementia [10], while in children and adolescents, inverse associations between UPF-subtypes

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(e.g., fast foods) and attention, inhibitory control, and working memory have been reported [8]. Neuroimaging evidence, however, remains limited and inconsistent: higher UPF intake has been associated with lower intracellular volume fraction in subcortical regions in adults [11], whereas in children, higher intake of added sugars, common in UPFs, has been linked to greater hippocampal volumes [12]. While mechanisms remain unclear, animal studies suggest roles for altered neuroplasticity [13] and neuroimmune signaling [14]. Longitudinal studies further note that early variation in subcortical regions is associated with poorer later physical [15] and mental health [16]. Together, these findings motivate investigation of associations between early UPF intake and brain development.

Interpretation of existing evidence is limited by methodological constraints. UPFs overlap with foods high in added sugars, sodium, and unhealthy fats, and many studies rely on restricted definitions (e.g., sugar-sweetened beverages [SSBs], snacks), complicating the separation of nutritional composition from processing. As a result, observed associations may reflect underlying nutritional content rather than processing per se, and there is no clear consensus on whether processing alone has adverse health effects. In addition, most pediatric studies rely on single dietary assessments, limiting characterization of cumulative exposure and critical windows of susceptibility. Consequently, it remains unclear when neurocognitive associations with UPF first emerge [5].

We examined whether cumulative UPF intake across early childhood is associated with cognitive outcomes and subcortical brain volumes in a prospective birth cohort of Latino/Hispanic children. UPF intake was assessed at 6, 12, 24, and 72 months using repeated 24-hour dietary recalls and classified according to the Nova system. Cognitive performance was measured at 24 and 72 months, and MRI-derived subcortical brain volumes were collected at 72 months. We examined cumulative UPF intake in relation to cognition at 24 and 72 months, and relative to subcortical brain volumes at 72 months. Additional analyses evaluated differences by exposure timing and UPF subtype. We hypothesized that higher cumulative UPF intake would be associated with lower cognitive performance and with differences in subcortical brain volumes, without specifying direction for the latter, given mixed prior evidence [11,12].

Methods

Participants

Between 2016 and 2019, mother-infant dyads were enrolled at 1 month postpartum for two related studies using the same methodology: Mother's Milk (n=219) and Mamitas (n=211). Mother's Milk was an observational cohort study examining links between lactation and infant development, while Mamitas was a home-based intervention targeting maternal SSB intake. In both studies, mothers self-identified as Latino/Hispanic and resided in the Southern California area at enrollment. These studies were interested in this population given the disproportionate burden of early childhood obesity and metabolic health disparities faced by the Latino/Hispanic community, compounded by culturally prevalent dietary patterns such as high UPF intake [17], including SSBs. To be eligible, mothers had to be over 18, fluent in English or Spanish, and have a singleton, healthy pregnancy. Exclusion criteria included the use of illicit drugs or maternal medication that could affect physical or mental heath, infant prematurity, low birth weight, or fetal malformations. Inclusion and exclusion criteria were identical across studies. Follow-up assessments were conducted at 6 (n=368), 12 (n=339), and 24 months (n=315).

At 72 months, 140 participants from both cohorts were followed in the El Sendero Study, a longitudinal follow-up expanding data collection into early childhood to explore the role of nutritional and environmental exposures on brain structure and function (NCT05551650). As infant dietary intake did not differ by intervention in Mamitas [18], the two cohorts were analyzed jointly. The study received IRB approval (CHLA-18-00576). Caregivers, defined as the child's primary guardian (i.e., the mother or father), gave written informed consent, and children provided assent.

Demographics and anthropometric assessments

At 1 month of age, maternal and perinatal characteristics were collected, including pre-pregnancy weight and height (self-reported; used to compute body mass index as kg/m^2), maternal age at delivery, mode of delivery (vaginal, C-section), gestational diabetes status, infant birth weight, delivery timing (more than two weeks early, less than two weeks early, on term, less than two weeks late, more than two weeks late), and highest educational attainment within the household by either parent (less than high-school, high-school graduate or similar, some college). At 1 and 6 months postpartum, mothers reported the daily frequency of lactation and formula feeding for the previous week. These data were used to estimate the ratio of human to formula milk at 1 and 6 months. The ratios at 1 and 6 months were weighted by the duration of the corresponding intervals (0–1 month and 1–6 months, respectively), and the weighted mean was computed, with higher values indicating a greater proportion of human milk feeding. The child's weight and height were measured at 1, 6, 12, 24, and 72 months.

Children's dietary recall collection and initial quality control of NDSR data

Two separate 24-hour dietary recalls, one on a weekday and one on a weekend day, were conducted at 6, 12, 24, and 72 months. A registered dietitian and trained staff reviewed recalls with mothers to estimate portion sizes using the Nutrition Data System for Research (NDSR) Food Amounts Booklet. Nutritional data were obtained via NDSR software (2021, University of Minnesota). When a participant was unable to recall one or more meals from the previous 24 hours, a third recall was attempted. Only valid, duplicated recalls were kept. Consequently, six participants (n=6) were removed at 6 months, 5 at 12 months, 6 at 24 months, and 2 at 72 months. Participants with recall data for two identical days (e.g., two weekend days) were removed: 16 at 6 months, 6 at 12 months, 4 at 24 months, and 2 at 72 months.

Ultra-Processed Food (UPF) classification

Across dietary recalls at 6, 12, 24, and 72 months, 2,159 unique food names were identified. After removing water, spices, and isolated ingredients (n=56), alongside early feeding entries such as formula and human milk (n=25), 2,074 items remained eligible. Infant formula, a major contributor to UPF exposure in early life, was not included in the UPF classification to avoid conflating UPF intake with early feeding mode, which is related to a range of developmental and socioeconomic factors [19–22]. Food items were classified as UPFs using level 4 of the Nova system, defined as industrial formulations containing little or no whole foods and including additives such as flavorings, sweeteners, emulsifiers, or other cosmetic ingredients, or substances added to compensate for nutrients lost during processing (e.g., synthetic vitamins and minerals) [23]. Classification was based on food descriptions and, when available, ingredient information to distinguish minimally processed or processed foods from ultra-processed formulations. The classification involved multiple steps: cross-checking against previous

studies, a first-pass review of food descriptions and ingredient information by trained raters, and a second-pass to resolve discrepancies. Each UPF item was assigned a certainty scale (1=probable, 2=very likely, 3=definitely UPF) by each rater based on the availability and specificity of information, with higher confidence assigned when ingredient lists or detailed descriptions clearly indicated industrial formulations. Of the 2,074 items, 1,167 were classified as UPF, accounting for 56.3% of the total items. Of these 1,167 UPF items, 1,036 were rated as definitely UPF (rating 3), 117 as very likely UPF (rating 2), and 14 as probably UPF (rating 1). Analyses included UPFs rated 1-3. The list of foods is available in the Online Supplementary Materials (see the file AJCN_UPF-brain_JOttino_foodlist.xslx). Supplementary analyses explored alternative ratings (e.g., only UPF ratings 1-2).

UPFs were further classified into SSBs, snacks, fast foods, and others (e.g., frozen and dry-instant meals, baked goods, cereals, lunchmeats, dairy products). To address the possibility that UPF intake reflects poor diet quality, we computed energy-adjusted nutrient densities (units per 1000 kcal) for selected nutrients relevant to neurodevelopment and overall health, including dietary fiber, docosahexaenoic acid (DHA), iron, zinc, magnesium, choline, and vitamins D, B9, and B12 [24]. These measures were examined in supplementary analyses.

Quality assurance and cumulative UPF intake calculation

To minimize misreporting of energy intake, including UPF, we employed a two-step quality-control procedure (see Supplementary Methods 1 for details) focused on total calories. We excluded implausible observations defined as ≥20% decrease in total calories consumed between consecutive visits and extreme values (±3SD) based on a model of energy intake accounting for age and key covariates. Twenty-five participants with only one visit remaining after this quality-control step were excluded as their cumulative UPF could not be calculated. After filtering, plausible dietary data were available for 328 participants at 6 months, 324 at 12 months, 301 at 24 months, and 133 at 72 months.

The percentage of calories from UPF (UPF%) was averaged across recall days within each visit, and cumulative UPF% intake was estimated using the area under the curve (AUC) across 6–24 and 6–72 months. AUC captures both the magnitude and duration of exposure over time. By incorporating measurement timing, this approach yields a time-weighted average exposure across the interval and reflects changes in exposure between timepoints, which is particularly important given their unequal spacing, as a simple mean would weight each visit equally regardless of its duration. AUCs were computed using trapezoidal integration when both endpoints (e.g., 6 and 24 months for AUC UPF% 6–24) were available, with in-between visits (e.g., 12 months) contributing if present. AUCs were divided by the window length (18 or 66 months), yielding a time-weighted-average AUC for UPF% consumption. AUCs were also derived for each UPF subtype (e.g., AUC SSBs 6–72) and selected nutrients (e.g., AUC choline 6–72) as well.

Cognitive assessments at 24 months and 72 months

At 24 months, the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) [25] was used to assess cognition, expressive and receptive language, and fine and gross motor skills in 194 infants. This study used raw scores. Evaluations were conducted by six trained examiners in the child's preferred language (Spanish, English, or both). In cases where both languages were used, examiners flexibly administered tasks across languages to support comprehension, and scoring was based on a single standardized assessment reflecting the child's overall performance. Assessments that were incomplete or deemed unreliable by the examiner (e.g., the child was inattentive, the child cried throughout the evaluation) were excluded. This resulted in 12 participants being excluded (n=182 in total).

At 72 months, 129 children completed, in English and under supervision, the evaluation from the NIH Toolbox® [26] (v2.1) on an iPad Pro (10,5 inches). This battery included assessments of attention and inhibitory control, cognitive flexibility, working memory, processing speed, and visual episodic memory. Here, we used uncorrected scores from the flanker attention-inhibitory control, dimensional change card sort, list sorting working memory, pattern comparison processing speed, and the picture sequence memory tests. We excluded entire tasks that ended prematurely due to application errors or accidental screen touches, as task-level scores may still be generated despite interruption. For this reason, analyses on the NIH toolbox have different sample sizes.

For the current study, two children diagnosed with a neurodevelopmental disorder were further excluded from the 24- and 72-month analyses to minimize major non-dietary influences on neurocognitive outcomes. Therefore, the eligible sample with valid cognitive data at 24 months and 72 months was, respectively, 180 and 127.

MRI acquisition and processing at 72 months

High-resolution T1-weighted images were acquired at 72 months for 113 children on a Philips 3T Achieva dStream scanner with a 32-channel head coil (1.0 mm^3 isotropic). Images were processed with CAT12 (version 12.9) in SPM12 (MATLAB R2024b) [27]. Segmentation, Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL)-based normalization, and modulation were applied. Estimated volumes (mL) of 16 bilateral subcortical regions were adjusted for individual differences in head size by residualizing each regional volume with respect to total intracranial volume (TIV) [28]. Residualized values were retained on the original measurement scale and used in all subsequent analyses. Subcortical regions included accumbens, amygdala, hippocampus, pallidum, putamen, caudate, thalamus, and ventral diencephalon (labeled by Neuromorpometrics, Inc). Quality control included Euler number and intensity-based metrics as in previous work [29], with visual inspection to confirm tissue classification and anatomical plausibility. In addition to the two children excluded due to neurodevelopmental diagnoses, three additional children were removed for quality concerns, thus resulting in an eligible sample of 108 individuals.

Statistical analysis

All data management and statistical analyses were conducted in R (version 4.5.2; R Core Team) and R Studio (version 2026.1.0.392; Posit). Outcomes and main exposures were assessed for severe skewness (>2) and kurtosis (>7) [30]. Missing values in nuisance covariates were median-imputed, whereas exposure (UPF%) and outcome variables (i.e., cognitive function and brain) were not imputed. Multiple univariate linear regression models examined associations among cumulative UPF intake (AUC UPF% 6–24 and 6–72) and cognitive and brain outcomes. Analyses adjusted for age, sex, the youth's current weight, study affiliation, and household education. Household education was used as a proxy for socioeconomic status, rather than household income, due to concerns about misreporting and the instability of the latter [31]. Continuous covariates (age, weight) were mean-centered, and categorical covariates (sex, study affiliation, and household education) were effect-coded (coded as -1 and 1 for binary variables, with multi-level variables coded to sum to zero). Multicollinearity was assessed using variance inflation

factors (all values <2). Normality and homoskedasticity of the models' residuals were assessed using visual inspection of Q-Q plots. A Benjamini-Hochberg [32] correction was applied separately for each outcome domain to control the false discovery rate (FDR): 24-month cognitive outcomes (5 scores), 72-month cognitive outcomes (5 scores), and 72-month brain outcomes (16 regions). Statistical significance was set at FDR-adjusted p (FDRp) < 0.05. Beta (β) estimates are reported on the original scale and additionally expressed as percent-relative change per one-unit increase in UPF% intake (in Tables) to help interpret the magnitude of effects. We also report adjusted percent differences in the outcome between the lowest (Q1) and highest (Q4) AUC UPF% intake quartiles (only in Tables).

Alternative UPF thresholds (e.g., only definitely UPF) were explored in sensitivity analyses. Joint analysis examined whether UPF-brain associations varied by region (Supplementary Methods 2). To confirm the robustness of the significant results, additional analyses were conducted controlling for early feeding practices (i.e., human milk ratio) and for a diet quality index, calculated as the mean of z-scored AUCs for dietary fiber, DHA, iron, zinc, magnesium, choline, and vitamins D, B9, and B12.

FDR-surviving outcomes underwent follow-up time-decomposition analysis to separate cumulative early UPF intake (e.g., AUC UPF % 6–24) from current UPF intake at the time of outcome assessment (e.g., UPF% 72). FDR-surviving outcomes were also submitted to UPF-decomposition to compare the contribution of specific UPF subtypes (e.g., AUC UPF% of SSBs) with that of all remaining UPFs (e.g., the sum of the AUC UPF% of snacks, fast foods, others). Because of differences in UPF exposure ranges, these were z-scaled for comparison. Wald tests of linear contrasts examined differences in regression coefficients for time- and UPF-decomposition analyses. Because these analyses are intended as a follow-up to the principal analyses, statistical significance is set at uncorrected $p < 0.05$.

The sample size was not determined through a prospective power calculation, as this study represents a follow-up of participants from two previously established longitudinal cohorts (Mother's Milk and Mamitas). Accordingly, the sample size is constrained by participant retention and the availability of valid data for each analysis.

Results

In the whole sample with valid dietary data (n=328 at 6 months), the average percentage of UPF calories (UPF%) increased significantly across visits, from 16.4% at 6 months to 55.5% at 72 months (see Figure 1). More details are provided in Supplementary Results 1.

Of the 180 infants with valid cognitive data at 24 months, 144 presented valid dietary data at 6 and 24 months, the endpoints minimally required to compute the AUC UPF% 6–24 for this analysis. At 72 months, 93 of 127 children showed both valid cognitive and dietary data at 6 and 72 months. Of the 113 children with MRI data at this visit, 79 presented valid dietary data. Table 1 presents the sample characteristics, including UPF% averages. The participant flowchart is shown in Figure 2. A more detailed flowchart is provided in Supplementary Results 2. The comparison between participants excluded from analyses at 24 and 72 months is available in Supplementary Results 3.

In the sample with cognitive data available at 24 months, the AUC UPF% intake from 6–24 months was negatively associated with the AUC of fiber (b=-0.11, p=0.003) and positively related to the AUC of iron (b=0.31, p<0.001), zinc (b=0.05, p<0.001), and vitamins D (b=0.07, p<0.001), B9 (b=1.60, p=0.029), and B12 (b=0.05, p<0.001). In contrast, in the sample with cognitive and MRI data available at 72 months, the AUC UPF% intake from 6–72 months was only negatively associated with dietary fiber and magnesium (all p's < 0.05; see Supplementary Results 4).

Cognitive assessments at 24 and 72 months

No significant relationships were found between the AUC UPF% 6–24 and any of the BSID-III scores, nor between the AUC UPF% 6–72 and the NIH Toolbox® tasks (see Table 2).

MRI assessments at 72 months

Several significant negative associations were found between AUC UPF% 6–72 months and subcortical volumes, including the bilateral accumbens, left amygdala, bilateral pallidum, left putamen, and

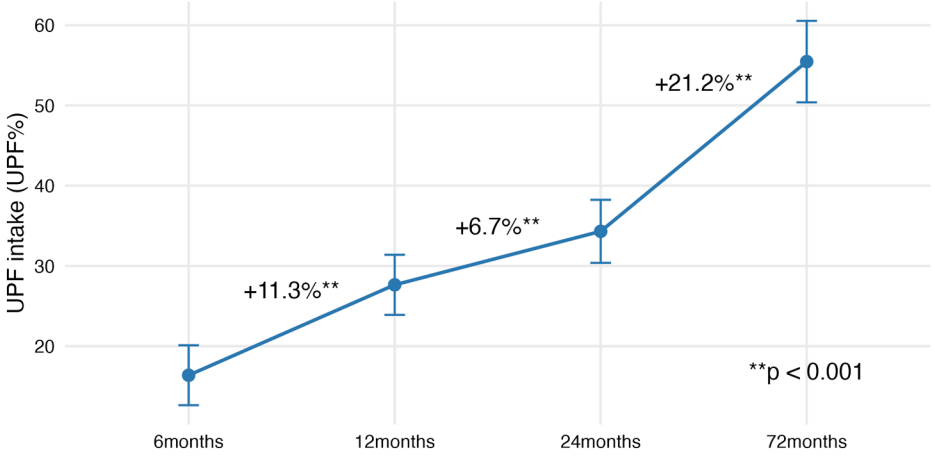

FIGURE 1. Percentage of calories derived from UPF across various visits. The results are derived from the linear mixed effects model analyzing longitudinal trajectories from 6 to 72 mo. The analysis incorporated visit, age in mo, sex, weight, household education, and study source as fixed covariates, with a random intercept assigned for each subject. In this analysis, successive comparisons were conducted (e.g., 6 mo vs. 12 mo, 12 mo vs. 24 mo, etc.) between timepoints (x-axis) for UPF% levels (y-axis). The differences (increases) in UPF% from one timepoint to the next are indicated. UPF, ultraprocessed food; UPF%, percentage of calories from ultraprocessed food.

TABLE 1
Characteristics of the sample by visit

	24-mo cognition (n = 144)	72-mo cognition (n = 93)	72-mo brain (n = 79)
Child age (mo)[1]	24.3 (1.6)	72.5 (1.1)	72.9 (1.4)
Infant weight (kg)[1]	13.0 (1.7)	24.8 (6.4)	24.7 (6.5)
Birth weight (kg) [1]	3.4 (0.4)	3.4 (0.4)	3.4 (0.4)
Pregravid BMI[1]	28.6 (6.1)	28.7 (5.9)	28.3 (5.9)
Age at delivery (y)[1]	29.1 (6.2)	29.7 (6.1)	29.0 (5.9)
Lactation ratio[1,3]	0.6 (0.4)	0.6 (0.4)	0.6 (0.4)
UPF% 6 mo[1]	19.5 (26.6)	18.9 (27.0)	18.5 (27.5)
UPF% 12 mo[1]	29.2 (18.8)	34.6 (20.1)	33.5 (19.2)
UPF% 24 mo[1]	36.4 (16.0)	40.2 (16.2)	39.8 (16.6)
UPF% 72 mo[1]	—	57.9 (16.2)	58.2 (16.4)
AUC UPF% 6–24[1]	29.9 (13.3)	32.2 (12.6)	31.7 (12.7)
AUC UPF% 6–72[1]	—	45.4 (12.1)	45.0 (12.1)
Sex (female)[2]	82 (57)	55 (59)	46 (58)
Vaginal delivery[2]	106 (74)	63 (68)	53 (68)
Study affiliation[2]			
Mother's milk	130 (90)	70 (75)	60 (76)
Mamitas	14 (9.7)	23 (25)	19 (24)
Prematurity[2]			
On time	74 (51)	50 (54)	43 (54)
<2 wk early	28 (19)	17 (18)	12 (15)
<2 wk late	32 (22)	20 (22)	17 (22)
>2 wk early	4 (2.8)	3 (3.2)	3 (3.8)
>2 wk late	4 (2.8)	2 (2.2)	3 (3.8)
Do not know	2 (1.4)	1 (1.1)	1 (1.3)
Household education[2]			
Less than high school	29 (20)	21 (23)	16 (21)
High school or GED	38 (26)	27 (29)	25 (32)
College graduate	77 (53)	45 (48)	38 (47)
BSID-III, examiner[2]			
Examiner 1	54 (38)	—	—
Examiner 2	12 (8.3)	—	—
Examiner 3	13 (9.0)	—	—
Examiner 4	8 (5.6)	—	—
Examiner 5	36 (25)	—	—
Examiner 6	21 (15)	—	—
BSID-III, language[2]			
English only	47 (33)	—	—
Spanish only	38 (26)	—	—
Both	59 (41)	—	—
NIH Toolbox, N task[2]			
Dimensional change card	—	90 (96.7)	—
Flanker inhibitory control	—	90 (96.7)	—
Picture sequence memory	—	92 (98.9)	—
Pattern comparison speed	—	91 (97.8)	—
List sorting working memory	—	69 (74.1)	—

No statistical tests were performed; this table is descriptive.
Abbreviations: BSID-III, Bayley Scales of Infant and Toddler Development, Third Edition; GED, general education development; UPF%, percentage of calories from ultraprocessed food.
[1] Continuous variables are presented as mean and SD.
[2] Categorical variables are presented as frequency and percentage (%).
[3] Lactation ratio indicates the proportion of human milk to formula milk from 1 to 6 mo (range: 0–1).

bilateral thalamus (all FDR p <0.05; see Table 2 and Figure 3). Q-Q plots are available in Supplementary Results 5. Results were robust to alternative UPF thresholds (see Supplementary Results 6–7), a joint modeling approach (see Supplementary Results 8), early feeding practices (see Supplementary Results 9), and diet quality (see Supplementary Results 10). Due to the thalamus's larger size and heterogeneity, exploratory analyses of subthalamic units were conducted (see Supplementary Results 11 for details).

Time-decomposition follow-up analysis on UPF-brain associations

These analyses involved a reduced sample size (n=67) owing to the absence of UPF% data at 24 months after quality control, thus precluding the calculation of the AUC UPF% 6–24 months. Early cumulative (AUC UPF% 6–24 months) and current UPF intake (UPF % 72 months) were unrelated (Pearson's r=-0.01, p=0.9). Current UPF intake was significantly and inversely related to most subcortical volumes (all uncorrected p's < 0.05). A Wald test showed that early and current UPF intake differed significantly in the left pallidum, which showed a stronger association with current UPF intake (Z = -2.55, p = 0.011; see Figure 4). See the Supplementary Results 12 for details.

UPF-decomposition follow-up analysis on UPF-brain associations

Analyses included the whole sample (n=79). The AUC UPF% 6–72 months was calculated separately for SSBs, snacks, fast food, and other UPFs (e.g., frozen and dry-instant meals, baked goods, cereals, lunchmeats, dairy products). The average Pearson's correlation coefficient among UPF subtypes was -0.038 (range -0.13 to 0.06). The Wald test showed no significant differences among UPF subtypes (in Supplementary Results 13).

Discussion

In this prospective birth cohort study, cumulative UPF intake from infancy to early childhood was inversely related to subcortical volumes at 72 months but not to cognitive performance at 24 or 72 months. Affected regions included the accumbens, amygdala, pallidum, putamen, and thalamus, which are involved in reward processing, emotional regulation, motivation, and sensorimotor integration. Associations were largely independent of exposure timing, except for a stronger association with current intake in the left pallidum, and were consistent across UPF subtypes. Our findings suggest that subcortical regions may be broadly vulnerable to UPFs across childhood and precede detectable cognitive differences, emphasizing childhood as a potentially important window for nutrition-focused prevention efforts.

No associations between UPF intake and cognitive outcomes were observed at 24 and 72 months. Previous work in infants and children reported associations between intake of specific UPF subtypes (e.g., artificially sweetened foods, snacks, fast foods, and SSBs) and poorer cognition [33–36]. However, these studies focused on selected components rather than overall UPF exposure [40-43]. This difference in exposure definition, along with variation in developmental timing (i.e., most studies included older children [36–38]), may contribute to the discrepant findings. Together, these factors suggest that previously reported links may emerge later in life or be specific to energy-rich UPF subtypes rather than food processing more broadly.

We found that cumulative UPF intake from 6 to 72 months was inversely associated with the volumes in the bilateral accumbens, left amygdala, bilateral pallidum, left putamen, and bilateral thalamus [27–30]. Specifically, each 10-percentage-point increase in cumulative UPF intake was associated with a 0.04-mL decrease in subcortical

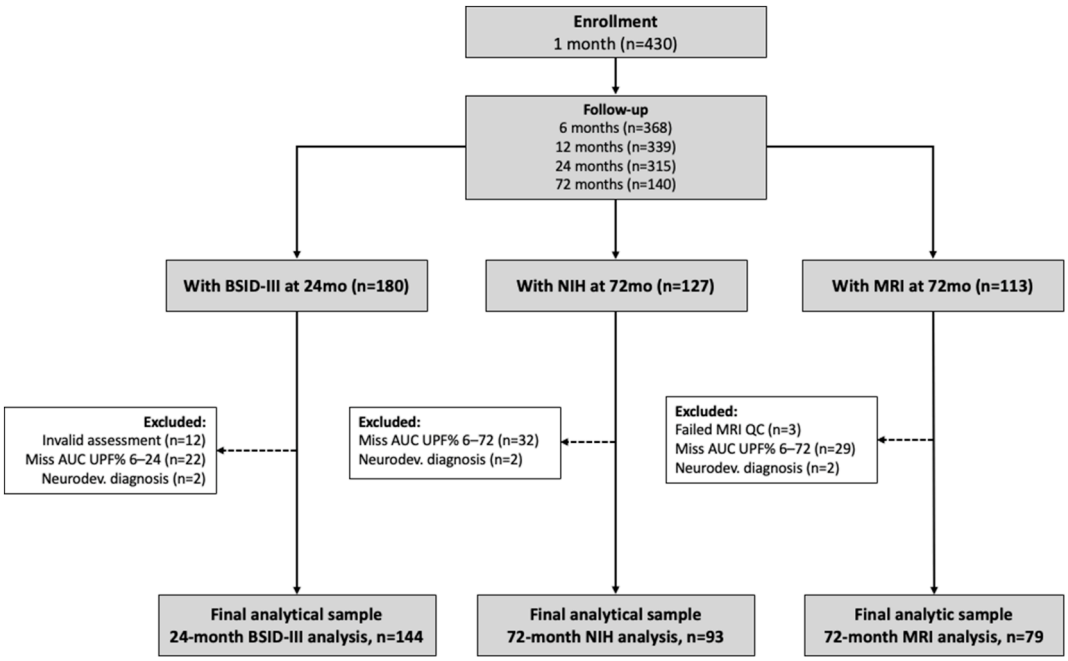

FIGURE 2. Participant flowchart from enrollment (1-mo visit) to final analytical sample sizes at 24 and 72 mo. BSID-III, Bayley Scales of Infant and Toddler Development, Third Edition; UPF, ultraprocessed food; UPF%, percentage of calories from ultraprocessed food.

volumes, corresponding to a 1.92% reduction. That is, children in the highest UPF quartile (62% UPF intake or more) had, on average, a 6% lower volume than those in the lowest quartile (31% UPF intake or less). Affected regions are key to reward processing, emotional regulation, motivation, and sensorimotor integration [37,38]. Animal work showed that greater intake of highly palatable foods, a characteristic of UPFs, can alter the structure of these regions [39–42]. Human studies showed that UPF intake is associated with increased food cravings [43], snack overeating [44], reward sensitivity [45], and stress responsivity [46]. Although not examined in this study, these behavioral and emotional associations align with the observed subcortical brain variations, thereby justifying further investigation into their long-term implications. Importantly, results were robust to alternative UPF thresholds, joint modeling approaches, and adjustment for early feeding practices (i.e., human milk ratio) and diet quality, as measured by a 9-nutrient index encompassing iron, zinc, and vitamins, among others.

Time-decomposition analyses indicated that, in most cases, subcortical volumes were similarly associated with early (6–24 months) and current (72 months) UPF intake. This suggests that subcortical vulnerability to UPFs may begin in infancy and persist across early childhood. The left pallidum, the only exception to this pattern, showed a stronger negative association with current UPF intake at 72 months. Given the pallidum's role in sensing food pleasantness [47], this might hint at heightened vulnerability of this region during a time when children's diets broaden. In UPF-decomposition analyses, we examined the associations of different UPF subtypes, namely SSBs, fast foods, snacks, and other UPFs (e.g., frozen and dry-instant foods, baked goods, cereals, lunchmeat, dairy products). Results suggested that UPF-brain associations were global rather than specific to any particular UPF subtype.

Differences in subcortical volumes associated with UPF intake should be interpreted cautiously, particularly in early childhood, when regional brain volumes do not map linearly onto neurodevelopmental advantage or impairment. Smaller volumes may reflect developmental timing differences, such as early synaptic pruning or circuit refinement, rather than pathological tissue loss. Because subcortical regions reach peak volumes at different rates [16], it is not possible to determine whether smaller volumes reflect accelerated or delayed maturation based on cross-sectional data alone. The absence of cognitive deficits further limits interpretation. Still, given prior evidence of associations between UPF intake and cognition in older children [34–36], these findings may represent a "first hit" preceding later-emerging functional consequences, although longitudinal studies are needed for confirmation.

Several biological mechanisms may underlie UPF-related differences in subcortical volumes, including nutritional composition (e.g., added sugars) and processing-related features (e.g., nonnutritional additives). Experimental studies have linked aspects of diet (e.g., high-fat content) to differences in neuroplasticity [40,48] and inflammatory processes [49–51]. UPF intake may also reflect displacement of nutrient-dense foods important for neurodevelopment [52], although associations in the present study were unchanged after controlling for diet quality. Additional processing-related factors, such as exposure to food-contact chemicals, including per- and polyfluoroalkyl substances, may also contribute [53], yet evidence in childhood remains limited. Overall, the relative contributions of compositional and processing-related factors cannot be distinguished in this study, and the previous explanations remain pure speculation.

This study presents several strengths. UPF-neurocognitive links were examined using the Nova system. This increasingly used classification framework does not rely solely on nutritional composition and more accurately reflects the current landscape of highly processed foods [23]. Dietary intake was assessed across multiple visits using open-ended 24-hour recalls on two separate days, including both weekdays and weekends, to better capture typical dietary patterns.

TABLE 2
Results of the models examining UPF% intake and cognitive outcomes at 24 and 72 mo, and brain outcomes at 72 mo.

	N	β (raw) and 95% CI[1]	β (%) and 95% CI[1]	Q1–Q4[2]	P[3]	FDRp
24-mo cognitive performance						
Cognition	144	0.033 (-−0.030, 0.098)	0.055 (−0.05, 0.16)	1.78	0.300	0.707
Receptive	144	0.025 (−0.033, 0.082)	0.111 (−0.148, 0.37)	3.6	0.398	0.707
Expressive	144	0.003 (−0.059, 0.064)	0.01 (−0.238 0.259)	0.33	0.935	0.935
Fine motor	144	0.013 (−0.018, 0.044)	0.032 (−0.047, 0.112)	1.05	0.424	0.707
Gross motor	144	0.004 (−0.046, 0.053)	0.007 (−0.085, 0.098)	0.21	0.887	0.935
72-mo cognitive performance						
Dimensional	90	−0.168 (−0.397, 0.061)	−0.493 (−1.17, 0.18)	−15.26	0.148	0.371
Flanker	90	−0.02 (−0.198, 0.158)	−0.056 (−0.56, 0.445)	−1.75	0.823	0.904
Picture	92	0.026 (−0.042, 0.095)	0.407 (−0.652, 1.46)	12.58	0.447	0.745
Pattern	91	0.109 (−0.015, 0.234)	0.427 (−0.057, 0.911)	13.21	0.083	0.371
List sorting	69	−0.005 (−0.083, 0.073)	−0.067 (−1.16, 1.027)	−2.06	0.904	0.904
72-mo subcortical volumes						
R Accumbens	79	−0.001 (−0.001, −0.0002)	−0.188 (−0.33, −0.046)	−5.86	**0.010**	**0.032**
L Accumbens	79	−0.001 (−0.001, −0.0002)	−0.166 (−0.296, −0.04)	−5.17	**0.013**	**0.032**
R Amygdala	79	−0.001 (−0.002, 0.0004)	−0.097 (−0.236, 0.04)	−3.03	0.170	0.194
L Amygdala	79	−0.002 (−0.003, −0.0003)	−0.171 (−0.31, −0.035)	−5.34	**0.014**	**0.032**
R Caudate	79	−0.001 (−0.006, 0.003)	−0.043 (−0.217, 0.13)	−1.36	0.618	0.659
L Caudate	79	−0.0005 (−0.005, 0.004)	−0.021 (−0.20, 0.161)	−0.64	0.823	0.822
R Hippocampus	79	−0.003 (−0.006, 0.0011)	−0.082 (−0.199, 0.04)	−2.56	0.165	0.194
L Hippocampus	79	−0.004 (−0.007, 0.0001)	−0.117 (−0.24, 0.003)	−3.66	0.056	0.100
R Pallidum	79	−0.002 (−0.003, −0.0003)	−0.266 (−0.49, −0.05)	−8.31	**0.019**	**0.038**
L Pallidum	79	−0.002 (−0.003, −0.0004)	−0.23 (−0.395, −0.065)	−7.18	**0.007**	**0.028**
R Putamen	79	−0.004 (−0.009, 0.001)	−0.1 (−0.218, 0.017)	−3.13	0.093	0.131
L Putamen	79	−0.007 (−0.012, −0.002)	−0.15 (−0.263, −0.044)	−4.8	**0.007**	**0.028**
R Thalamus	79	−0.011 (−0.016, −0.005)	−0.17 (−0.257, −0.082)	−5.29	**0.0002**	**0.002**
L Thalamus	79	−0.012 (−0.018, −0.007)	−0.2 (−0.294, −0.106)	−6.25	**0.0001**	**0.001**
R Ventral DC	79	−0.002 (−0.004, 0.0003)	−0.135 (−0.289, 0.02)	−4.22	0.084	0.131
L Ventral DC	79	−0.002 (−0.004, 0.0003)	−0.119 (−0.261, 0.023)	−3.72	0.098	0.131

All models were adjusted for age, sex, child weight, household education, and study affiliation.
Abbreviations: CI, confidence interval; DC, diencephalon; FDRp, false discovery rate–adjusted *P*; L, left; R, right; UPF%, percentage of calories from ultra-processed food.
[1] Values represent *β* coefficients and 95% CI from multivariable linear regression models, reported on the original scale (raw) and as relative percentage change (%).
[2] Q1–Q4 represents the adjusted percentage difference in the outcome between the lowest (Q1) and highest (Q4) quartiles of UPF exposure. For interpretation only.
[3] *P* values were corrected for multiple comparisons using the Benjamini–Hochberg false discovery rate (FDR), applied separately within each outcome domain.

Time and UPF-subtype decomposition analyses provided additional insights. Dietary, cognitive, and MRI assessments were subjected to rigorous quality control procedures, and the results were robust across different UPF thresholds, statistical approaches, and additional adjustment for early feeding practices and diet quality.

Several limitations should be noted as well. The modest sample size may have limited statistical power and model complexity. Dietary recalls are susceptible to reporting bias and may underestimate UPF intake. In addition, the Nova system presents its own definitional challenges: the boundary between processed (level 3) and ultra-processed (level 4) foods relies on contextual judgment about the extent and purpose of processing, and the same ingredient may or may not signal ultra-processing depending on the product in which it appears. These ambiguities introduce classification uncertainty that cannot be fully resolved. Moreover, the Nova system cannot separate nutritional composition from food processing. Performance on cognitive tasks can be impacted by motivation and contextual factors (e.g., fatigue, examiner, environment). The Bayley Scales provide relatively coarse measures of cognitive function and may not capture more subtle differences. Additionally, household education was used as a proxy for socioeconomic status, which may not fully reflect its multidimensional nature. The MRI assessments used in this study lack the resolution to speculate on the mechanisms underlying volumetric differences. Cross-sectional neurocognitive assessments precluded examination of individual developmental trajectories and limited causal inference. Unmeasured confounders, including maternal diet during pregnancy and lactation, may also play a role. Finally, the sample consisted of Latino/Hispanic families in Southern California, limiting generalizability.

In conclusion, higher cumulative UPF intake from 6 to 72 months was associated with smaller subcortical brain volumes in areas involved in reward processing, emotional regulation, motivation, and sensorimotor integration. Associations did not vary across exposure timing, except in the left pallidum, which showed a more negative association with current UPF intake. Importantly, our results suggest overall vulnerability to UPFs rather than UPF-specific. The lack of associations with cognitive function suggests that subcortical variation may precede functional deficits. These findings highlight childhood as a sensitive period for UPF exposure, with potential long-term implications for physical, behavioral, and mental health. Future studies are needed to clarify sensitive windows, neurobiological mechanisms, and late-life implications.

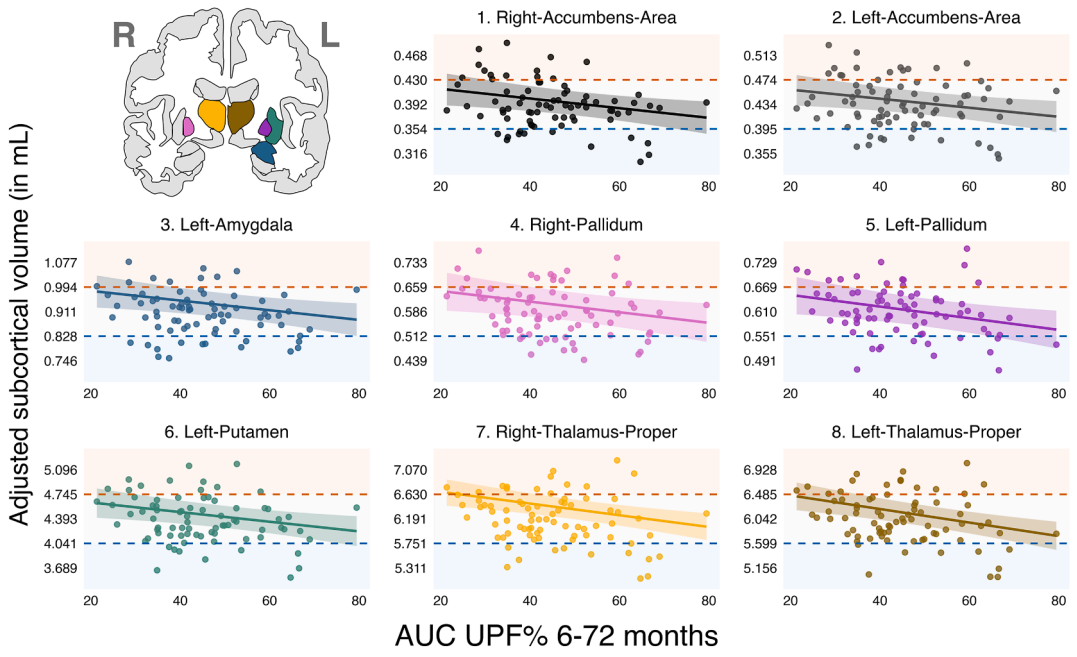

FIGURE 3. Main analysis of associations between cumulative UPF intake and subcortical brain volumes. Each panel shows the association between cumulative UPF intake from 6 to 72 mo (AUC UPF%; x-axis) and TIV-adjusted subcortical regions at 72 mo (in mL; y-axis) that passed FDR-correction. Analyses controlled for age, sex, infant weight, household education, and study source. Solid lines represent fitted regression slopes with 95% confidence intervals. Dashed vertical lines indicate ±1 SD of adjusted volumes to help the interpretation of negative UPF-brain associations. FDR, false discovery rate; L, left; R, right; TIV, total intracranial volume; UPF, ultraprocessed food; UPF%, percentage of calories from ultraprocessed food.

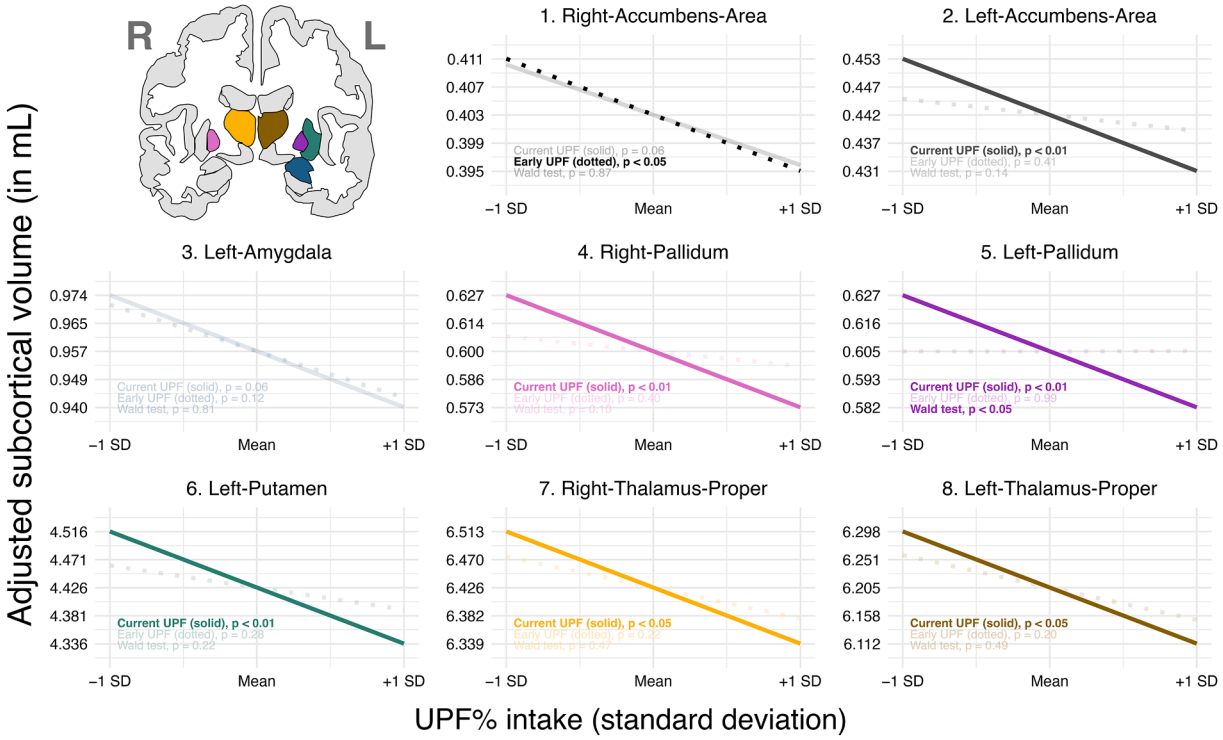

FIGURE 4. Time-decomposition analysis results. Each panel displays regression slopes for early cumulative (AUC UPF% 6–24; dashed lines) and current UPF intake (UPF% 72; solid lines) in relation to TIV-adjusted subcortical regions (y-axis). UPF% intake (x-axis) was standardized (*z*-scored) to account for differences in exposure ranges. Highlighted labels (bold) indicate statistically significant associations (uncorrected $P < 0.05$) and whether slopes significantly differed (Wald test, uncorrected $P < 0.05$). All models were adjusted for age, sex, infant weight, household education, and study source. L, left; R, right; TIV, total intracranial volume; UPF, ultraprocessed food; UPF%, percentage of calories from ultraprocessed food.

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Authors' contributions

JOG was responsible for writing the manuscript, conducting the analyses, and interpreting the data. JOG, AD, SE, KMM, and DP assisted with the classification of ultra-processed foods. SA, AD, SE, KMM, DP, HL, TA, RB, BSP, and MIG critically revised the manuscript and contributed significantly to its intellectual content. MIG obtained primary funding and conceived the overall study design. All authors approved the final version of the manuscript.

Disclaimers

None to declare.

Conflict of interest

The authors declared no conflict of interest.

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Data sharing

Data described in the manuscript, code book, and analytic code will be made available upon request, pending application and approval.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2026.101350.

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