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ORIGINAL PAPER

Obesity and Risk of Pediatric-Onset Multiple Sclerosis (POMS): a Systematic Review and Meta-Analysis

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ABSTRACT

Background: *Childhood obesity is a health care problem with increasing incidence all over the world. The literature shows that obesity in childhood will increase the risk of MS, but the results are not consistent. Accordingly, we conducted this systematic review and meta-analysis to quantify the pooled risk of developing multiple sclerosis (MS) among children with obesity.*

Methods: *Two independent researchers systematically searched PubMed, Scopus, EMBASE, Web of Science and Google Scholar on May 1, 2023. Gray literature was also searched, including theses, reference lists of included studies and conference abstracts.*

Results: *The literature search identified 4,100 articles. After removing duplicates, 2,539 unique records remained. Of these, four studies met the eligibility criteria and were included in the meta-analysis. Two studies were done in the UK, one study was carried out in Germany and the fourth one was conducted in Saudi Arabia. The publication period was between 2019 and 2022. The total number of cases and controls was 17812 and 660757, respectively. The odds ratio (OR) of included studies ranged between 1.26-3.79 and the estimated pooled OR was 1.67 [95% confidence interval (CI) 1.25–2.24] (I^2=84.2%, p<0.001)*

Conclusion: *The results of this systematic review and meta-analysis show that the pooled OR of developing MS in children with obesity is significantly high.*

Keywords: multiple sclerosis, pediatric, obesity.

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INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system (CNS) and ranks among the most disabling diseases worldwide (1, 2). Pediatric onset of MS (POMS) is defined as the onset of MS before 18 years of age and contributes to up to 10% of the total MS population (3-5). Higher relapse rate but, better recovery after relapses, and slow progression toward secondary progressive MS (6, 7). POMS is the interaction between genetics and environmental factors including latitude, vitamin D levels, Epstein-Barr virus infection, diet, microbiota, and smoking (8-10). Childhood obesity is a healthcare problem with increasing incidence all over the world (11). Obesity mediates inflammation by blood-brain barrier (BBB) disruption or activation of microglia in the CNS (12-14). There is a genetic link between childhood obesity and susceptibility to multiple sclerosis, partly driven by the continuation of obesity into early adulthood (15). The literature shows that obesity in childhood could increase the risk of MS, but the results are not consistent. Accordingly, we conducted this systematic review and meta-analysis to quantify the pooled risk of developing MS in children with obesity. ❑

METHODS

This systematic review and meta-analysis was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (16).

Eligibility criteria

Case control or cohort studies reporting the risk of MS in cases with childhood obesity (age less than 18) were included in the present study. Studies on obesity in adults, narrative reviews, systematic reviews and cases reports/case series, as well as those that reported adjusted odds ratios (ORs) were all excluded.

Information sources

Two independent researchers systematically searched PubMed, Scopus, EMBASE, Web of Science and Google Scholar on May 1, 2023. Gray literature was also reviewed, including theses, reference lists of included studies and conference abstracts.

Search strategy

Obesity OR (Obesity AND Pediatric) OR "Obesity in Childhood" OR "Childhood Onset Obesity" OR (Obesity AND "Childhood Onset") OR "Child Obesity" OR (Obesity AND Child) OR "Childhood Obesity" OR (Obesity AND Childhood) OR "Adolescent Obesity" OR (Obesity AND Adolescent) OR "Obesity in Adolescence" OR "Infantile Obesity" OR (Obesity AND Infantile) OR "Infant Obesity" OR (Obesity AND Infant) OR "Childhood Overweight" OR (Overweight AND Childhood) OR "Infant Overweight" OR (Overweight AND Infant) OR "Adolescent Overweight" OR (Overweight AND Adolescent)) AND ((Sclerosis AND multiple) OR (sclerosis AND disseminated) OR "disseminated sclerosis" OR "multiple sclerosis" OR "acute fulminating").

Selection method, and collection

After retrieving the search results from multiple databases, all records were imported into EndNote. Duplicates were removed and the titles and abstracts of the remaining studies were screened for eligibility. Full texts of potentially relevant articles were retrieved. Data were extracted independently by two reviewers using a standardized Microsoft Excel spreadsheet. A third reviewer checked the extracted data and any disagreements were resolved by consensus.

Data items

The first author of the publication, country of the study, publication year, number of case and control participants, age at the time of study, obesity criteria, OR and key findings.

Study risk of bias assessment

The risk of bias in the included studies was assessed using the Newcastle–Ottawa Scale (NOS) checklists for case-control studies (1).

Effect measures

We estimated the pooled OR of developing MS in individuals with childhood obesity.

Synthesis methods

All statistical analysis was done using STATA (Version 14.0; Stata Corp LP, College Station, TX, USA). We also assessed heterogeneity by the

I-square index (I2). The random effect model was used.

Pooled OR was estimated for developing MS in cases with childhood obesity.

P-values less than 0.05 were considered significant.

Certainty assessment

For all estimated effect sizes, we reported 95% confidence interval (CI). ❑

RESULTS

A total of 4,182 records were identified through database searches (n = 4,100) and registers (n = 82). After removing 1,659 duplicate records and three records having been marked as ineligible by automation tools and one record being removed for other reasons, 2,539 records remained for title and abstract screening. Of these, 1,943 records were excluded, and 152 reports were sought for retrieval. Forty reports could not be retrieved, leaving 112 full-text articles for eligibility assessment. Following full-text review, 108 articles were excluded for the following reasons: not reporting childhood obesity (n = 52), insufficient information for analysis (n = 27), review articles (n = 23) and duplicate publications (n = 6). Ultimately, four studies met the inclusion criteria and were included in the systematic review and meta-analysis (Figure 1).

Table1 summarizes four case–control studies from Saudi Arabia, Germany and the United Kingdom that have evaluated the association between obesity or larger body size and the risk of MS. Across all studies, obesity-related measures were positively associated with MS. The stron-

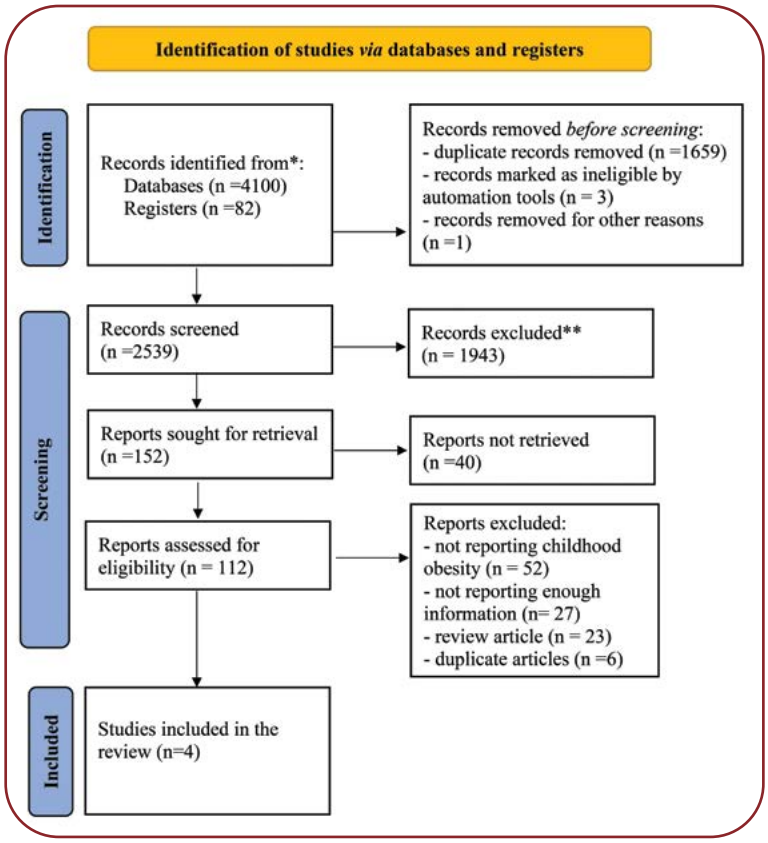

FIGURE 1. Flowchart of the included studies

Author	Year	Country	Study design	T. case Female Male	T. control Female Male	Age at examination Case Control	Obesity meaning	Odds ratio (OR), 95% confidence interval (CI)	Q.A. NOS[1]
Osama A. Al-Wutayd (18)	2022	Saudi Arabia	Case-control	307 230 77	307 230 77	32.9 (8.8) 32.9 (8.6)	BMI WHO classification and body size≥6 (Stunkard's silhouettes)	Large body size (≥6) 3.79 [1.76-8.17]	6/9
Brenda Huppke (19)	2019	Germany	Case-control	453 306 147	147747	13.7 (2.7)	BMI category using the definitions recommended by the European Childhood Obesity Group	2.2 (1.7-2.9)	6/9
Adil Harroud (2)	2021	UK	Case-control	14,802	26,703	56	Childhood BMI	1.26 [1.07-1.5]	7/9
Benjamin Meir Jacobs (20)	2021	UK	Case-control	2,250 1,635 615	486,000 263,058 222,942	55.17 (7.66) 56.54 (8.09)	Body size aged 10 years	1.36 [1.2-1.55]	6/9

TABLE 1. Data extracted from included studies

gest association was observed in the Saudi Arabian study, where individuals with a large body size (Stunkard silhouette score ≥6) had nearly four-fold higher odds of MS (OR 3.79, 95% CI 1.76–8.17). The German study reported more than a twofold increase in odds among obese children (OR 2.2, 95% CI 1.7–2.9). Two large UK studies also demonstrated significant associations, with ORs of 1.26 (95% CI 1.07–1.50) for higher childhood body mass index (BMI) and 1.36 (95% CI 1.20–1.55) for larger body size at age 10 years. These findings consistently indicate that excess body weight, particularly during childhood or early life, is associated with an increased likelihood of developing MS.

Several methodological features strengthen the overall evidence. The UK studies considered very large populations, including one analysis with more than 486,000 controls, providing substantial statistical power and narrow confidence intervals. The studies also used different but conceptually related measures of adiposity, including BMI categories, childhood BMI and recalled body size, and all pointed in the same direction. Quality assessment scores ranged from 6/9 to 7/9, suggesting generally moderate methodological quality across studies (Table 1).

The study conducted by Jacobs *et al* had the highest weight, followed by the studies carried out by Adil Harroud and Huppke *et al*.

The estimated values for heterogeneity chi-square and I^2 were 18.94 ($p<0.001$) and 84.2%, respectively (Table 2).

The OR of included studies ranged between 1.26-3.79 and the estimated pooled OR was 1.67 (95% CI 1.25–2.24) ($I2=84.2\%$, $p<0.001$) (Figure 2). ❑

TABLE 2. Meta-analysis findings

Study	ES	[95% Conf.	Interval]	% Weight
Osama A. Al-Wutayd	3.790	1.760	8.170	10.07
Brenda Huppke	2.200	1.700	2.900	26.69
Adil Harroud	1.260	1.070	1.500	30.90
Jacobs	1.360	1.200	1.550	32.35
D+L pooled ES	1.674	1.254	2.236	100.00

Heterogeneity calculated by formula
Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

Heterogeneity chi-squared = 18.94 (d.f. = 3) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 84.2%
Estimate of between-study variance Tau-squared = 0.0631

DISCUSSION

The exact etiology of MS remains unclear. However, interactions between genetic predisposition and environmental factors are thought to play a key role in its development (18). Obesity is currently a health problem on a global scale and its prevalence has dramatically increased among children and adolescents over the past 30 years (21, 22).

Two studies that first highlighted the relationship between obesity and MS were the Nurses' Health Study (NHS) I and II (23). Researchers found that women who were obese (BMI ≥ 30 kg/m^2) at age 18 had a 2.25 times higher risk of developing MS than those with a normal BMI. This

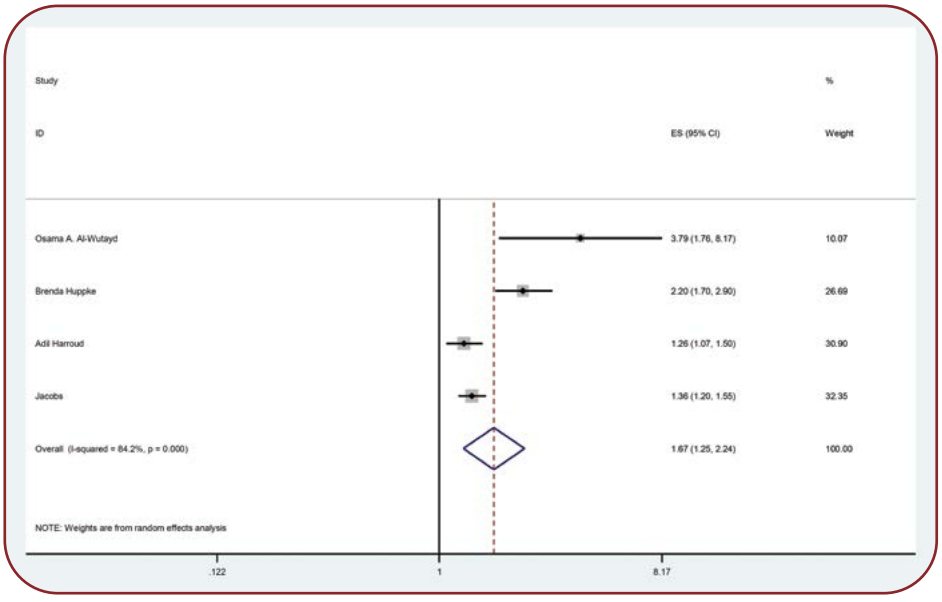

FIGURE 2. The forest plot

association remained significant after adjusting for age, latitude of residence at age 15, race/ethnicity and smoking status.

In Sweden, Hedstrom *et al* conducted a population-based study recruiting 1571 MS cases and 3371 controls. After adjusting for age, sex, residential area, ancestry and smoking, the researchers reported that obese individuals (both men and women) had approximately two-fold higher odds of developing MS (24).

Our findings indicate that childhood obesity is significantly associated with an increased risk of developing MS (pooled OR = 1.67, 95% CI 1.25–2.24).

A study by Al-Wutayd included 307 patients with MS and 307 healthy controls from three cities in Saudi Arabia. They found that the odds of developing MS in individuals with a large body size during intermediate school was three times higher than among those with a small body size (18).

In a study conducted by Huppke *et al* in Germany, obesity was associated with pediatric-onset MS. The ORs was 2.19 (95% CI 1.5–3.1) for obese girls and 2.14 (95% CI 1.3–3.5) for obese boys. Overall, obese children had 2.2 times higher odds of developing pediatric-onset MS (95% CI 1.7–2.9) (19). The authors also found that obese patients had higher odds of switching to second-line disease modifying therapies (DMTs). Along with Yamamoto *et al*, they determined that obese children experience higher rates of relapse than non-obese children (19, 25).

In a large case control study using UK biobank (14,802 MS cases and 26,703 controls), Harroud *et al* found that childhood BMI was significantly associated with the development of MS (OR=1.26, 95% CI 1.07-1.5) (15).

Multiple sclerosis is an autoimmune disease in which chronic inflammation plays a central role (26). On the other hand, obesity is associated with low grade inflammation and proinflammatory cytokines that could be found in the adipose tissue, leading to hypertrophy and hyperplasia of adipocytes (27).

On the other hand, fat cells secrete endogenous hormones such as leptin, adiponectin and cytokines such as IL-6 or TNFα that lead to the excessive recruitment of immune cells (28).

Additionally, in both MS and obesity, the alteration in the number of Th1 and Th2 cells is obvious (a decrease in Th2 levels and an increase in Th1 levels); for instance, Th17 is found to be increased in both obesity and MS, which induces insulin resistance (29). Leptin, which is produced by adipose tissue, is a link between obesity, metabolic state and autoimmune diseases (30).

Furthermore, children and adults with obesity have lower circulating levels of metabolites of vitamin D which is a risk factor of developing MS (8, 9, 31-33).

All above-described findings could confirm the association between obesity and pediatric-onset MS.

This systematic review and meta-analysis has some strengths. We only included studies that reported crude OR and excluded those that reported adjusted OR. So, we estimated the crude pooled OR of developing MS in individuals with childhood obesity. Our study has also limitations. Firstly, there was a small number of included studies. Secondly, we did not have studies from most countries. ❑

CONCLUSION

The result of this systematic review and meta-analysis shows that the pooled OR of developing MS in children with obesity is significantly high [1.67 (95% CI 1.25–2.24)]. ❑

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Conflicts of interest: none declared.

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Authors' contributions: study design, data analysis and article writing – S.M.; data extraction and article writing – M. R., N.E. and M.G.

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