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ORIGINAL CONTRIBUTION

Association between parental body mass index and autism spectrum disorder: a systematic review and meta-analysis

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Abstract

Studies have examined the association between parental body mass index (BMI) and autism spectrum disorder (ASD) in offspring, with inconsistent results, especially regarding maternal obesity, overweight and underweight. Cochrane Library, EMBASE, PubMed and PsycINFO databases were searched up to March 2018 for relevant observational studies with no language restriction. Our literature search identified 13 eligible studies for meta-analysis (involving 943,293 children and 30,337 cases). For maternal BMI (13 studies), both maternal obesity [OR 1.41 (95% CI 1.19–1.67)] and maternal overweight [OR 1.16 (95% CI 1.05–1.27)] were significantly associated with ASD, while maternal underweight was not associated with ASD [OR 1.08 (95% CI 0.98–1.20)]. For paternal BMI (three studies), no association was found (paternal obesity: OR 1.28, 95% CI 0.94–1.74; overweight: OR 1.07, 95% CI 0.99–1.15; underweight: OR 1.12, 95% CI 0.87–1.44). Pooled estimates were robust in sensitivity analysis and subgroup analyses. Publication bias may exist for studies assessing maternal BMI and ASD risk, but the filled estimates were not altered. Relative to normal weight, maternal obesity and overweight were significantly associated with increased ASD risk, while maternal underweight was not associated with ASD. Although no association between paternal BMI and ASD was found, current evidence is limited (three studies). Future studies are warranted to address more confounding factors and to identify potential mediators of the association, but pre-pregnancy weight control is suggested.

Keywords Body mass index · Pre-pregnancy · Autism spectrum disorder · Meta-analysis

Introduction

Autism spectrum disorders (ASDs) are a class of neurodevelopmental disorders characterized by impairments in social communication, developmental delay, and repetitive behaviors with serious consequences for the children and the families [1]. The prevalence of ASD has been increasing over the years and the recently estimated prevalence in the USA was 1.34% among 4-year-old children [2].

While genetics play an important role in the etiology of ASD, environmental risk factors are not well understood. Recent studies evidenced that environmental factors contributed to about 40–50% of variance in ASD [3–5]. As the developing brain in utero is susceptible to environmental factors [6], evaluating non-genetic influences contributing to ASD is of significance for identifying potential risk factors and may help to mitigate the risk [7]. Of note, the increased prevalence of ASD has been paralleled by an increasing trend in prevalence of maternal obesity [8, 9], which is a nutritional and metabolic disorder with long-term health consequences to both the mother and the child [10], and has led to the speculation that the two trends might be related.

In 2011, Layll et al. firstly reported that maternal late adolescent obesity may have a doubling of the risk of ASD in offspring [11]. Since then, a growing number of studies

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that reported a significant association between maternal obesity and ASD have been published [12–15]. Further, a large number of observational studies have explored the issue of the different weight categories, providing inconsistent results [16–23]. Until recently, several studies have taken paternal obesity into account, with no definitive conclusion [14, 17, 20]. Therefore, the magnitude of the overall effect of parental obesity, overweight or underweight on ASD is unknown, mainly due to substantial differences in sample characteristics and study methodology.

Previous meta-analysis found a significant association between maternal obesity and ASD [24], but it only included five relevant studies and did not follow the standard BMI categories. More importantly, a large number of studies in this area have been published in recent years and have explored this issue on paternal BMI, with inconsistent outcomes [16, 17, 19–22]. To better quantitatively analyze this growing literature on parental BMI and ASD, we performed this systematic review and meta-analysis to comprehensively evaluate the association between parental obesity, overweight or underweight and ASD.

Methods

Search strategy

Cochrane Library, EMBASE, Pubmed and PsycINFO databases were searched up to March 2018. Medical Subject Headings (MeSH), Emtree Headings and other relevant key words were used to find studies related to parental BMI and risk of ASD in offspring. The terms we used were as follows: autism/autistic/ASD/Asperger/Autism Spectrum Disorder and weight/obesity/overweight/underweight/obese/body mass index/BMI and parental/maternal/paternal/mother/father/prenatal/perinatal. There was no language restriction applied. In addition, reference lists of other articles were reviewed to find studies that might be potentially eligible for our inclusion criteria.

Inclusion and exclusion criteria

Two investigators screened records independently. First, titles and abstracts of articles were reviewed and full texts would be retrieved by investigators if necessary. Then, a study was included if all the following inclusion criteria were met:

(1) The study was an original observational study;
(2) The study evaluated maternal or paternal BMI and risk of ASD in offspring;
(3) Studies addressed the outcome of interest (ASD);
(4) The study reported associated odds ratio (OR), relative risk (RR) or hazard ratio (HR).

A study would be excluded if it met one or more of the following exclusion criteria:

(1) The study used obesity, overweight or other ambiguous terms rather than BMI for the definition of exposure;
(2) The study included other developmental disorders, such as intellectual disability and developmental delay as the outcome of interest but did not exclude them from ASD in their statistical analysis;
(3) The parental BMI used was not measured at baseline (pre-pregnancy).

Data extraction

The information of included studies was extracted by two investigators using a standardized data collection form independently, and all the differences and contradictions were addressed by the primary author. The following information was extracted: first author's name, published years, the country of the study conducted, study design (cohort or case–control), data source, age of offspring, study period, sample size, ASD criteria, maternal or paternal weight categories, exposure information, main findings and adjusted covariates. OR, RR, or HR with corresponding 95% confidence interval (CI) was also extracted from each included study.

Study quality assessment

For the assessment of study quality, we used the Newcastle–Ottawa Quality Assessment Scale (NOS), which is recommended by Cochrane Collaboration [25]. The NOS comprises three domains: Selection (maximum 4 stars), Comparability (maximum 2 stars) and Exposure (maximum 3 stars). A study with 6 or more stars was regarded as high quality. Any discrepancy during study quality assessment was resolved by discussion with the primary author after referring to the original paper.

Statistical analysis

The Cochrane Collaboration Review Manager Software (RevMan version 5.3) and Stata statistical software (version 12.0; Stata Corporation, College Station, TX, USA) were used for performing meta-analysis and associated statistical analysis. HR, RR or OR with corresponding 95% CIs was used as the common measure of the association in included studies. Heterogeneity, the differences between studies, was valued by I^2 statistics, and the I^2 value of 25%, 50%, 75% was regarded as low, medium and high degrees

of heterogeneity [26]. A random-effects model was used for performing meta-analysis since substantial heterogeneity was identified.

Sensitivity analysis was performed to examine the robustness of pooled results. Subgroup analyses were performed first to explore the source of heterogeneity between studies and second to examine the consistency of pooled estimates in subgroups. Nine subgroups regarding characteristics and methodological aspects of included studies were set up, including study design (cohort vs. case–control), geographical area (America vs. Europe vs. Asia), number of cases (≥ 200 vs. < 200), data source (population based vs. hospital based), ASD ascertainment (standard measure vs. parental report), exposure information (medical record vs. self-report), NOS score (≥ 6 vs. < 6), and whether adjusted for covariates of child sex, maternal age and maternal diabetes (Yes vs. No) in their multivariable statistical analysis. The test of publication bias, sensitivity analysis and subgroups analyses were not performed for our secondary outcomes (paternal BMI and ASD risk) as the number of included studies was limited ($N = 3$). Potential publication bias was assessed by visually observing funnel plot, and Egger's and Begg's regression model. If asymmetry of the funnel plots were observed, the Duval and Tweedie nonparametric 'trim and fill' method for estimating the number of missing studies, would be applied by adjust the funnel plot and recalculate the pooled estimates [27].

Results

Literature search

A total of 1795 records (1792 from online database and 3 from hand search) were retrieved by our search strategy. After removing duplicates, 1456 records remained for screening. Then, full text of 25 articles was reviewed after excluding studies of irrelevant topics (Fig. 1). Finally, 13 studies that met all the inclusion criteria were included for meta-analysis (Table 1) [7–13, 15–19].

Study characteristics

Of the 13 included studies, three were case–control studies and ten were cohort studies, four were based on the sample of hospital and nine collected data from population-based observations. For the geographical area of included studies, six were conducted in America, five in Europe, and one in Asia. The ASD cases ranged from 14 to 6420. All studies measured pre-pregnancy BMI as exposure, and standard BMI categories were applied in most studies. All studies were published in recent years. Quality scores of the most of the included studies were high. Details of study quality assessment are provided in the Table S1 and Table S2 in the Supplement.

Meta-analysis

The pooled ORs for maternal obesity, overweight and ASD were 1.41 (95% CI: 1.19–1.67, $P_{\text{heterogeneity}} < 0.001$, $I^2 = 79.3\%$) and 1.16 (95% CI: 1.05–1.27, $P_{\text{heterogeneity}} = 0.005$, $I^2 = 60.0\%$), respectively, with substantial and moderate heterogeneity (Fig. 2). While, the OR for maternal underweight and ASD was 1.08 (95% CI: 0.98–1.20) with low heterogeneity ($P_{\text{heterogeneity}} = 0.359$, $I^2 = 9.1\%$).

As for paternal BMI and ASD, the pooled ORs for paternal obesity, overweight and underweight were 1.28 (95% CI: 0.94–1.74, $P_{\text{heterogeneity}} = 0.006$, $I^2 = 80.3\%$), 1.07 (95% CI: 0.99–1.15, $P_{\text{heterogeneity}} = 0.855$, $I^2 = 0$) and 1.12 (95% CI: 0.87–1.44, $P_{\text{heterogeneity}} = 0.229$, $I^2 = 31.0\%$), respectively (Fig. 3).

Sensitivity analysis

For maternal BMI and ASD, sensitivity analysis was performed to examine the effect of individual study by excluding each study at one time and rerunning meta-analysis of the rest. As a result, none of the exclusion of any specific study would significantly change the pooled estimated results (Figure S1, S2 and S3 in the Supplement); for maternal obesity and ASD, we also found that the heterogeneity was decreased to be moderate ($I^2 = 53.3\%$, $P_{\text{heterogeneity}} = 0.023$) when the study by Gardner et al. [13] was excluded but the result was not changed [OR 1.34 (95% CI 1.17–1.53)].

Subgroup analyses

In our subgroup analyses, results in most subgroups remained the trend of the main analysis. While results in several subgroups were changed to be statistically insignificant, such as self-report of BMI, parental report of ASD and case number < 200, those subgroups were limited in number of studies or less methodological sound. Subgroup analyses were also performed to explore the heterogeneity; however, none of the nine subgroups were identified as important sources as the between-study heterogeneity was statistically significant in most categories (Table 2).

Publication bias

We first visually observed funnel plots and then used Begg's and Egger's regression model to assess the publication bias. Although asymmetry (publication bias) was revealed by funnel plot, results of Begg's (maternal obesity: $P = 1.000$; maternal overweight: $P = 0.876$; maternal underweight: $P = 0.788$) and Egger's (maternal obesity: $P = 0.665$; maternal overweight:

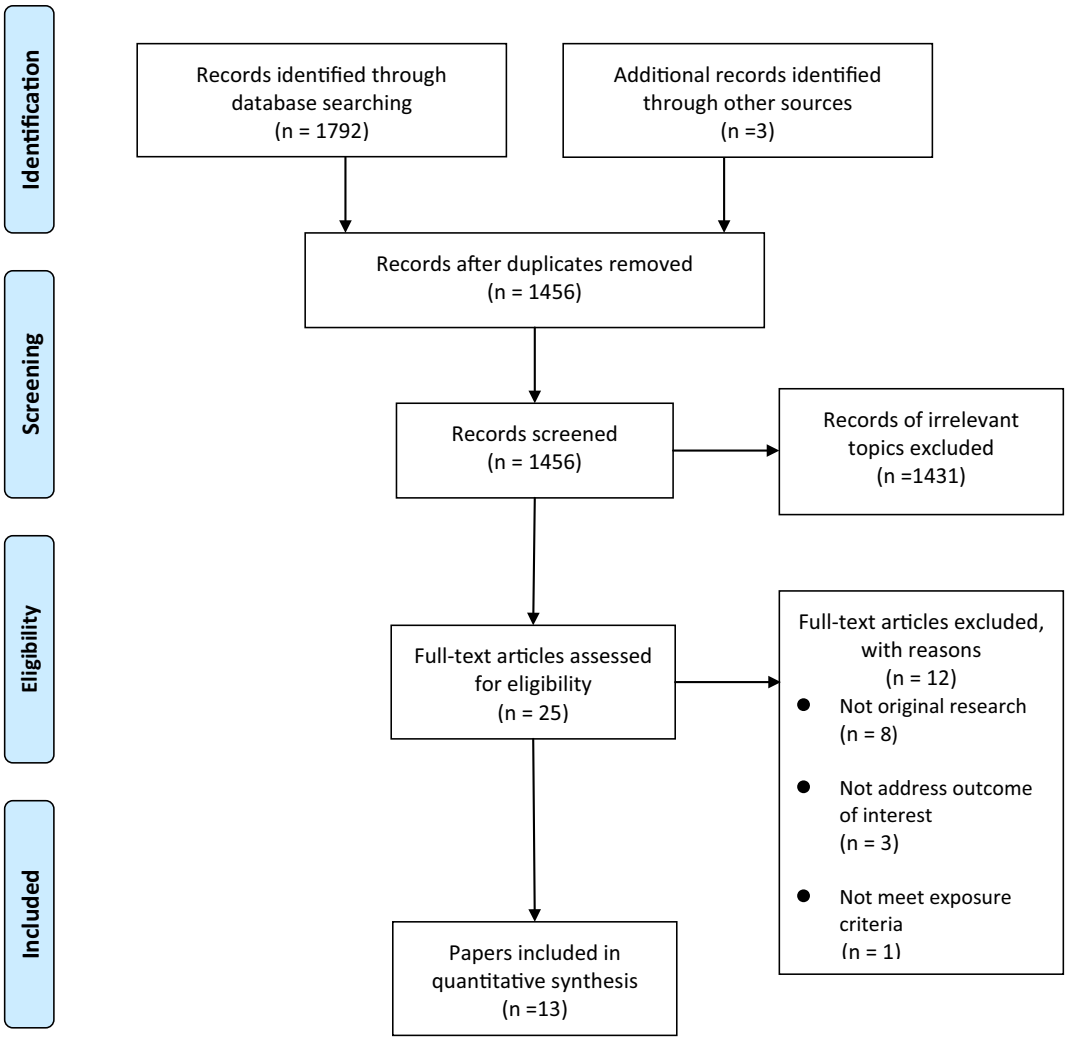

Fig. 1 Flow diagram of the study selection process

$P = 0.893$; maternal underweight: $P = 0.671$) regression showed no obvious publication bias. Since potential publication bias was detected by asymmetry of the funnel plots, the 'trim and fill' method was used. As a result, one and three studies with negative results were respectively missing for maternal obesity, overweight and underweight (Figure S4, S5 and S6 in the Supplement); however, the filled estimates did not lead to dissimilar results [maternal obesity: OR 1.33 (95% CI 1.13–1.57); maternal overweight: OR 1.14 (95% CI 1.05–1.24); maternal underweight: OR, 0.97 (95% CI 0.85–1.10)]. Summary of meta-analysis, test of publication bias and trim and fill analysis were presented in Table 3.

Discussion

Main findings

This meta-analysis is based on current epidemiological evidence pertaining to ASD risk in children of parents of different BMI categories. Our findings suggest that maternal obesity and overweight increase odds of ASD in offspring by 40% and 16%, respectively; while there is no significant association of maternal underweight or paternal BMI with ASD. Maternal obesity may not contribute much

Table 1 Baseline characteristics of included studies in the meta-analysis

Authors and published years (country)	Study design	Data source	Children's age	Study period	Sample size[a]	ASD ascertainment	Weight categories	Exposure (BMI) information	Main Findings	Adjusted covariates
Lyall et al. 2011 (USA)	Cohort	The population-based Nurses' Health Study II	NA	1989–2005	743/60853	Parental report of ASD	Maternal pre-pregnancy BMI < 20 20–21.9 22–24.9 25–29.9 ≥ 30	Self-report	Maternal BMI was not associated with ASD	Age at baseline, Race, Household income, Age at menarche, Menstrual cycle regularity—high school, Time to cycle regularity, Cycle length ages 18–22, BMI at 18, BMI at baseline
Krakowiak et al. 2012 (USA)	C–C	The population-based CHARGE study in California	Range 2–5 years	2003–2010	517/315	ADI-R, ADOS	Maternal pre-pregnancy BMI 18.5–24.9 ≥ 30	Medical record	The risk of having a child with ASD was significantly increased among obese women (ASD, OR: 1.67, 95% CI: 1.10–2.56)	Mother's age at delivery, race/ethnicity, education level, delivery payer, calendar time, child's age at enrollment and gender, and catchment area
Moss et al., 2014 (USA)	Cohort	The nationally representative population-based Early Childhood Longitudinal Study—birth cohort	Range 4–5 years	2001	100/4800	Parent report of autism	Maternal pre-pregnancy BMI < 18.5 25–29.9 ≥ 30	Self-report	Maternal underweight or obese was not directly associated with ASD, but being underweight or obese during pre-pregnancy may indirectly increase risk for autism from increased odds of low birth weight and accelerated postnatal growth	Maternal age, child sex, birthweight, rates of height growth and weight gain
Reynolds et al. 2014 (USA)	Cohort	The hospital cohort study took place in a level-III, 75-bed neonatal intensive care unit in the Midwestern United States	Infants at 2 years	2007–2010	14/62	M-CHAT	Maternal pre-pregnancy BMI 18.5–24.9 ≥ 30	Medical record	Maternal obesity was associated with positive screen for autism (OR = 1.67, 95% CI: 1.10–2.56)	Gestational age at birth and markers of sociodemographics

Table 1 (continued)

Authors and published years (country)	Study design	Data source	Children's age	Study period	Sample size[a]	ASD ascertainment	Weight categories	Exposure (BMI) information	Main Findings	Adjusted covariates
Suren et al., 2014 (Norway)	Cohort	The population-based prospective Norwegian Mother and Child Cohort Study.	Range 4.0–13.1 years	1999–2009	419/92909	ADI-R, ADOS	Maternal pre-pregnancy BMI <18.5 18.5–24.9 25–29.9 ≥30 Paternal pre-pregnancy BMI <25 25–29.9 ≥30	Self-report	Maternal obesity was not associated with ASD risk (OR = 1.09, 95% CI: 0.74–1.59), whereas paternal obesity is an independent risk factor for ASDs in children (OR = 1.53, 95% CI: 1.07–2.17)	Parental education levels, paternal BMI, child's year of birth, and maternal parity
Gardner et al. 2015 (Sweden)	Cohort	A prospective register-based Stockholm Youth Cohort study	Range 0–17 years	1984–2007	6420/333 057	Ascertained by ICD-9 (299) or ICD-10 (F84) and DSM-IV (299)	Parental pre-pregnancy BMI <18.5 18.5–24.9 25–29.9 ≥30	Medical record	Higher maternal BMI at pregnancy and paternal BMI were independently associated with increased risk of ASD in offspring. But the maternal BMI-ASD association may be affected by residual confounding.	Sex, birth year of the child, parity, maternal age at the time of birth, paternal age at the time of birth, maternal country of birth, SES factors, parental history of psychiatric treatment and parental BMI
Ling et al. 2015 (China)	C–C	A hospital-based study recruited in Changsha, Xiamen, Wuhan and Liuzhou	Median 3.5 (range 1–5) years	2013–2014	181/181	DSM—IV including autistic disorder, Asperger disorder or PDD-NOS	Maternal pre-pregnancy BMI <18.5 18.5–24.9 ≥25	Medical record	Overweight or obesity before pregnancy were associated with autism in children (OR = 3.71, 95% CI: 1.34–10.24)	Maternal education level, age, parity, threatened abortion, pregnancy nutrition, history of diseases, medication history
Xiang et al. 2015 (USA)	Cohort	Retrospective longitudinal cohort study at Kaiser Permanente Southern California hospitals	1.5–2 years	1995–2009	3388/322323	M-CHAT	Maternal pre-pregnancy BMI <18.5 18.5–24.9 25–29.9 ≥30	Medical record	Maternal BMI was slightly associated with ASD (HR = 1.22, 95% CI: 1.00 –1.49)	Maternal age at delivery, parity, education, self-reported maternal race/ethnicity, median family household income based on census tract of residence, history of comorbidity, and sex of the child

Table 1 (continued)

Authors and published years (country)	Study design	Data source	Children's age	Study period	Sample size[a]	ASD ascertainment	Weight categories	Exposure (BMI) information	Main Findings	Adjusted covariates
Connolly et al. 2016 (USA)	C–C	The electronic medical records at Cincinnati Children's Hospital Medical Center and the Ohio state birth records	Mean 5.5 years	2009–2014	503/38810	Ascertained by ICD-9 code 299 autism (299.00) and/or pervasive developmental disorder not otherwise specified (299.90)	Maternal pre-pregnancy BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	Medical record	Maternal obesity was associated with a statistically significant increased odds of having a child with an ASD (OR = 1.50, 95% CI: 1.21, 1.86)	Maternal age at birth, maternal race, year of birth
Li et al. 2016 (USA)	Cohort	A subset of the population-based Boston Birth Cohort recruited at birth at the Boston Medical Center	Median 5.6 (range 1–13.8) years	1998–2014	102/2734	Ascertained by ICD-9 code 299 autism (299.00), Asperger syndrome (299.80), and/or pervasive developmental disorder not otherwise specified (299.90)	Maternal pre-pregnancy BMI < 24.9 25–29.9 ≥ 30	Self-report	Maternal pre-pregnancy obesity and was associated with increased risk for ASD (HR = 1.92, 95% CI: 1.20–3.07)	Child year of birth, child gender, maternal age, parity, smoking during pregnancy, and preterm birth

Table 1 (continued)

Authors and published years (country)	Study design	Data source	Children's age	Study period	Sample size[a]	ASD ascertainment	Weight categories	Exposure (BMI) information	Main Findings	Adjusted covariates
Getz et al. 2016 (UK)	C–C	A population-based General Practice Research Database maintained by the Boston Collaborative Drug Surveillance Program	Average 6.2 (SD ± 3.2) years	1993–2008	889/3530	Ascertained by Read Codes: E140.00 (Infantile autism), E140.12 (Autism), E140.13 (Childhood autism), E140z00 (Infantile autism NOS), Eu84000 (Childhood autism), Eu84011 (Autistic disorder), Eu84012 (Infantile autism), Eu84z11 (ASD NOS), Eu84500 (Asperger syndrome), Eu84100 (Atypical autism), Eu84y00 (Other PDD), and Eu84z00 (PDD unspecified)	Maternal pre-pregnancy BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	Medical record	The association between maternal BMI and ASD occurrence was non-linear and J-shaped	Maternal age (continuous), maternal pre-pregnancy depression, diabetes, smoking status, drug abuse, alcoholism, in addition to matching factors (birth year, sex, and general practice)

Table 1 (continued)

Authors and published years (country)	Study design	Data source	Children's age	Study period	Sample size[a]	ASD ascertainment	Weight categories	Exposure (BMI) information	Main Findings	Adjusted covariates
Andersen et al. 2017 (Denmark)	Cohort	The Danish National Birth Cohort	Average age of 13.3 years	1996–2002	1118/81892	Ascertained by ICD-10 including F84.0, F84.1, F84.5, F84.8 and F84.9	Maternal pre-pregnancy BMI < 18.5 18.5–24.9 25–29.9 30–34.9 ≥ 35	Self-report	An elevated risk of ASD in children with underweight (OR = 1.30, 95% CI: 1.01 – 1.69) or obese mothers (OR = 1.39, 95% CI: 1.11–1.75)	Socioeconomic status, maternal smoking, maternal psychiatric diagnoses, parental age, gestational age and birth weight
Casas et al. 2017 (Spain)	Cohort	The population-based birth cohort INMA	Mean 4.8 (SD ± 0.6) years	2003–2008	NA/1827	Childhood Asperger Syndrome Test	Parental pre-pregnancy BMI < 18.5 18.5–24.9 25.0–29.9 ≥ 30.0	Self-report	Parental BMI was not associated with autism symptoms	Age, sex of the child, maternal and paternal education and social class, maternal age, parity, maternal employment status during pregnancy and at 5 years, maternal IQ, breast feeding duration, daycare attendance, and child physical activity, paternal or maternal BMI

ASD autism spectrum disorder, *ADI-R* Autism Diagnostic Interview-Revised, *ADOS* Autism Diagnostic Observation Schedule, *BMI* body mass index, *CI* confidence interval, *CHARGE* Childhood Autism Risks from Genetics and the Environment, *C–C* case–control, *DSM-IV* diagnosis and statistical manual of mental health disorders, fourth edition. *HR* hazard ratio, *INMA* INfancia y Medio Ambiente, *ICD* international classification of diseases, *M-CHAT* Modified Checklist for Autism in Toddlers, *NA* not available, *NOS* not otherwise specified, *OR* odds ratio, *PDD* pervasive developmental disorder, *SD* Standard deviation

[a]Sample sizes were incident cases/participants for cohort studies, and cases/controls for case–control studies

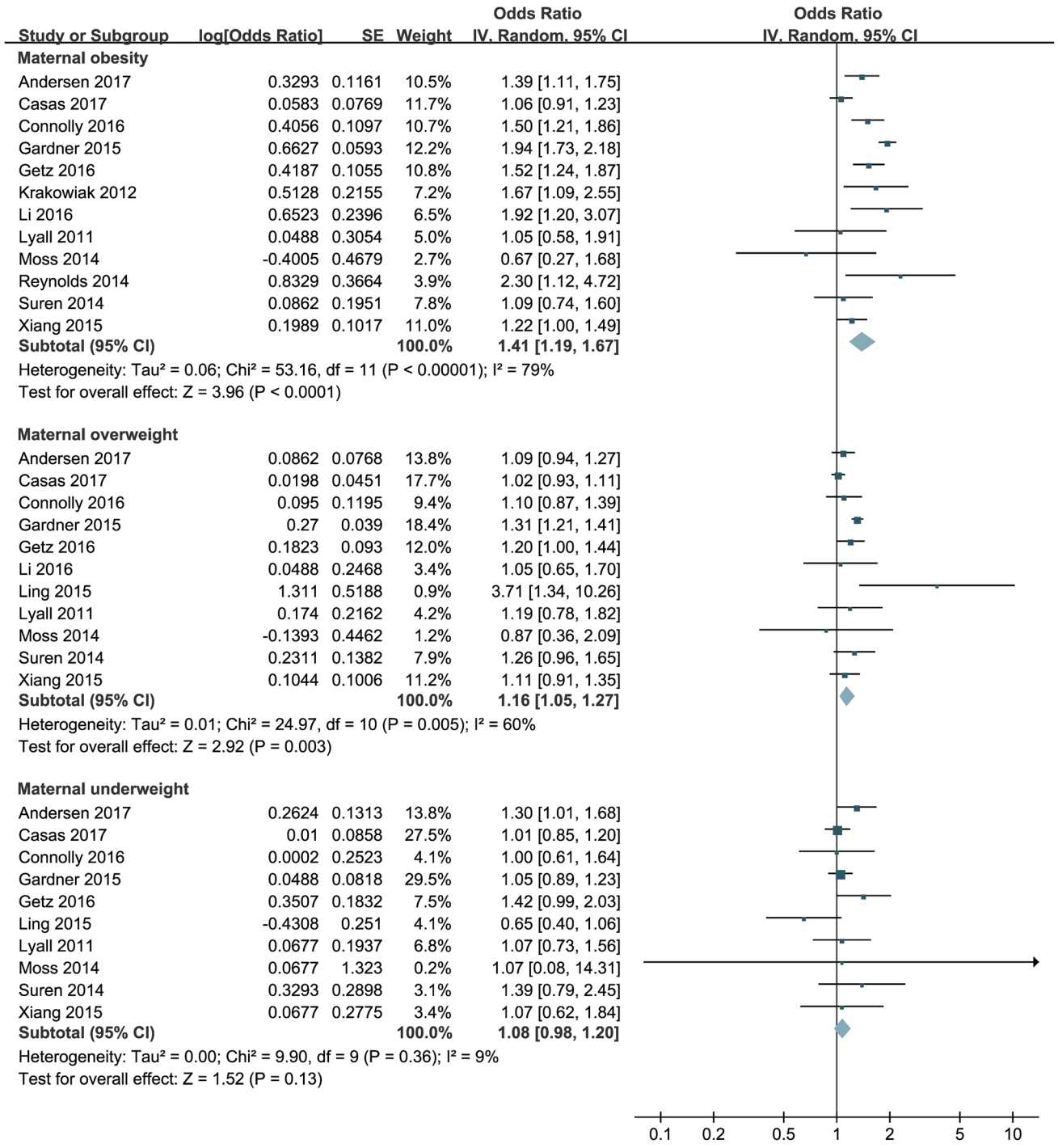

Fig. 2 Meta-analysis on maternal body mass index and autism spectrum disorder

to the etiology of ASD and could only explain a part of the remaining variance, compared to other environmental risk factors, such as birth complications and advanced age, that have shown strong links to ASD [28–30]. However, pre-pregnancy weight control as precaution seems to be practical and should be encouraged because maternal elevated BMI may lead to numerous adverse maternal and infant outcomes [31–34].

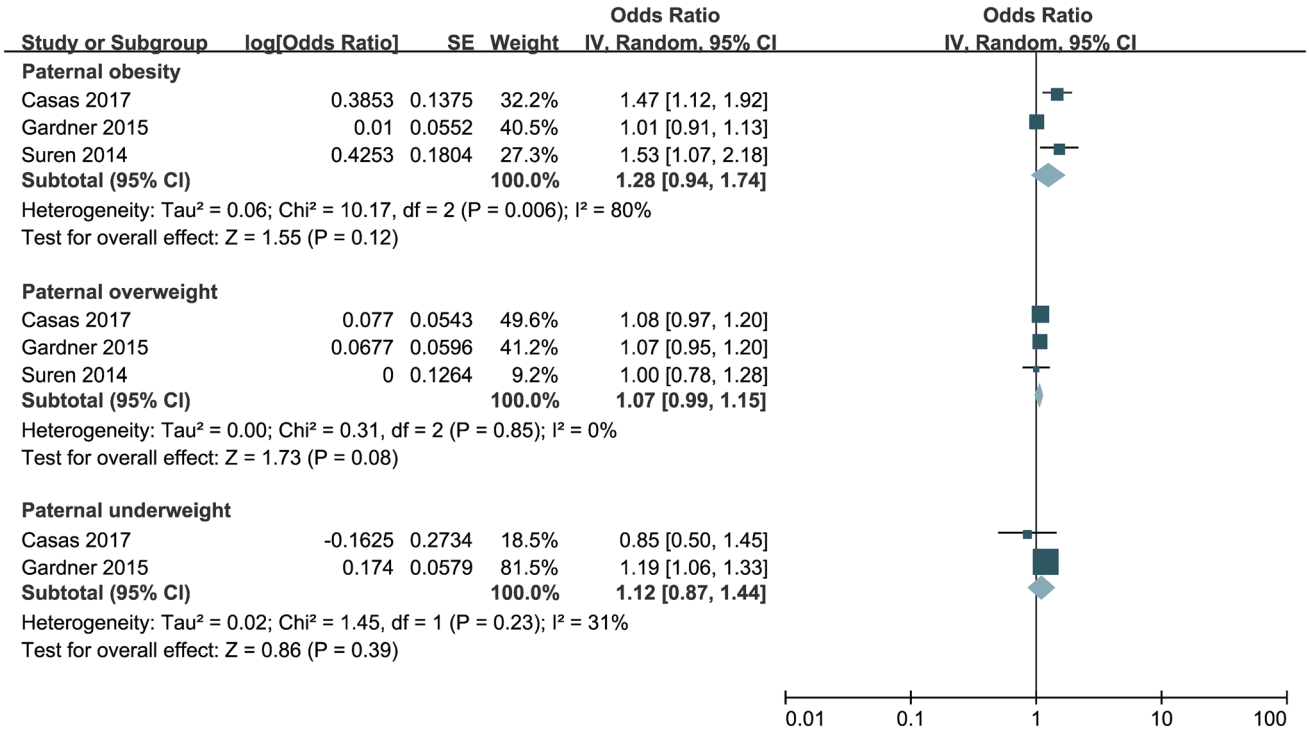

Fig. 3 Meta-analysis on paternal body mass index and autism spectrum disorder

Strengths and limitations

There are certain strengths of this meta-analysis. The first is the inclusion of all eligible observational studies with comprehensive quantitative data analysis presented in a systematic fashion. In addition to maternal BMI, we also analyzed paternal BMI and ASD risk as secondary outcomes to provide more information. The second is the robustness of the pooled estimates. Our results were generally robust in sensitivity analysis as well as in subgroup analyses; although publication bias may exist, the filled estimates results were unchanged.

Several limitations in our present study may have influenced the combined results. First, the number of eligible studies is limited and may impact the accuracy of the combined results, especially for studies on paternal BMI and ASD risk. Sensitivity analysis, subgroup analyses and test of publication bias were, thus, not performed for the group of paternal BMI and ASD as the number of estimates in each subgroup would be insufficient to permit meta-analysis. Second, marked heterogeneity was observed in the meta-analysis. Results from subgroup analyses also failed to determine sources of heterogeneity. Third, publication bias may have occurred. Among three maternal BMI categories, obesity, overweight and underweight, all were not symmetric in funnel plots and several missing studies were detected. Fourth, several known risk factors for ASD such as family history of psychiatric disorders, maternal age and child's sex have not been fully considered in the statistical analysis in several included studies. Therefore, the reported overall effect sizes were differed and may contribute to the heterogeneity.

Interpretation

Several mechanisms for the association between maternal obesity and increased ASD risk have been proposed. Immunological factors are the most often mentioned explanations. Maternal overweight and obesity would induce placenta inflammation [35] and may subsequently result in a fetal systemic inflammatory response and abnormalities in cytokines or inflammatory mediators levels in children with ASD [36, 37]. Also, maternal obesity contributed to modification of the expression of several important genes, such as apolipoprotein D, which affects fetal neurodevelopment [38]. Besides, maternal nutritional balance, which is linked to obesity, has been shown to have direct influence in fetal neurodevelopment [39]. However, one should not ignore that the association observed may be simultaneously mediated by multiple factors since maternal high BMI could also induce several other consequences which may play as mediators in the association. For example, obesity is associated with hypertension and diabetes mellitus which were reported to be associated with increased risk of ASD in offspring [16, 40]. Besides,

Table 2 Summary of subgroup analyses on maternal BMI and risk of ASD in offspring

Variables	BMI ≥ 30					BMI 25–30					BMI ≤ 18.5				
	No. of studies	Pooled estimates	95% CI	$P_{heterogeneity}$ value	I^2 %	No. of studies	Pooled estimates	95% CI	$P_{heterogeneity}$ value	I^2 %	No. of studies	Pooled estimates	95% CI	$P_{heterogeneity}$ value	I^2 %
Study design															
Cohort	9	1.35	1.07, 1.71	< 0.0001	84.8	8	1.14	1.02, 1.27	0.006	64.3	7	1.08	0.98, 1.19	0.746	0.0
Case–control	3	1.53	1.33, 1.76	0.904	0.0	3	1.25	0.94, 1.67	0.073	61.9	3	1.01	0.72, 1.42	0.038	69.4
Geographical Area															
America	7	1.43	1.18, 1.73	0.132	39.0	5	1.10	0.96, 1.26	0.978	0.0	4	1.02	0.88, 1.18	0.986	0.0
Europe	5	1.38	1.05, 1.82	< 0.0001	81.2	5	1.16	1.03, 1.32	0.001	78.8	5	1.13	0.99, 1.28	0.238	27.5
Asia	0	–	–	–	–	1	3.71	1.34, 10.26	–	–	1	0.65	0.40, 1.06	–	–
Case number															
≥ 200	8	1.45	1.23, 1.71	< 0.0001	72.5	7	1.21	1.13, 1.30	0.310	15.8	7	1.10	1.00, 1.21	0.446	0.0
< 200	4	1.36	0.86, 2.16	0.014	71.7	4	1.15	0.80, 1.66	0.098	52.4	3	0.90	0.66, 1.22	0.251	27.7
Data source															
Population based	9	1.38	1.11, 1.72	< 0.0001	83.3	8	1.15	1.03, 1.29	0.007	64.1	7	1.10	1.00, 1.21	0.476	0.0
Hospital based	3	1.42	1.12, 1.79	0.137	49.8	3	1.21	0.80, 1.63	0.070	62.5	3	0.93	0.73, 1.18	0.248	28.3
ASD ascertainment															
Standard measure	10	1.46	1.23, 1.74	< 0.0001	81.7	9	1.16	1.04, 1.29	0.002	67.4	8	1.07	0.96, 1.20	0.166	32.9
Parental report	2	0.92	0.56, 1.52	0.421	0.0	2	1.12	0.77, 1.64	0.528	0.0	2	1.07	0.73, 1.56	1.000	0.0
Exposure information															
Medical record	6	1.59	1.32, 1.67	0.002	72.9	5	1.22	1.08, 1.39	0.076	52.8	5	1.04	0.88, 1.21	0.317	13.7
Self-report	6	1.21	0.99, 1.47	0.081	49.0	6	1.05	0.98, 1.13	0.717	0.0	5	1.10	0.97, 1.25	0.512	0.0
Adjusted for child sex															
Yes	7	1.43	1.11, 1.83	< 0.0001	87.4	6	1.14	1.00, 1.31	0.002	73.1	5	1.06	0.95, 1.18	0.579	0.0
No	5	1.39	1.18, 1.63	0.312	16.1	5	1.17	1.00, 1.37	0.187	31.5	5	1.06	0.87, 1.30	0.110	47.0
Adjusted for maternal age															
Yes	10	1.41	1.18, 1.69	< 0.0001	81.7	10	1.15	1.03, 1.27	0.003	63.4	9	1.06	0.96, 1.17	0.299	16.1
No	2	1.48	0.72, 3.05	0.072	69.1	1	1.26	0.96, 1.65	–	–	1	1.39	0.79, 2.45	–	–
Adjusted for maternal diabetes															
Yes	3	1.44	1.24, 1.66	0.655	0.0	1	1.20	1.00, 1.44	–	–	1	1.42	0.99, 2.03	–	–
No	9	1.34	1.06, 1.68	< 0.0001	84.5	10	1.15	1.03, 1.28	0.003	63.8	9	1.06	0.96, 1.14	0.457	0.0

Table 2 (continued)

Variables	BMI ≥ 30					BMI 25–30					BMI ≤ 18.5				
	No. of studies	Pooled estimates	95% CI	$P_{heterogeneity}$ value	I^2 %	No. of studies	Pooled estimates	95% CI	$P_{heterogeneity}$ value	I^2 %	No. of studies	Pooled estimates	95% CI	$P_{heterogeneity}$ value	I^2 %
NOS score															
≥ 6	10	1.40	1.17, 1.68	< 0.0001	82.2	9	1.14	1.04, 1.25	0.011	59.5	8	1.08	0.99, 1.17	0.482	0.0
< 6	2	1.51	0.70, 3.26	0.100	63.0	2	1.91	0.64, 5.71	0.003	63.6	2	0.86	0.53, 1.39	0.116	59.5

ASD Autism spectrum disorder, *BMI* body mass index

maternal lifestyle factors, such as high fat intake, may also affect obesity and subsequently increase ASD risk [41]. Therefore, studies need to be more methodologically rigorous to minimize the influences of other risk factors.

Several inconsistencies in the published studies should also be mentioned. First, the ascertainments of ASD in included studies were highly variable, which may affect the results and contribute to the heterogeneity because data collected from parental reports may not be valid. Second, study results may be biased by confounding effects. For example, previous studies have evidenced that maternal diabetes is a risk factor for ASD [42]; however, only one included study has adjusted maternal diabetes as a potential confounder in their multivariable models [19]. Diabetes is often accompanied by obesity and, thus, may directly or indirectly increase ASD risk. Third, different weight categories may have resulted in discrepant outcomes. Although we excluded studies not using standard BMI categories, weight categories were not consistent in all included studies. For example, Ling et al. [23]. set up weight categories: Maternal BMI < 18.5; 18.5–24.9; ≥ 25; but the obesity group (BMI ≥ 30) was not subdivided due to a small number of cases, and we extracted data for BMI ≥ 25 and pooled in the maternal overweight group. Forth, the exposure information is an important factor which could impact the findings. For the six studies that collected BMI information from self-report, the pooled estimates showed an insignificant association of maternal BMI with ASD, suggesting that the weight status may have been under-reported. Therefore, the effect size in the main analysis could have been slightly underestimated. Fifth, the time point is a potential contributing factor for heterogeneity. While studies used pre-pregnancy BMI, it was not clear how close the time point was to the pregnancy. The estimates may vary considerably depending on BMI at different time point. For example, Layll et al. reported that maternal obesity at age 18 may have a doubling of the risk of ASD in offspring, but their later analysis found that maternal BMI at baseline was not significantly associated with ASD [11].

Conclusions

In conclusion, this meta-analysis evidenced an association between maternal obesity, overweight and ASD, but not maternal underweight and paternal. High-quality data regarding this issue appear to be significantly lacking and further detailed studies investigating the association are warranted to address more confounding factors and to identify potential mediators of these associations; however, pre-pregnancy weight control is suggested.

Table 3 Summary of meta-analysis, test of publication bias and trim and fill analysis

Category	No. of studies	Overall effect		Heterogeneity		Publication bias		Trim and fill method	
		Pooled OR	95% CI	I^2 (%)	P	Begg's test	Egger's test	No. of potential missing studies	Filled estimates
Maternal									
Obesity	12	1.41	1.19, 1.67	79.3	< 0.0001	1.000	0.665	1	1.33 (1.13, 1.57)
Overweight	11	1.16	1.05, 1.27	60.0	0.005	0.876	0.893	0	1.14 (1.05, 1.24)
Underweight	10	1.08	0.98, 1.20	9.1	0.359	0.788	0.671	4	0.97 (0.85, 1.10)
Paternal									
Obesity	3	1.28	0.94, 1.74	80.3	0.006	–	–	–	–
Overweight	3	1.07	0.99, 1.15	0.0	0.855	–	–	–	–
Underweight	2	1.12	0.87, 1.44	31.0	0.229	–	–	–	–

OR odds ratio

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent No patients were involved in the design, conduct or interpretation of our review.

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