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Maternal pre-pregnancy obesity and child neurodevelopmental outcomes: A Meta-analysis

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Abstract

This review examined evidence of the association between maternal pre-pregnancy overweight/obesity status and child neurodevelopmental outcomes. PubMed and PsycInfo databases were systematically searched for empirical studies published before April 2017 using keywords related to prenatal obesity and children's neurodevelopment. Of 1483 identified papers, 41 were included in the systematic review, and 32 articles representing 36 cohorts were included in the meta-analysis. Findings indicated that compared with children of normal weight mothers, children whose mothers were overweight or obese prior to pregnancy were at increased risk for compromised neurodevelopmental outcomes (overweight: OR=1.17, 95% CI [1.11, 1.24], $I^2 = 65.51$; obese: OR=1.51; 95% CI [1.35, 1.69], $I^2 = 79.63$). Pre-pregnancy obesity increased the risk of ADHD (OR=1.62; 95% CI [1.23, 2.14], $I^2 = 70.15$), ASD (OR=1.36; 95% CI [1.08, 1.70], $I^2 = 60.52$), developmental delay (OR=1.58; 95% CI [1.39, 1.79], $I^2 = 75.77$), and emotional/behavioral problems (OR=1.42; 95% CI [1.26, 1.59], $I^2 = 87.74$). Given the current obesity prevalence among young adults and women of childbearing age, this association between maternal obesity during pregnancy and atypical child neurodevelopment represents a potentially high public health burden.

Keywords

prenatal obesity; maternal weight; child neurodevelopment; meta-analysis

Introduction

The prevalence of children diagnosed with a mental, behavioral and neurodevelopmental disorder has increased markedly in recent years, and 15% of children ages 2 to 8 are estimated to have one or more neurodevelopmental disabilities.¹ Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) are of particular public health concern with current prevalence estimates in the United States ranging

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between 5% and 11% for ADHD; and 0.8% and 1.1% for ASD.² While genetic factors play an important role in the etiology of ADHD, ASD, and related conditions, non-genetic influences on these neurodevelopmental disorders are not well understood. Understanding the factors contributing to ADHD, ASD and childhood neurodevelopmental capacity is critical to identifying solutions to improve child mental health outcomes and reduce the population prevalence of these conditions.

Prenatal exposure to environmental toxins, stress and nutrition have all been linked to neurodevelopmental outcomes in children.³ Of note, the increase in prevalence of neurodevelopmental problems has also been paralleled by an increase in prevalence of obesity in society. This parallel along with pre-clinical data linking high-fat diet and pre-pregnancy obesity to errant brain and behavioral development in offspring have led to speculation that there may be a link between these two recent trends.⁴ Correspondingly, there has been growing attention to maternal weight status, either pre-pregnancy weight or excess gestational weight gain, on children's neurodevelopmental outcomes.⁵

Early reports suggested that children born to mothers with gestational diabetes, which is linked with maternal obesity, are at higher risk for lower cognitive test scores and behavioral problems.^{6,7} Further, women who are obese have a higher risk of preterm birth,⁸ which is an established risk factor for unfavorable child neurodevelopmental outcomes, including ADHD.⁹ More recently there have been several observational studies reporting associations between pre-pregnancy obesity and neurodevelopmental outcomes in offspring^{10–13} though there are exceptions that find null associations.^{14–16}

The magnitude of the overall effect of pre-pregnancy overweight or obesity on child neurodevelopment is unknown. Current studies vary substantially with respect to differences in the country of origin of the cohort, samples sizes, the types of outcomes being examined, and variation in analytic methods being used. Poor assessment of the outcomes of interest and/or inadequate control for potential genetic effects, such as controlling for maternal cognitive functioning, have been consistent critiques of these studies.^{4,17–19} Thus the true effect of maternal pre-pregnancy weight on children's neurodevelopmental and behavioral functioning has been difficult to determine. To better summarize this growing literature on maternal pre-pregnancy weight and children's neurodevelopmental outcomes, we performed a synthesis and meta-analyses of this literature. The review focused on observational, prospective, retrospective and case-control studies that evaluated the association between pre-pregnancy overweight or obesity (in relation to normal weight) and subsequent childhood neurodevelopmental outcomes.

Methods

This systematic review and meta-analysis was conducted according to established guidelines.^{20,21}

Study Selection

We conducted a comprehensive search of Pubmed (1946 to April 2017) and PsycInfo (1597 to April 2017) using terms (see S-Table 1) related to prenatal, obesity, offspring and

neurodevelopment. The term ‘neurodevelopmental’ included ASD, ADHD, cognitive and intellectual delay and emotional/behavioral problems. We included observational studies irrespective of publication status, language, sample size, follow-up duration or BMI classification standard.

Three coders (CES, KR, AM) examined each article’s title, abstract, and keywords from the search results. Each coder worked independently to determine whether an article met inclusion criteria. If disagreements between coders could not be resolved, the senior author (BFF) was consulted. If relevant articles were misclassified during the initial coding process, two other techniques (see below for more detail) were used to help uncover the reports again. In total, 1483 abstracts were examined – 57 (4%) were deemed to meet inclusion criteria.

Two other types of searches were conducted on any empirical study report and/or literature review that was determined to be relevant. We examined reference lists of all reports that met inclusion criteria to determine whether they cited any potentially relevant article (*backward search*). We then conducted a cited reference search to determine whether the reports that met inclusion criteria had been later cited by any potentially relevant article (*forward search*). For backward and forward searches, titles and abstracts were initially reviewed by the first author (CES), and if deemed potentially relevant, the full-text was obtained. These search strategies yielded an additional 6 reports.

To minimize publication bias, we contacted authors whose articles reported maternal obesity and neurodevelopmental outcomes but did not provide adjusted or unadjusted ORs, and requested raw data so that we could calculate unadjusted ORs. For 12 articles (with publication dates within the past 10 years), we received 4 responses that allowed us to include the report in the meta-analysis and 2 responses that provided information to include in the synthesis.

Data Extraction

Numerous characteristics of each study were retrieved using a standardized data collection form. These characteristics encompassed six broad domains: (a) *the research report* included basic information about authorship and date of publication; (b) *study characteristics* included information about the cohort, source of study population, and study design; (c) *quality indicators* to assess observational studies (see below); (d) *sample information* included demographic characteristics of the cohorts; (e) *outcome measures* included information pertaining to the neurodevelopmental outcomes and covariates; and (f) *estimate of effect size* detailed the information needed to derive an unadjusted OR or adjusted OR and 95% confidence intervals (CIs).

Data extraction was completed by 4 reviewers (CB, KR, AS, AM), with each article being independently coded twice. If there was a discrepancy in coding, the two coders discussed each disagreement until agreement was reached. If the disagreement could not be resolved, the first author was consulted. This method results in high effective reliability.²²

Quality assessment—A Quality Assessment Scale was developed based on Tooth et al.²³ and similar to Yu et al.²⁴ (see S-Table 2). We assessed the quality of all included studies based on 8 indicators: type of study, loss to follow-up, sample size, participant selection, comparability of groups, statistical methods, criteria for determining and categorizing pre-pregnancy weight, and measurement of neurodevelopmental outcome. The quality of each study was classified as high (>14), medium (11–14), or low (<11) by summing scores from the 8 indicators.

Identification of statistical outliers—We examined the distribution of ORs to determine if any statistical outliers existed using the maximum normed residual test and any outlier identified was set equal to the value of their next nearest neighbor.²⁵

Statistical Analysis—For all outcomes, the ORs and 95% CI extracted from each eligible study were used as the common measure of association. Adjusted ORs were given preference when both unadjusted and adjusted ORs were reported. A random effects model was used to account for possible heterogeneity between studies.

We performed subgroup analyses according to the BMI pre-pregnancy categories specified in the article. In most cases, the article defined weight groups according to WHO categories^{26,27} (i.e., BMI 18.5 – 24.99 for normal weight; BMI 25 – 29.99 for overweight; and BMI > 30 for obese, reported in kg/m² metric), although there were some exceptions. Three articles grouped overweight and obese mothers together^{28–30}; thus, these were analyzed only as a combined obese and overweight category. Other articles defined pre-pregnancy obesity as >30 BMI and all other participants were defined as non-obese at <30 BMI; they were analyzed as obese/normal categories, respectively.^{31–33} Two articles collapsed underweight and normal weight into the same category (BMI < 24.99); which was analyzed collectively as normal weight.^{10,34}

We also performed subgroup analyses for the different outcomes: ADHD, ASD, cognitive and intellectual development, and emotional/behavioral problems (i.e., internalizing and externalizing behavior). Several different assessment and/or diagnostic methods were used to determine each neurodevelopmental outcome (see S-Table 3).

A robust variance estimation (RVE) method using random effects assumptions, with small sample correction was used to address the problem of dependence between multiple effect sizes from a single cohort (e.g., separate publications on different outcomes using the same cohort).^{35–37} The small sample correction maintains appropriate Type I error rates. To estimate the effect size weights, an intraclass correlation of $\rho = 0.8$ was specified. The RVE method is limited when the $df < 4$ (or the number of studies < 5 for a single predictor analysis). In these cases, summary statistics were computed with Comprehensive Meta-Analysis software without controlling for study clustering. Heterogeneity was assessed using the I^2 statistic. Approximate guidelines for interpreting I^2 values have been established at 25%, 50% and 75% for low, medium, and large heterogeneity, respectively.^{38,39}

Publication bias—The Duval and Tweedie^{40,41} Trim-and-Fill procedure tested the degree to which the distribution of effect sizes were consistent with variation in effect sizes that

would be predicted if the estimates were normally distributed. The Trim-and-Fill procedure determines publication bias by estimating the values from missing studies that would need to be present for there to be a normal distribution.

Sensitivity analysis—Sensitivity analysis examined effects of varying methodological quality on a study level. We defined higher-quality studies as those that had high scores on the quality measure, employed a prospective study design, had larger sample sizes, controlled for genetic effects and maternal/paternal effects, and computed adjusted ORs.

Software—The Comprehensive Meta-Analysis Version 3.3.070-November 21, 2014 software package was used to calculate the within-study variance for each cohort, to examine publication bias, or to calculate summary statistics when the number of cohorts was less than 5. RVE was conducted using R Package⁴² with syntax provided by Tanner-Smith et al.⁴³ when the number of cohorts was more than 5.

Results

From 1483 articles, 41 articles met our inclusion criteria for the systematic review and 32 of the articles were included in the meta-analysis (Figure 1; S-Table 4 contains excluded studies). Six articles reported the results of case-control studies and 26 reported on cohort studies. Note, four articles included in their analysis 2 cohorts, thus the 32 articles represent analysis of 36 cohorts (see Table 1).^{10–16,28–34,44–61} Geographic regions represented among the cohorts included: United States (20), Netherlands (3), United Kingdom (3), Denmark (2), Finland (3), Sweden (2), Australia (2), Norway (1). Analysis sample sizes ranged from 62 to 333057 offspring (Median = 2087). Of the 146 ORs reported across the 32 studies, one outlier was identified and converted to its next nearest neighbor (9.24 changed to 5.20).²⁶ Cognitive and intellectual development, which included global developmental delay, intellectual disabilities and language disorders, was the most frequently reported neurodevelopmental outcome, followed by ASD, emotional/behavioral symptoms, which included broad-based assessment of internalizing or externalizing behaviors, and diagnosis of ADHD or ADHD symptoms. Table 2 contains summary statistics for all meta-analyses.

Risk of Any Adverse Neurodevelopmental Outcome

For overweight mothers, 22 cohorts from 23 articles contributed to the analysis. The average cohort contributed more than two effect sizes ($M = 2.59$, $MEDIAN = 1.00$, $MIN = 1.00$, $MAX = 15.00$), with a total of 57 ORs (range 0.58 – 2.00). Across these studies, mothers who were overweight prior to pregnancy were 17% more likely to have a child with any adverse neurodevelopmental outcome (OR, 1.17; 95% CI, 1.11, 1.24; $P < .001$, $I^2 = 65.51$). Analysis for publication bias suggests that this OR is underestimated by 0.003.

For obese mothers, 25 cohorts from 27 articles contributed to the analysis. The average cohort contributed three effect sizes ($M = 3.00$, $MEDIAN = 2.00$, $MIN = 1.00$, $MAX = 15.00$). The 75 ORs ranged from 0.26 to 5.20. Results across these studies indicated that mothers who were obese prior to pregnancy were 51% more likely to have a child with any adverse neurodevelopmental outcome (OR, 1.51; 95% CI, 1.35, 1.69; $P < 0.001$, $I^2 = 79.63$). Publication bias analysis suggested that this OR is overestimated by 0.006.

An additional 9 articles were not included in the meta-analyses because of methodological differences in either the quantification of pre-pregnancy BMI, the outcome, or the association: 1 article reported continuous BMI data, 7 articles reported continuous outcome data and 1 article reported hazard ratios. In the study using a continuous BMI data⁶² the investigators found no association between ASD risk at 8 years of age and pre-pregnancy BMI (though they did find ASD risk was associated with pregnancy weight gain).^{62,63} With respect to the studies that examined outcome data continuously, 2 studies investigated cognitive development during infancy and 5 others reported on cognitive and intellectual development in children 3 to 7 years. Among infants, one study reported an association between maternal pre-pregnancy obesity and reduced cognitive development (an adjusted mean difference between normal weight and obesity of -2.7 in one cohort and -3.7 in another) and the other reported no significant associations.^{64,65} Among children 3 to 7 years of age, a significant negative association between maternal pre-pregnancy BMI and child IQ (beta values ranged from -0.10 to -4.03), academic achievement (a mean difference between normal weight and obesity of -3 points or 0.23 SD units) and emotional/behavioral dysregulation (beta values ranged from 0.36 to 4.28) was reported.^{66–70} Finally, Chen et al.⁷¹ investigate maternal pre-pregnancy BMI and offspring's risk of ADHD using a sibling-comparison design and Stratified Cox proportional hazards models. Findings suggested that sibling comparison attenuated the dose-dependent increased risk of offspring's ADHD, indicating that the association may be due to unmeasured familial confounding.

Risk of Specific Neurodevelopmental Outcomes

Compared to children born to mothers who were normal weight prior to their pregnancy, children of overweight mothers were 30% more likely to have ADHD (OR, 1.30; 95% CI, 1.10 – 1.54; $P = 0.01$, $I^2 = 52.97$), 10% more likely to have ASD (OR, 1.10; 95% CI, 1.01 – 1.21; $P = 0.026$, $I^2 = 0.00$) and 23% more likely to have a cognitive/intellectual developmental delay (OR, 1.19; 95% CI, 1.09 – 1.29; $P = .003$, $I^2 = 40.05$). Children of overweight mothers did not exhibit a statistically significant increased odds of emotional or behavioral problems (OR, 1.14; 95% CI, 0.93 – 1.39; $P = .16$, $I^2 = 70.78$).

Compared to children born to mothers who were normal weight prior to their pregnancy, children of obese mothers were 62% more likely to have ADHD (OR, 1.62; 95% CI, 1.23 – 2.14; $P = 0.006$, $I^2 = 70.15$; Figure 2), 36% more likely to have ASD (OR, 1.36; 95% CI, 1.08 – 1.70; $P = 0.015$, $I^2 = 60.52$; Figure 3), 58% more likely to display cognitive or intellectual delay (OR, 1.58; 95% CI, 1.39 – 1.79; $P < 0.001$, $I^2 = 75.77$; Figure 4), and 42% more likely to have an emotional or behavioral problems (OR, 1.42; 95% CI, 1.26 – 1.59; $P < 0.001$, $I^2 = 87.74$; Figure 5).

Sensitivity Analysis

Studies ranked as having a higher quality score produced an overall effect size that was lower than those with lower quality scores. Slightly attenuated effects sizes were observed for those studies with a prospective study design, a larger sample size and methods to control for maternal/paternal or genetic effects in multivariate regression or in study design. (see Table 3).

Discussion

This is the first meta-analysis of studies investigating pre-pregnancy overweight/obesity and child neurodevelopment. Results show that children born to mothers who are overweight or obese are at a higher risk of neurodevelopmental problems, including ADHD, ASD, greater emotional/behavioral problems, and cognitive delay. Relative to children born to mothers who were normal weight during their pregnancy, the risk for any adverse neurodevelopmental outcome was 17% higher among children to mothers who were overweight prior to their pregnancy and 51% higher among children born to mothers who were obese prior to their pregnancy. Higher risk for specific problems (e.g., ADHD) was also observed among children of overweight and obese mothers. These results are summarized across 41 reports with cohorts representing 8 developed countries and sample sizes ranging from 62 to 333,057. Studies of higher quality produced effect sizes that were attenuated, but still statistically significant.

Study Limitations and Strengths

An underlying assumption here was that measured outcomes in the various studies were comparable with respect to the quality. Studies were not excluded based on method of assessment (e.g., health professional diagnosis vs parent self-report). Also, some studies did not use standardized scales, relying instead on selected items from different scales. Those that used standardized scales differed in defining levels of problematic functioning, with some studies using cutoff score defined by normative data and others using data-driven cutpoints (e.g., higher than the 90th percentile). To advance the literature it would be useful for future studies to use standardized scales as well as include individually-administered measures of child cognitive and neurodevelopmental functioning.

A broad limitation of this field is that pre-pregnancy BMI is almost always based on maternal report of weight prior to last menstrual period, ascertained either via medical records or via self-report. There is some evidence that women who are obese underreport their weight status;^{72,73} however, data from birth cohort studies find that the discrepancy between maternal self-reported weight and weight measured by trained staff in the clinic is highly correlated.⁷⁴ It is difficult to know what effect this potential misclassification has on the associations observed across the various studies reviewed, but if the trend was toward under-reporting then the associations may underestimate the effect size.

The methods for addressing confounding differed across studies. One critique of this literature is that the associations between pre-pregnancy obesity and adverse outcomes may be due to unmeasured confounding by genetic or shared family environmental factors and that the association may not be causal. A method proposed to mitigate sources of confounding shared within families has been the use of sibling designs where the analysis involve comparing outcomes among siblings that are discordant for the exposure. We identified five studies that used this design.^{13,34,44,59,71} Two were included in the meta-analysis and three in the systematic review. All but one⁴⁴ found that the sibling comparison design nullified the dose-dependent increased risk of child neurodevelopmental outcome in relation to pre-pregnancy weight. Such designs, while informative, are not without potential limitations (e.g., carryover effects)⁷⁵ and do not completely rule out a causal effect of pre-

pregnancy obesity. Continued research using a variety of study designs such as these and others (e.g., propensity score methods, Mendelian randomization) would be helpful in further clarifying the magnitude of the overall effect size.

Another caveat to this review was that we did not focus on gestational weight gain in relation to neurodevelopment due to the limited number of studies that examined this variable. Gestational weight gain, whether it is insufficient or excessive, may be important to neurodevelopment. Some studies that did assess gestational weight gain found it was not related to neurodevelopmental outcomes beyond pre-pregnancy weight,^{59,66} whereas others found significant positive associations with neurodevelopmental outcomes.^{44,52,58,62} Continued research is needed that will help elucidate the degree to which gestational weight gain and pre-pregnancy obesity independently or synergistically relate to an increased risk of adverse neurodevelopmental outcomes in children.

Strengths of this review were the inclusion of methods to evaluate sources of potential bias through missing studies estimation (publication bias) and sensitivity analysis. Our analyses of publication bias suggested that the summary estimates are approximately correct with very little evidence of publication bias influencing the results. Sensitivity analyses evaluating overall quality were also conducted. In general, these sensitivity analyses show that the overall effect of pre-pregnancy obesity on neurodevelopment ranged from an OR of 1.90 in the lower quality studies to 1.33 in the higher quality studies. This suggests that in order to produce more accurate assessments of the effect size of this relationship between pre-pregnancy weight and neurodevelopment, future studies should consider quality indicators evaluated here such as, the use of prospective designs, sufficient sample size for analysis, and inclusion of covariates in multivariate models. Another strength of this study was the use of the robust variance estimation (RVE) method, which allowed for analyses of all collected effect sizes to be used in the same meta-analysis. This was important since many studies reported on multiple outcomes. In addition, we also contacted researchers who reported results with regression coefficients only and obtained additional information to calculate an OR. This resulted in 6 additional studies being included in our synthesis and strengthened our estimation of the overall effect size.

Potential Mechanisms

There are a number of proposed mechanisms to help account for the observed association between pre-pregnancy obesity and neurodevelopment outcomes. A prevailing hypothesis is that the inflammatory milieu that accompanies an obese state before and during pregnancy leads to a cascading series of events that affect brain development and subsequent neurodevelopmental functioning.^{5,54,76,77} Preclinical models support this hypothesis and show that gestational obesity induced by a high dietary fat produces changes in inflammatory signaling that have downstream effects on offspring microglial functioning, brain development and subsequent offspring neurobehavioral patterns.^{5,76} Other processes may include metabolic hormone-induced changes, such as exposure to increased circulating levels of leptin or insulin, or suppression of serotonergic functions by disrupting the normal development of the serotonin (5HT) system.⁵ Maternal pre-pregnancy obesity may also be a marker for nutritional differences. For example, maternal high-fat diet during

pregnancy has been linked with dopamine functioning and impulsive responding of offspring.^{78,79}

Although preclinical studies have been useful in explaining some of the potential mechanisms, fewer studies have examined similar mechanisms in human population studies. Notably, there are methodological challenges in human studies that make it difficult to disentangle the effects of maternal diet and maternal pre-pregnancy weight on offspring neurodevelopmental outcomes. Some preliminary evidence, however, does suggest a link between aberrant prenatal inflammatory cytokines levels and early childhood intelligence and risk for ASD.^{80,81} A critical next step could be to begin to link prenatal exposure to maternal obesity to childhood cognitive capacity via inflammatory signaling.

Implications

This meta-analysis supports the notion established in pre-clinical and observational studies that offspring born of mothers who are obese prior to and during their pregnancy are at increased risk for neurodevelopmental problems, including a higher risk of ADHD-related symptoms. The effect size across these studies (e.g., OR of 1.62 or Cohen's $d = 0.27$ for maternal pre-pregnancy obesity and ADHD) is comparable to the effect size seen in studies of lead exposure and ADHD (Cohen's $d = 0.32$)⁸² and studies of prenatal smoking and ADHD (Cohen's $d = .20$).⁸³ Further confirmation of these associations could have significant clinical implications by 1) allowing for the identification of a group of women who may be at risk for delivering children with neurodevelopmental problems and 2) increasing maternal awareness of the harmful health effects of obesity not only on her pregnancy but on her child's brain development. Current 2016 estimates of obesity for women in the US are 40.4% which has increased from previous estimates in 2005–2014.⁸⁴ At a population level, arresting the obesity epidemic among women in the childbearing age not only has the potential to improve delivery outcomes, but, if these findings continue to bear out, has the potential to have downstream effects on the prevalence of neurodevelopmental problems in children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ASD	Autism Spectrum Disorder
BMI	body mass index

OR	Odds Ratio
CI	confidence interval
RVE	robust variance estimation
NR	not reported

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Figure 1. Study Identification and Selection

Figure 2. Forest plot for Obese Mothers and Their Offsprings' Risk of ADHD

^aThe attention deficit hyperactivity problem subscale consists of 7 statements about the child that reflect attention deficit hyperactivity problems (in accordance with the DSM-IV). ^b30–35 kg/m². ^c35–40 kg/m². ^d>40 kg/m².

Note: ADHD = Attention Deficit Hyperactivity Disorder. CBCL = Child Behavior Checklist. ICD-9, 10 = International Statistical Classification of Diseases and Related Health Problems, 9th Edition, 10th Edition. TRF = Teacher Report Form. ASD = Autism Spectrum Disorder. DSM-IV = Diagnostic and Statistical Manual for Mental Disorders, 5th Edition.

Figure 3. Forest plot for Obese Mothers and Their Offsprings' Risk of ASD

^aRisi et al. criteria uses combined information from the Autism Diagnostic Interview, Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS) to diagnose ASD.

Note: ASD = Autism Spectrum Disorder, ICD-9, 10 = International Statistical Classification of Diseases and Related Health Problems, 9th Edition, 10th Edition, DSM-IV = Diagnostic and Statistical Manual for Mental Disorders, 5th Edition, ADI-R = Autism Diagnostic Interview, Revised, ADOS = Autism Diagnostic Observation Schedule.

Figure 4. Forest plot for Obese Mothers and Their Offsprings' Risk of Cognitive and Intellectual Delay

^aFSIQ < 80. ^bComposite score < 85 ^cSS < 70. ^dOther developmental disorder based on diagnosis of language delay, coordination disorders or learning disorders (315.0–315.5, ICD-9). ^eDefined as Intellectual Disability of any severity. ^fIQ < 89.

Note: WPPSI-R = Wechsler Preschool and Primary Scale of Intelligence-Revised, ICD-9= International Statistical Classification of Diseases and Related Health Problems, 9th Edition, BSID-II= Bayley Scales of Infant and Toddler Development, 2nd Edition, BSF-R = Bayley Short Form-Revised, WISC-I = Wechsler intelligence Scale for Children, 1st Edition, ASQ = Ages and Stages Questionnaire, MSEL = Mullen Scales of Early Learning, VABS =

Vineland Adaptive Behavior Scales, SBIS-4 = Stanford Binet Intelligence Scale 4th Edition. WHO (2000) defines obese categories as obese class I = BMI 30.0–34.9, obese class II = BMI 35–39.99, and obese class III = BMI > 40.

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Figure 5. Forest plot for Obese Mothers and Their Offsprings' Risk of Emotional/Behavioral Problems

^a>6 symptoms present. ^b>7 symptoms present. ^c>6 month duration. ^dTotal Behavioral Scores 90th percentile

Note: CBCL = Child Behavior Checklist, SDQ = Strength and Difficulties Questionnaire. WHO (2000) defines obese categories as obese class I = BMI 30.0–34.9, obese class II = BMI 35–39.99, and obese class III = BMI > 40.

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Table 1

Selected characteristics of the 32 articles representing 36 cohorts included in the meta-analysis

Study	Quality Grade of Study	Country (Year of Cohort Initiation)	Cohort Name	Analysis Sample <i>n</i>	Age at Follow-Up in Years <i>M</i> (SD)	Age Range (yrs)	Heritable Characteristics Related to Neurocognitive Outcomes	Other Adjusted Covariates			Source of BMI	BMI Standard, Year
								Maternal/Parental Covariates	Child Covariates	Environmental Covariates		
Li et al. (2016) ¹⁰	14	US (1998)	Boston Birth Cohort	1767	6.30 (NR)	3.6–9.0	--	--	--	--	Self-report	CDC, 2014
Krakowiak et al. (2012) ²⁹	11	US (2003)	Childhood Autism Risks from Genetics and the Environment Cohort	1004	3.65 (NR)	2–5	--	Age, Maternal Education, Race/Ethnicity	Gender, Child's Age	Insurance Payer, Number of Years Since Enrollment, Catchment Area	Medical Records and Research Staff	WHO, NR
Connolly et al. (2016) ¹¹	11	US (2006)	Cincinnati Children's Hospital Medical Center's Cohort	39313	5.50 (NR)	5.5	--	Age, Race/Ethnicity	Birth Year	--	Medical Records	WHO, NR
Huang et al. (2014) ⁴⁴	15	US (1959)	Collaborative Perinatal Project	30212	7.00 (NR)	7	--	--	--	--	Self-report and Medical Staff	WHO, 2000
Bliddal et al. (2014) ¹⁶	11	Denmark (1996)	Danish National Birth Cohort	1783	5.16 (NR)	5–5.3	Parental Intelligence	--	--	--	Self-report	WHO, NR
Hinkle et al. (2012) ⁴⁵	15	US (2001)	Early Childhood Longitudinal Study Birth Cohort	6850	2.00 (NR)	0.8–2	--	--	--	--	Self-report	WHO, 1998
Hinkle et al. (2013) ⁴⁶	12	US (2001)	Early Childhood Longitudinal Study Birth Cohort	5200	5.67 (NR)	4.8–7.1	--	--	--	--	Self-report	WHO, 2000
Moss & Chugani (2014) ¹⁴	12	US (2001)	Early Childhood Longitudinal Study Birth Cohort	4800	4.50 (NR)	0.8–2	--	Age	Birth Weight, Gender, Rate of Child's Height and Weight Growth	--	Self-report	WHO, 1995
Helderman et al. (2012) ⁴⁷	10	US (2002)	Extremely Low Gestational Age Newborns Cohort	921	2.00 (NR)	2	--	--	--	--	Self-report	NR
Getz et al. (2016) ⁴⁸	18	United Kingdom (1993)	General Practice Research Database Cohort	4419	6.2 (3.2)	6.2	Parental Psychiatric Disorder	Age, Smoking, Maternal Diabetes, Drug Abuse, Alcoholism	Gender, Birth Year	General Practice	Medical Records	WHO, NR
Brion et al. (2011) ²⁸	14	England (1991)	British Avon Longitudinal Study of Parents and Children	4712	3.00 (NR)	3.2–3.9	--	Smoking, Maternal Education, Family Income, Paternal Education	--	--	Research Staff	WHO, NR
		Netherlands (2002)	Generation R Study Cohort	2046								

Study	Quality Grade of Study	Country (Year of Cohort Initiation)	Cohort Name	Analysis Sample <i>n</i>	Age at Follow-Up in Years <i>M</i> (SD)	Age Range (yrs)	Heritable Characteristics Related to Neurocognitive Outcomes	Other Adjusted Covariates			Source of BMI	BMI Standard, Year
								Maternal/Parental Covariates	Child Covariates	Environmental Covariates		
van Mil et al. (2015) ¹²	14	Netherlands (2001)	Generation R Study Cohort	5482	6.00 (NR)	4.9–8.0	Parental Psychiatric Disorder	--	--	--	Research Staff	WHO, NR
Jo et al. (2015) ⁴⁹	12 or 14 [*]	US (2005)	Infant Feeding Practices Study II Cohort	1311	6.00 (NR)	6	Parental Psychiatric Disorder	Age, Smoking, Maternal Education, Race/Ethnicity, Parity, Family Income, Family Structure/Marital Status, Gestational Weight Gain, Gestational Diabetes, Postpartum Depression, Current Maternal BMI	Birth Weight, Gender, Gestational Age, Child's Enrichment	Breastfeeding Duration	Self-report	WHO, 2000
Kersijens et al. (2013) ³¹	12	Netherlands (2002)	Longitudinal Preterm Outcome Project Cohort	760	3.83 (NR)	3.6–4.1	Parental Psychiatric Disorder	Age, Smoking, Maternal Education, Race/Ethnicity, Parity, Family Income, Preexisting Maternal Somatic Illness, Pregnancy-related Maternal Hypertension, Pregnancy-related Maternal Diabetes, Antepartum Hemorrhage, Antenatal Steroids and In-vitro Fertilization, Paternal Education, Alcohol Consumption	Birth Weight, Gender, Gestational Age, Being Part of a Multiple Birth	SES	Medical Records	WHO, NR
Pugh et al. (2016) ⁵⁰	10	US (1983)	Maternal Health Practices and Child Development Cohort	511	10 (NR)	10	Parental Psychiatric Disorder (Depression, Anxiety), Parental Intelligence	--	--	--	Self-report	WHO, 1995
Pugh et al. (2015) ⁵¹	10	US (1983)	Maternal Health Practices and Child Development Cohort	530	10 (NR)	10	Parental Psychiatric Disorder (Depression, Anxiety), Parental Intelligence	--	--	--	Self-report	WHO, 1995
Tanda & Salsberry (2014) ⁵²	15	US (1976)	National Longitudinal Survey of Youth Cohort	2127	8.96 (NR)	8–9.2	Maternal Intelligence	Age, Smoking, Maternal Education,	Birth Weight, Gender, Gestational Age, Child	Home Environment (Emotional Support at Home)	Self-report	WHO, NR

Study	Quality Grade of Study	Country (Year of Cohort Initiation)	Cohort Name	Analysis Sample <i>n</i>	Age at Follow-Up in Years <i>M</i> (SD)	Age Range (yrs)	Heritable Characteristics Related to Neurocognitive Outcomes	Other Adjusted Covariates			Source of BMI	BMI Standard, Year	
								Maternal/Parental Covariates	Child Covariates	Environmental Covariates			
Rodriguez et al. (2008) ³⁰	15	Finland (1985)	Nordic Network on ADHD	9297	7.50 (NR)	7–8	--	Age, Smoking, Maternal Education, Family Structure/Marital Status, Weight Gain	Birth Order, Child Weight Status	--	Medical Staff	IOM, 1990	
	13	Denmark (1990)		5039		10–12		Birth Weight, Gender, Gestational Age					
	Heikura et al. (2008) ⁵³	10	Finland (1966)	Northern Finland Birth Cohorts	12058	11.50 (NR)	< 11.5	--	Age, Smoking, Maternal Education, Parity, Family Structure/Marital Status	--	Place of Residence, Number of Visits to Maternity Health Center, SES	Self-report and Medical Staff	NR
			Finland (1986)		9527								
Suren et al. (2014) ¹⁵	15	Norway (1999)	Norwegian Mother and Child Cohort	50116	7.4 (NR)	4–13.1	Parental Psychiatric Disorder	Age, Smoking, Maternal Education, Parity, Paternal Education, Psychiatric Disorders, Maternal Use of Folic Acid, Diabetes, Fertilization Techniques, Preeclampsia	Birth Weight, Gestational Age, Birth Year	Obesity of Co-parent	Self-report	WHO, 2013	
Hendrix (2011) ³⁴	11	US (1992)	NR	140	NR	3–18	Parental Psychiatric Disorder (ASDs)	Maternal High Blood Pressure During Pregnancy, Maternal Anemia During Pregnancy, Maternal Gestational Weight Gain, Prenatal Care Visits	Gender, Birth Order, Birth Date/Birth Season, Fetal Gender Known	Residential Move During Pregnancy	Self-report	IOM, 2009	
Buss et al. (2012) ⁵⁴	10	US (NR)	NR	174	7.30 (0.90)	7.30	--	--	--	--	Medical Records and Research Staff	IOM, 2009	
Craig et al. (2013) ⁵⁵	12	US (2004)	NR	101	2.40 (.40)	2.40	--	Age, Smoking, Parity	Gender	SES	Medical Records	WHO, NR	
		US (1987)	NR	118	8.0 (1.0)	8.0							
Reynolds et al. (2014) ³²	7	US (2007)	NR	62	2.00 (NR)	2	Familial Intellectual Disability	Age, Maternal Education, Family Structure, Prenatal Care	Gender, Gestational Age	--	Medical Records	NR	

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Study	Quality Grade of Study	Country (Year of Cohort Initiation)	Cohort Name	Analysis Sample <i>n</i>	Age at Follow-Up in Years <i>M</i> (SD)	Age Range (yrs)	Heritable Characteristics Related to Neurocognitive Outcomes	Other Adjusted Covariates			Source of BMI	BMI Standard, Year
								Maternal/Parental Covariates	Child Covariates	Environmental Covariates		
							Structure/Marital Status, Occupation and Employment Status of Primary Income Earner, Insurance Status, Absence/Presence of Gestational Diabetes, Hypertension, Pre-eclampsia					
Musser et al. (2016) ¹³	14	US (1995)	NR	4682	7.60 (1.80)	5–12	Parental Psychiatric Disorder (ADHD)	--	--	--	Medical Records	WHO, NR
Lyall et al. (2011) ⁵⁶	9	US (1989)	Nurses' Health Study II	61596	NR	NR	--	Age, Race/Ethnicity, Family Income, Age at Menarche, BMI and Body Shape	--	--	Self-report	NR
Rodriguez (2010) ⁵⁷	15	Sweden (1999)	Pregnancy Cohort from Sweden	1009	5.00 (NR)	5	Parental Psychiatric Disorder (Depression, ADHD)	Age, Smoking, Maternal Education, Family Structure/Marital Status, Maternal Depressive Symptoms at Follow-up, Stress During Pregnancy	Birth Weight, Gender, Gestational Age, Child Overweight (at Follow-up)	--	Medical Records	WHO, NR
Mann et al. (2012) ⁵⁸	12	US (2004)	South Carolina Medicaid Programme-insured Cohort	78675	4.50 (NR)	3–6	Familial Intellectual Disability, Parental Neurological Disorder	Age, Smoking, Maternal Education, Race/Ethnicity, Gestational Weight Gain, Intrapartum Fever, Maternal Chlamydia, Gonorrhea, and Syphilis During Pregnancy, Maternal Diabetes Mellitus, Maternal Hypertension	Birth Weight, Gender, Gestational Age	--	Self-report	WHO, NR

Study	Quality Grade of Study	Country (Year of Cohort Initiation)	Cohort Name	Analysis Sample <i>n</i>	Age at Follow-Up in Years <i>M</i> (SD)	Age Range (yrs)	Heritable Characteristics Related to Neurocognitive Outcomes	Other Adjusted Covariates			Source of BMI	BMI Standard, Year
								Maternal/Parental Covariates	Child Covariates	Environmental Covariates		
Antoniou et al. (2014) ⁶⁰	13	United Kingdom (2003)	Twins and Multiple Birth Association Heritability Study Cohort	788	3.25 (NR)	1.5–5		Age, Smoking	Birth Weight, Gender, Age of Twins at Time of Study	--	Self-report	WHO, NR
Robinson et al. (2013) ⁶¹	16	Australia (1989)	Western Australian Pregnancy Cohort (Raine)	2765	10.80 (NR)	5–17	Maternal Stress During Pregnancy	Age, Smoking, Maternal Education, Family Income, Family Structure/ Marital Status, Maternal Alcohol Consumption, Gestational Diabetes, Maternal Hypertensive Disorders of Pregnancy, Paternal BMI, Maternal Age at Conception, Stress During Pregnancy	Birth Weight, Gestational Age	Duration of Breastfeeding	Self-report and Research Staff	WHO, 2004
Whitehouse et al. (2014) ⁶³	14	Australia (1989)	Western Australian Pregnancy Cohort (Raine)	1823	7.67 (NR)	5–10	--	--	--	--	Self-report	WHO, 2004

* Score higher when used standard neurocognitive assessment

Table 2

Summary of Meta-analyses

BMI weight group	Cohorts, No.	Summary Estimates		
		OR (95% CI)	P Value	<i>I</i> ² Heterogeneity Index
Overweight ^{10-16,29,34,44,45,47-49,51-53,56-61a}	22	1.17 (1.11, 1.24)	< 0.001	65.51
Obese ^{10-16,29,31-34,44-49,51-59,61b}	25	1.51 (1.35, 1.69)	< 0.001	79.63
Obese + Overweight ^{10-12,14,15,28-34,44-61c}	29	1.33 (1.22, 1.45)	< 0.001	93.07
<u>Neurodevelopmental Outcome</u>		Overweight		
ADHD ^{10,12,13,49,50,57}	6	1.30 (1.10, 1.54)	0.01	52.97
ASD ^{*10,11,14,15,29,34,48,49,56,59}	10	1.10 (1.01, 1.21)	0.026	0.00
Cognitive/Intellectual Delay ^{10,11,16,29,44,46,47,49,51,53,58}	11	1.19 (1.09, 1.29)	0.003	40.05
Emotional/Behavioral Problems ^{46,49,50,52,57,60,61}	7	1.14 (0.93, 1.39)	0.16	70.78
		Obese		
ADHD ^{12,13,17,49,50,54,57}	7	1.62 (1.23, 2.14)	0.006	70.15
ASD ^{10,11,14,15,29,32,34,48,49,56,59}	11	1.36 (1.08, 1.70)	0.015	60.52
Cognitive/Intellectual Delay ^{10,11,16,29,31,33,44,45,47,49,50,53,55,58}	14	1.58 (1.39, 1.79)	< 0.001	75.77
Emotional/Behavioral Problems ^{46,49,50,52,57,61}	6	1.42 (1.26, 1.59)	< 0.001	87.74
		Obese + Overweight Combined		
ADHD ^{10,12,13,49,50,54,57}	8	1.51 (1.28, 1.77)	< 0.001	82.11
ASD ^{10,11,14,15,29,32,34,48,49,56,59}	11	1.23 (1.06, 1.42)	0.013	77.36
Cognitive/Intellectual Delay ^{10,11,16,28[^],29,31,33,44-47,49,51,53,55,58}	17	1.35 (1.15, 1.57)	0.001	94.03
Emotional/Behavioral Problems ^{28[^],45,46,49,50,52,57,60,61}	10	1.22 (1.09, 1.37)	0.004	90.37

Note: Each study contained at least two independent samples (i.e. obese and overweight); thus, one study will be referenced in multiple analyses.

Abbreviations: BMI, body mass index; CI, confidence interval; ADHD, Attention Deficit Hyperactivity Disorder; ASD, Autism Spectrum Disorder

* Computed with CMA

^aHinkle et al. (2012) & Moss & Chugani (2014) analyzed as a single cohort.

^bHinkle et al. (2012) (2013) & Moss & Chugani (2014) analyzed as a single cohort, Pugh et al. (2015) & Pugh et al. (2016) analyzed as a single cohort, and Robinson et al. (2013) & Whitehouse et al. (2014) analyzed as a single cohort.

^cBrion et al. (2011)b & van Mil et al. (2015) analyzed as a single cohort as Generation R, Hinkle et al. (2012, 2013) & Moss & Chugani (2014) analyzed as a single cohort, Robinson et al. (2013) & Whitehouse et al. (2014) analyzed as a single cohort, and Pugh et al. (2015) & Pugh et al. (2016) analyzed as a single cohort.

[^]Brion et al. (2011) contained two cohorts.

Table 3

Sensitivity Analysis of the Relationship between Pre-pregnancy Obesity and Neurodevelopmental Outcomes

	Number of Studies (<i>n</i>)	Summary Estimates (95% CI)	<i>P</i>	<i>I</i> ²
Quality Grade of Study				
High ^{15,44,45,48,52,57,59,61}	8	1.33 (1.18, 1.49)	< .001	80.11
Medium ^{10–14,16,29,31,33,34,45,49,51,55,58^b}	14	1.60 (1.41, 1.80)	< .001	74.94
Low ^{32,47,50,51,53,54,56[*]}	6	1.90 (1.03, 3.49)	0.04	83.48
Study Design				
Prospective ^{10,12,14–16,31–33,44,45,47–49,51,54,56,57,59,61^{b,c}}	17	1.41 (1.23, 1.63)	< .001	80.93
Retrospective ^{11,13,29,34,45,52,53,55,58}	9	1.68 (1.42, 1.99)	< .001	79.36
Sample Size				
1800 ^{10–15,33,44,45,48,52,53,56,58,59,61^{b, c}}	14	1.41 (1.24, 1.61)	< .001	73.56
800 ≤ <i>x</i> < 1800 ^{32,34,51,54,55,85}	6	1.62 (1.19, 2.21)	0.01	89.88
< 800 ^{32,34,51,54,55}	5	2.41 (1.42, 4.10) ^a	0.001	58.76
Genetics				
Controlled for genetic effects and maternal or paternal effects ^{10,12,13,31,32,34,44,45,48,52,55,57–59}	14	1.52 (1.34, 1.73)	< .001	81.08
Controlled for maternal or paternal effects ^{15,16,49,51,54,61}	6	1.5 (1.08, 2.1)	0.03	81.78
Did not control for maternal or paternal effects ^{11,14,29,33,47,53,56}	7	1.46 (0.96, 2.22)	0.07	80.12
Use of Covariates in Final Model				
Adjusted OR ^{11,14,15,29,31,34,48,49,52,53,55,57,59,61}	14	1.44 (1.25, 1.67)	< .001	79.04
Unadjusted OR ^{10–13,16,29,32,33,44,45,47,51,54,56}	14	1.52 (1.32, 1.74)	< .001	80.96

^aComputed with CMA.^{*}Pugh et al. (2015) & Pugh et al. (2016) analyzed as a single cohort.^bHinkle et al. (2012) & Moss & Chugani (2014) analyzed as a single cohort,^cRobinson et al. (2013) & Whitehouse et al. (2014) analyzed as a single cohort