**Maternal pre-pregnancy overweight/obesity and the risk of attention-deficit/hyperactivity disorder in offspring: a systematic review, meta-analysis, and a quasi-experimental family-based study**

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**Word count:** 5272 words

**ABSTRACT:**

**Background:** Previous studies are inconclusive concerning the association between maternal pre-pregnancy overweight/obesity and risk of attention-deficit/hyperactivity disorder (ADHD) in offspring. We therefore conducted a systematic review and meta-analysis to clarify this association. To address variation in confounding adjustment between studies, especially inadequate adjustment of unmeasured familial confounding in most studies, we further performed cousin and sibling comparisons in a nationwide population-based cohort in Sweden.

**Methods:** We searched PubMed, Embase and PsycINFO during 1975-2018. We used random-effects models to calculate pooled risk ratios (RRs) with 95% confidence interval (CI). In the population-based study, Cox proportional hazard models were used to calculate the unadjusted hazard ratios (HRs) and HRs adjusted for all confounders identified in previous studies. Stratified Cox models were applied to data on full cousins and full siblings to further control for unmeasured familial confounding.

**Results:** Eight cohorts with a total of 784 804 mother-child pairs were included in the meta-analysis. Maternal overweight [RRoverweight=1.31(1.25-1.38), I2=6.80%] and obesity [RRobesity=1.92(1.84-2.00), I2=0.00%] were both associated with an increased risk of ADHD in offspring. In the population-based cohort of 971 501 individuals born between 1992-2004, unadjusted Cox models revealed similar associations [HRoverweight=1.30(1.28-1.34), HRobesity=1.92(1.87–1.98)]. These associations gradually attenuated toward the null when adjusted for measured confounders [HRoverweight=1.21(1.19–1.25); HRobesity=1.60(1.55–1.65)], unmeasured factors shared by cousins [HRoverweight=1.10(0.98–1.23); HRobesity=1.44(1.22–1.70)], and unmeasured factors shared by siblings [HRoverweight=1.01(0.92–1.11); HRobesity=1.10 (0.94–1.27)].

**Conclusion**: Pre-pregnancy overweight/obesity is associated with an increased risk of ADHD in offspring. The observed association is largely due to unmeasured familial confounding.

**Key words:** ADHD, obesity, meta-analysis, confounding, sibling comparison, cousin comparison

**Introduction**

Attention-deficit/hyperactivity disorder (ADHD) is a common and persistent neurodevelopmental disorder that is associated with adverse psychosocial, educational, occupational, and health-related outcomes throughout life (1, 2). ADHD affects approximately 6.5% of children and 2.5-3.4% of adults (2). The heritability of ADHD has repeatedly been found to be high, at 70-80% (3), but several environmental factors have been suggested to increase the risk of ADHD, e.g. prenatal and perinatal risks, dietary factors, and psychosocial adversity (4, 5). However, the mechanisms through which such risk factors influence ADHD remain unclear.

Maternal overweight and obesity prior to pregnancy are increasingly being recognized as potential modifiable risk factors for ADHD in offspring (6). Systematic reviews have suggested that maternal pre-pregnancy overweight/obesity may be associated with suboptimal neurodevelopment in offspring, including an increased risk for ADHD (6-8). Sanchez et.al conducted a meta-analysis on the association between maternal pre-pregnancy obesity and child neurodevelopmental outcomes (7) and reported an overall effect of maternal pre-pregnancy overweight [ORoverweight=1.30 (1.10-1.54), I2=52.97%] and obesity [(ORobesity=1.62 (1.23-2.14), I2=70.15%] on ADHD in offspring but no sensitivity or subgroup analyses focused on ADHD specifically.

To date, the precise mechanisms underlying the association between maternal pre-pregnancy overweight/obesity and ADHD in offspring remain unclear. Some biological mechanisms have been proposed as mediators for a causal association, including fetal programming (9), placental and intrauterine environment alterations and inflammatory mechanisms (10). Alternatively, the association might be explained by unmeasured confounders. Indeed, recent register-based within-family studies (11, 12) have suggested that the associations of ADHD with high body mass index (BMI), including clinically diagnosed obesity, could be attributed to genetic factors shared by the two conditions. Additionally, a large genome-wide association study (13) of clinically diagnosed ADHD reported a modest genetic correlation (rg) between ADHD and obesity-related phenotypes, including BMI (rg = 0.26), waist-to-hip ratio (rg = 0.30), and childhood obesity (rg = 0.22). Unmeasured environmental confounders, such as lifestyle factors (e.g. dietary habits and physical activity), might also influence maternal overweight/obesity (14), as well as the risk of ADHD in offspring (15).

Cross-generation observational studies evaluating the effect of maternal exposure on risk of ADHD in offspring also face the challenge of fully adjusting for genetic and environmental variables that are confounded with the hypothesized causal pathway. Previous systematic review and meta-analyses studies have discussed the limitations of trying to obtain a single answer using meta-analysis (16, 17). These studies also provided examples on how to evaluate findings from meta-analyses by using population-based studies with fully adjusted measured confounding (17), and suggested using genetically-informative study designs (e.g. sibling or cousin comparisons) to help adjust for unmeasured genetic and environmental factors, and to advance the understanding of the underlying processes through which early-life exposures influence later outcomes (16, 18). However, only two previous studies (19, 20) have utilized sibling comparison designs to address the role of unmeasured familial confounding in the context of maternal pre-pregnancy overweight/obesity and ADHD in offspring. Based on a nationwide population-based cohort study in Sweden including 272 790 full siblings born 1992-2000, Chen et al. (19) reported that the association between maternal pre-pregnancy overweight/obesity and ADHD in offspring was largely due to unmeasured familial factors. This finding was further replicated in a sample including 1958 siblings (20). However, these two studies were unable to fully examine the dose-response association between maternal pre-pregnancy overweight/obesity and risk of ADHD in offspring due to the limited numbers of included mothers with severe obesity (BMI ≥35). Indeed, the reduction of sample size and statistical power is an important limitation of the sibling-comparison design. Additionally, sibling comparisons rely on strong assumption (e.g. absence of carryover effects) (21). Therefore, also the interpretation of these findings is unclear, given that women who change pre-pregnancy weight between pregnancies may be systematically different from women whose pre-pregnancy weight remain stable (22-24). Therefore, complementary designs, such as cousin comparisons, are needed to address these limitations.

In the current study, we first performed an updated systematic review and meta-analysis of the associations between maternal pre-pregnancy overweight/obesity and risk of ADHD in offspring with an extended included literature, detailed sub-analyses, and detailed description for our confounding adjustment. To explain the findings of the meta-analysis, and further evaluate the impact of confounding, a nationwide population-based cohort study was conducted by: a) adjusting for all relevant measured covariates identified from Swedish medical registers, b) comparing first-born maternal full cousins and c) full siblings discordant with respect to maternal overweight/obesity to control for shared familial factors in extended families and nuclear families, respectively.

**Methods**

***Systematic review and Meta-analysis***

We applied the standard methodological guidelines of the PRISMA (the Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement (25) and registered our systematic review and meta-analysis on PROSPERO (CRD42018092267).

*Search Strategy and Selection of Studies*

We systematically searched PubMed, Embase and PsycINFO using a pre-specified search strategy to identify all pertinent studies on humans published from 1975 1st January to 31st December, 2018, evaluating the association between maternal overweight or obesity and risk of ADHD in offspring. Detailed information on the search terms and syntax for each database are reported in the **Table S1**. No restrictions were imposed on language and date of publication. References of selected papers were hand searched by two authors (LL and TL) to retrieve any possible additional pertinent publication that could have been missed with the electronic search.

Published studies were included according to the following inclusion criteria: (a) case-control and cohort studies; (b) offspring with ADHD defined with any of the following: DSM criteria (III, III-R, IV, IV-TR or 5), hyperkinetic disorder according to ICD-9 or ICD-10, ADHD medication prescriptions as a proxy to diagnosis, physician diagnosis of ADHD, ADHD symptoms based on value above cut-off on a validated self-reported ADHD questionnaire, ADHD diagnosed via a structured psychiatric interview, or positive answer by parents to the question: “Has the child ever been told it has ADHD by a doctor?” or similar ones; (c) BMI calculated from either directly measured or self-reported body weight and height; (d) studies reporting results as risk ratio (RR), hazard ratio (HR), or odds ratio (OR) with its corresponding 95% confidence interval (CI), or sufficient data (e.g. sample size, prevalence of ADHD, overweight and obesity) to calculate them. When needed, we contacted the corresponding author to acquire unpublished data to calculate related effect size. When multiple reports containing overlapping participants were available, the article with largest number of subjects and most applicable information was preferred.

*Data Extraction*

The following data were extracted from each study retained for the qualitative synthesis: name of the first author, publication year, study location, number of participants, definition of exposure (maternal pre-pregnancy overweight or obesity), definition of outcome (ADHD), covariates and how these were handled, crude and adjusted effect size (OR/RR/HR/ β) with 95% CIs.

*Assessment of study quality*

The Newcastle-Ottawa Scale (NOS), a validated tool for assessing the quality of observational studies, was used to assess possible bias in the included studies (26). The following three categories were evaluated with a maximum score of nine: selection (definition/ representativeness of exposed subjects, selection of non-exposed subjects), comparability (controls or adjustment for confounding factors), and outcome (assessment of outcome, adequate non-response rate or follow-up time). Authors LL and TL independently graded all included studies using the NOS criteria, and the discrepancies were solved by consensus.

*Statistical analysis*

The characteristics of the included studies and the heterogeneity in confounding adjustment strategies (i.e., various confounding adjustment strategies adopted by the available studies) were described in detail. ORs from logistic regression and HRs from Cox regression were combined because they closely approximate each other (16, 27, 28). The ORs were considered equivalent to RRs given the low prevalence of ADHD diagnosis (29) . To be as inclusive as possible, we chose teacher-rated inattention symptoms as the main outcome in the studies with multiple definitions of ADHD. Fewer studies presented covariate adjusted effect estimates for obesity, so crude RRs were included in the primary analyses, while adjusted RRs and 95%CIs were obtained for sensitivity analyses. A leave-one-out analysis was also conducted to assess whether a single study markedly affected the overall findings.

The following subgroup analyses were conducted: a) Including only studies with an ADHD diagnosis based on DSM (III, III-R, IV, IV-TR or 5) or ICD-10 or previous versions; b) Analyzing ADHD assessed from rating scales by parents, teachers and self-ratings and diagnostic criteria separately; c) Analyzing studies with self-reported vs measured BMI/overweight/obesity separately; d) Analyzing studies with pre-pregnancy and early-pregnancy BMI/overweight/obesity separately; e) Removing studies based on Swedish samples (to avoid any concern about possible overlap with the empirical study presented in this paper); f) Analyzing outcomes of overweight, and different levels of obesity (obesity class I, II and III) separately.

Pooled effect estimates were calculated using random-effects models to take into account heterogeneity between studies, and the results were summarized in forest plots. Heterogeneity among studies was assessed by the Cochran Q test and I2 statistic (level of significance P<0.10 and I2>70%, respectively). The presence of publication bias was first assessed through visual inspection of funnel plot symmetry assessed and then assessed quantitatively with the Begg’s test and Egger’s test. All statistical analyses were conducted using Stata, version 15.1 (Stata Corp, College Station, TX, United States).

***Nationwide population-based cohort study***

The nationwide population-based cohort study was approved by the regional ethical review board in Stockholm, Sweden. The requirement for informed consent was waived because the data were pseudonymized from population-based registers.

*Data sources*

With individual-specific personal identification numbers we linked the following seven Swedish registers: (a) The Medical Birth Register (MBR) provided data on more than 95% of pregnancies in Sweden since 1973 (30); (b) The National Patient Register (NPR) contained data on inpatient psychiatric care since 1973 (ICD-9 to ICD-10) and outpatient psychiatric care since 2001 (ICD-10) (31); (c) The Multi-Generation Register (MGR) provided information on biological relationships for all residents in Sweden since 1932 ; (d) The Prescribed Drug Register (PDR) included detailed information on drug identity [Anatomical Therapeutic Chemical (ATC) code] and dates of all registered prescriptions for all individuals residing in Sweden since 1 July 2005 (32); (e) The Swedish Register of Education provided data on highest education level through 2008; (f) The Cause of Death Register (CDR) provided detailed information on all registered deaths since 1958; (g) The Migration Register included information on all migrations in or out of Sweden since 1969.

A total of 1 232 207 live-born individuals in Sweden were identified from the MBR between 1992 and 2004. We excluded those who had severe congenital malformations (N=45 533), died (N=3437) or emigrated (N=21 715) before 3 years of age, lacked mother’s identification number (N=382), received an ADHD diagnosis before 3 years of age (N=76), or lacked information on maternal BMI (N=189 563), resulting in 971 501 individuals as the final study population. We further identified 463 474 full biological siblings nested within 216 084 families and 155 841 first-born maternal full cousins nested within 74 057 extended families from the entire study population. All individuals were followed from the 3rd birthday until a diagnosis of ADHD, death, emigration, or 31th December 2013, whichever occurred first.

*Exposure definition*

Data on self-reported height and measured weight in light indoor clothing without shoes at the first prenatal visit (within the first 14 gestational weeks for 90% of pregnant women) were obtained from the MBR. Maternal BMI during early pregnancy (as a proxy of pre-pregnancy BMI) was calculated from weight in kilograms divided by height in meters squared and classified into underweight (BMI<18.5), normal weight (18.5≤BMI<25.0), overweight (25.0≤BMI<30.0), obesity class I (30.0≤BMI<35.0), obesity class II (35.0≤BMI<40.0), or obesity class III (BMI≥40.0), according to the World Health Organization guidelines (33). In line with previous studies (19, 34-38), we also identified an obesity group with all obesity classes combined (BMI ≥30). In addition, BMI was treated as a continuous exposure in some sensitivity analyses.

*Outcome definition*

Outcome was defined as time since the 3rd birthday to first-ever ADHD diagnosis or prescription of ADHD medication. Information on date of ADHD diagnosis was retrieved from the NPR, based on ICD codes (ICD-9: 314; ICD-10: F90). Information on date of ADHD medication prescription was extracted from the PDR according to ATC codes (ATC: N06BA04, N06BA01, N06BA02, and N06BA09).

*Covariates*

We constructed a directed acyclic graph (DAG) (39), based on covariates used in previous studies and available data in the Swedish national registers, for covariate selection (**Figure 2-1**). In the current study, the selected covariates (potential confounders) included offspring sex, birth order (first, second, third or fourth) and year of birth (1992–95,1996–99 and 2000–04); mother’s country of birth (Sweden, other Scandinavian country or other); maternal education (≤9 years, 10–12 years or postgraduate education); maternal age at delivery (≤19, 20–24, 25–29, 30–34 or ≥35 years); smoking during pregnancy (0, 1–9 or ≥10 cigarettes per day); and cohabitation with child’s father at childbirth (yes or no). Information on parental ADHD was not available but shared by full siblings and thus implicitly adjusted by sibling-comparison design.

*Statistical analyses*

We used Cox proportional hazards models to estimate the association between maternal overweight and obesity and risk of ADHD in offspring at the entire population level. Maternal overweight, obesity, and obesity class I-III were all compared with normal weight. In accordance with the meta-analysis part, underweight women were not included in the analyses. The Cox models were adjusted for all measured confounders mentioned above. The results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs) based on robust standard errors.

To explore the effects of unmeasured shared familial confounding on the observed association between maternal pre-pregnancy overweight and obesity and ADHD in offspring, stratified Cox proportional hazards models were used for cousin and sibling comparisons with each set of maternal full cousins and full siblings representing separate strata. A total of 24 521 extended families and 31 906 nuclear families contained first-born maternal full cousins and siblings discordantly exposed to maternal pre-pregnancy weight status (normal-overweight/obesity and overweight/obesity-normal). The cousin comparison models were implicitly adjusted for all unmeasured factors shared by cousins within each extended family (e.g. 12.5% shared genetic factors, racial and ethnic factors), and all measured birth-specific covariates as in the models at the population level, because all these measured covariates show variation within cousins. The sibling comparisons were implicitly adjusted for all factors shared by siblings within each nuclear family (e.g. 50% shared genetic factors, racial and ethnic factors, lifestyle factors), including maternal factors (birth country, highest education level), thus, only non-maternal birth-specific covariates were controlled in the sibling comparisons (offspring sex, birth order, year of birth, maternal age at delivery, smoking during pregnancy and cohabitation with child’s father at childbirth). Finally, continuous BMI was then used as exposure to examine the robustness of all above results.

We performed three sensitivity analyses to examine the robustness of our results. First, the included families differed in family size (2-8 siblings per family), but most of the families (86.79%) contributed with two siblings. In addition, later-born offspring were more often exposed to overweight or obesity. Therefore, we identified a sub-sample (N=432 168) including only first- and second-born siblings from each family for sensitivity analysis. Second, using BMI as continuous variable, we conducted a bidirectional case-crossover analysis by dividing participants with different weight patterns between pregnancies and repeated the main analyses. Hence, we could explore the potential influence of changing weight status and carryover effects (e.g. the exposure during first pregnancy may affect the outcomes during the second pregnancy) from one pregnancy to the next caused by different types of between-pregnancy variation in BMI (Normal-Normal, Normal-Overweight/Obesity, Overweight/Obesity-Normal and Overweight/Obesity-Overweight/Obesity). Finally, as suggested in a previous review (40), bariatric surgery for the severely obese has been consistently shown to lead to long-term weight loss and dramatic improvement in medical comorbidity (e.g. metabolic syndrome). Moreover, previous research (41, 42) showed improvement of cognitive functions and some ADHD symptoms after surgery. Together, this may indicate that bariatric surgery could confound the link between maternal pre-pregnancy obesity and risk of ADHD in offspring. Thus, to rule out potential bias by bariatric surgery, we excluded those whose mother had bariatric surgeries prior to any delivery (N=14 028) and repeated our main analyses. Individuals who had undergone bariatric surgeries were identified from the NPR by using a Swedish adaption of the Classification of Surgical Procedures (NOMESKO) codes: 4750–4754, 4759, JDF00, JDF01, JDF10, JDF11, JDF20, JDF21, JDF32, JDF96, JDF97, JDF98, JFD00, JFD03, JFD04, JFD10, JFD13, JFD20, JFD23, JFD96.

All statistical analyses were conducted in SAS version 9.3 (SAS Institute, Cary, NC, USA).

**Results**

***Meta-analysis***

*Study characteristics*

A total of 784 804 mother-child pairs from eight pertinent cohort studies (19, 20, 34, 35, 43-46) were included in the meta-analysis (**Figure 1-1**). Another 41 825 pairs from six studies were only included in the qualitative synthesis because of limited information for effect size calculation (36, 37, 47, 48), different definitions of exposure (49), or overlapping study populations (38). **Table 1-1** shows the demographic and statistical details of the fourteen studies published between 2008 and 2017 included in the systematic review. The size of the cohorts ranged from 112 to 673 632.For those included in the meta-analysis, overweight and obesity was the most frequent measure of exposure while four of the studies further divided obesity into Obesity Class I, II, III (or II/III). ADHD in offspring was assessed by mother reported previous ADHD diagnosis, clinical diagnosis from national patient registers, or teacher/mother reported ADHD symptoms based on DSM-IV, Child Behavior Checklist (CBCL) and the Strengths and Difficulties Questionnaire (SDQ). For crude and full adjusted effect size, maternal overweight, obesity, and obesity class I-III were all compared with normal weight (18.5≤BMI<25.0).

The quality scores based on the NOS ranged from six to nine, suggesting an overall high quality of the included studies. As shown in **Table 1-2,** the number of stars represented the score of each item. Most studies used well-defined exposures and outcomes, with strict selection criteria. However, some included studies with one star in “Comparability” did not consider familial factors as potential confounders (e.g. genetic factors, paternal characteristics). The adjusted covariates in each of the included study are listed in **Table 1-3**. A total of twelve studies evaluated the impact of maternal age, and most studies evaluated maternal smoking during pregnancy, offspring sex, maternal educational level, parity, and year of birth. Adjustment for birth weight, gestational age, weight gain during pregnancy, maternal country, paternal BMI, children BMI, and parental ADHD occurred less often.

*Meta-analysis*

The meta-analysis showed increased risk of ADHD in offspring born to mothers with overweight (RR=1.31, 95%CI=1.25-1.38, I2=6.80%) and obesity (RR=1.92, 95%CI=1.84-2.00, I2=0.0%), compared with those born to normal weight mothers (**Figure 1-2**). The adjusted RRs were somewhat attenuated for both maternal overweight (RR=1.28, 95%CI=1.17-1.40, I2=35.3%) and obesity (RR=1.64, 95%CI=1.47-1.73, I2=0.0%), but the same pattern was observed (**Figure 1-3**). Among the studies estimating the association between maternal pre-pregnancy overweight and ADHD in offspring, the pooled RRs of the leave-one-study-out analysis were similar to those in the main analysis. When we repeated the analysis among studies evaluating the association between maternal pre-pregnancy obesity and ADHD in offspring, the overall estimate of the RR was slightly decreased to 1.77 (95%CI=1.59-1.97, I2=0.0%) after excluding the previous study based on a large Swedish sample. However, the direction of the association was still stable and the effect size was close to the pooled RR in main analysis (**Figure 1-4**). Using definitions of ADHD other than teacher-rated inattention symptoms produced similar results as in the main analysis (**Table 1-4**).

Subgroup analyses based on different measurements of ADHD (CBCL/SDQ/self-reported), different informants (parents/teachers) and time of maternal BMI (pre-pregnancy/early pregnancy) suggested that the association between maternal overweight or obesity and risk of ADHD in offspring was robust. However, the stratified analyses of different informants of children’s ADHD symptoms generated imprecise estimates, as only two previous studies (43, 44) provided information on parent-rated ADHD of offspring (**Table 1-5**). When we further repeated the main analysis among the studies that reported results for different obesity groups (obesity class I, obesity class II/III), the risk of having offspring with ADHD was still elevated for obesity I (RR=1.56, 95%CI=1.36-1.80, I2=0.0%) and obesity II/III (RR=2.24, 95%CI=1.86-2.71, I2=0.0%) mothers (**Figure 1-5**).

*Publication bias*

There was no evidence of publication bias according to Begg’s test and Egger’s test (all *P* > 0.5) and Funnel plots (**Table 1-6)**.

***Nationwide population-based cohort study***

In total,43 916 (4.52%) offspring with a diagnosis of ADHD were identified in the entire cohort. **Table 2-1** shows the distribution of offspring and maternal covariates. Offspring exposed to maternal overweight or obesity were more likely to be of late parity (*P* <0.01), and to have mothers who: were born outside Sweden (*P* <0.01), smoked during pregnancy (*P* <0.01), had lower education (*P* <0.01), and did not live together with the biological father at childbirth (*P* <0.01) (**Table S2**).

*Main analysis*

At the population level, the overall crude risk of ADHD in offspring was elevated in mothers with overweight or obesity (**Table 2-2**). The more severe the obesity, the higher the hazard of ADHD, with a *P*-value for trend < 0.01. The HRs for overweight and obese mothers were 1.30 (95%CI=1.28-1.34) and 1.92 (95%CI=1.87-1.98), respectively. Mothers with obesity class I, II and III had HRs of 1.82 (95%CI=1.76-1.88), 2.24 (95%CI=2.12-1.38) and 2.87 (95%CI=2.50-3.31), respectively. After adjustment for measured covariates, the associations of maternal pre-pregnancy overweight (HRoverweight=1.21, 95%CI=1.19-1.25) and obesity (HRobesity=1.60, 95%CI=1.55-1.65) with ADHD in offspring were slightly attenuated. Mothers with obesity class I, II and III had adjusted HRs of 1.53 (95%CI=1.48-1.59), 1.78 (95%CI=1.67-1.89) and 2.20 (95%CI=1.89-2.57), respectively. Consistent with the analyses at the population level, crude HRs attenuated when adjusting for measured covariates in the first-born full cousin comparisons and full sibling comparisons (**Table S3**).

The associations were further attenuated in first-born maternal full cousin comparison models when taking measured covariates and unmeasured factors shared by first cousins into consideration (HRoverweight=1.10, 95%CI=0.98-1.23; HRobesity=1.44, 95%CI=1.22-1.70). Sibling comparison models showed that the observed association at the entire population level were largely attenuated toward the null (HRoverweight=1.01, 95%CI=0.92-1.11; HRobesity=1.10, 95%CI=0.94-1.27). The associations of maternal pre-pregnancy obesity class I to III with ADHD in offspring were also largely attenuated and the dose-response association was no longer existed in the sibling comparison analysis, but the point estimate and the upper confidence interval for obesity class III indicated a potential association with ADHD in offspring (HR=1.70, 95%CI=0.99-2.91).

When analyzing BMI as a continuous trait, the attenuated effect within full cousins (HRBMI=1.03, 95%CI=1.02-1.04) and the null effect within full siblings (HRBMI=1.00, 95%CI=0.99-1.03) were replicated, demonstrating the robustness of our main results (**Table 2-2**).

*Sensitivity analyses*

First, analyses restricted to first- and second-born sibling pairs yielded similar results to those in the main analyses (HRoverweight=1.00, 95%CI=0.91-1.11; HRobesity=1.04, 95%CI=0.88-1.24; HRobesity I=1.05, 95%CI=0.88-1.24; HRobesity II=0.97, 95%CI=0.73-1.28; and HRobesity III=1.73 , 95%CI=0.94-3.16), indicating that the results of the main analysis are robust (**Table 2-3**). To further explore the effect modification by birth order, we conducted stratified analyses based on first- and second-born siblings. Comparing to first-born siblings (HRoverweight=1.29, 95%CI=1.22-1.37; HRobesity=1.66, 95%CI=1.52-1.81), similar associations were found in second-born siblings (HRoverweight=1.27, 95%CI=1.20-1.34; HRobesity=1.78, 95%CI=1.66-1.91) (**Table S4**), indicating the modification by birth order was oflimited importance. Second, weight-gain and weight-loss between two pregnancies may indicate different biological mechanisms and the effect of familial confounding may differ across different types of between-pregnancy variation in BMI (19). However, similar associations were observed in the population level and stratified sibling comparisons when we conducted the bi-directional case-cross analysis (**Table 2-4**), suggesting that the influence of changing weight status and carryover effects between two pregnancies were of limited importance. Third, to rule out potential confounding by bariatric surgery, we restricted the analysis to those who never had bariatric surgeries before delivery (N=957 473). All results were consistent with the main analyses among mothers with overweight or obesity at population level, first-born maternal full cousin comparisons and first- and second-born sibling pairs (**Table S5**).

**Discussion**

By combining a systematic review, meta-analysis based on previous studies with a nationwide population-based cohort study with sibling and cousin comparisons, we rigorously explored the association between maternal pre-pregnancy overweight/obesity and risk of ADHD in offspring, assessing dose-response effects and the role of unmeasured confounding. The meta-analysis revealed a positive association between maternal pre-pregnancy BMI and risk of ADHD in offspring. Similar results were observed in the nationwide population-based cohort study based on Swedish registers after adjusting for measured covariates. However, in cousin and sibling comparisons, the associations were largely attenuated toward the null, suggesting that the association between maternal pre-pregnancy BMI and risk of ADHD in offspring could be largely ascribed to unmeasured familial confounding.

Consistent to the results from previous meta-analysis studies (7, 50), we also found a positive association between maternal pre-pregnancy overweight/obesity and ADHD in offspring. However, our study strengthens and extends previous findings in three ways: First, we found robust results across different definitions and assessment approaches of both overweight/obesity and ADHD. Second, previous meta-analytic findings need to be interpreted with caution since these meta-analysis studies suffered from important methodological limitations: a) the estimates may not be corrected for including more than one estimate from the same study when pooled estimates were calculated (7, 50) , which may introduce over-representation bias; b) some studies in these meta-analyses were based on highly selected samples, such as high-risk population with ADHD prevalence of 11.0% (51), alcohol and marijuana cohort (only includes women who drank more than three drinks per week, or smoked more than two joints per month) (52), a cohort where joint effects of diabetes and severely obesity were explored (53), or only preterm birth samples (54), which may limit generalizability; c) several recent and important studies were not included in the Sanchez’s (11, 12) and Jenabi’s meta-analysis work (43, 46). Third, combined with a nationwide family-based cohort study, we further evaluated the results from the pooled estimates of previous studies by adjusting for measured confounding identified via a DAG, and unmeasured confounding by using various genetically informative designs, an approach similar to the one used in Cortese et al. (17). Therefore, we could further explore potential alternative explanations for the observed associations.

 Similar to previous sibling comparison studies (19, 20), we found that the association between maternal pre-pregnancy overweight/obesity and increased risk of ADHD in offspring was largely explained by unmeasured familial confounders. Maternal pre-pregnancy overweight/obesity probably represent, at least in part, a genetic predisposition to ADHD in offspring, as both population-based familial co-aggregation studies (12) and a recent genome-wide association study (13) have suggested a genetic overlap between overweight/obesity and ADHD. Importantly, even though twin studies consistently have demonstrated that shared environmental factors probably are of limited importance in ADHD (55), influences from such factors cannot be ruled out completely (56). We were able to extend the previous family-based quasi-experimental studies (i.e., sibling comparison studies) (19, 20) in three important ways. First, our bi-directional case-cross analysis indicated that carryover effects between two pregnancies were of limited importance. Second, findings from both sibling-comparisons and first-cousin comparisons consistently suggested the presence of unmeasured familial confounding indicating that findings from sibling-comparisons generalize to other settings. This is important given that women who varied in their weight status between pregnancies might not be comparable to women who were constantly overweight/obese. Third, with the largest sample size, we could further explore and confirm the dose-response associations of maternal pre-pregnancy obesity class I to III with ADHD in offspring.

*Limitations*

The results of the meta-analysis should be interpreted with caution. First, the assessment of ADHD varied across the studies. However, the subgroup analyses on the different ADHD measurements suggested that the results were robust independent of the assessment approaches of the studies included in the meta-analysis. Second, three studies based on Nordic national medical registers used maternal early pregnancy BMI as a proxy for pre-pregnancy BMI. Although early gestational weight and pre-pregnancy weight were highly correlated in a previous study (49), somewhat lower overall risk ratios were found among studies with pre-pregnancy overweight/obesity as exposure compared with those that used early pregnancy overweight/obesity as exposure. Thus, the associations reported in the current meta-analysis might be overestimations. Third, we were not able to calculate a pooled risk ratio among studies using sibling comparisons, as the two available studies (19, 20) used different methods [Cox proportional hazards model and generalized estimating equations (GEE)], which cannot be combined. Therefore, we further compared the pooled risk ratios obtained from current meta-analysis with those observed from an original cohort study with family-based quasi-experimental study design. Fourth, all included studies were conducted in Europe (in particular, the large cohorts in Nordic countries) and the US, which limit generalizability to other populations across the world. We therefore suggest future studies to examine the associations using different samples, especially in countries outside Europe and the US. Future studies with different study designs, e.g. intergenerational Mendelian randomization or children-of-twins design are also needed to triangulate our findings.

The nationwide population-based cohort study also had limitations. First, as already discussed and similar to previous register-based observational studies included in our meta-analysis (19, 34, 35), we used early pregnancy BMI (around 10 weeks of gestation) as a proxy for pre-pregnancy BMI. Based on evidence from the above meta-analysis, we might overestimate the magnitude of the association, although this overestimate was unlikely to affect our conclusion on sibling comparisons. Second, the current cohort study suffered from common limitations among register-based studies, such as measurement errors using information from the medical records and limited availability of measured confounding variables. Third, BMI may not be an accurate proxy for total body fat and overweight/obesity related metabolic conditions (57). Future studies would benefit from using more direct measurement/observation/diagnosis of obesity, or specific maternal pre-pregnancy conditions (e.g. metabolic syndrome). Fourth, sibling and cousin comparisons are not able to control for time-varying family-wide confounders, like maternal age, which may, although not necessarily, invalidate unmeasured familial confounding as the main explanation for the observed association. Another limitation of the sibling-comparison design is the loss of power to make definitive conclusions about the highest level of obesity (obesity class III), as there were only nine families with siblings discordant for maternal pre-pregnancy extreme obesity (obesity class III), of which only one family was also discordant for ADHD (**Table S6**). That is, this double discordant family contributed with the main information to the analysis of obesity class III, and in the adjusted Cox proportional hazards model, siblings discordant for exposure time (e.g. differences in the length of follow-up) or other covariates are also informative. Fifth, despite the large sample size, we cannot completely rule out a potential causal link from maternal pre-pregnancy overweight/obesity to ADHD in offspring. Compared with the previous Swedish sibling study (19) (HRobesity=1.15, 95%CI=0.85-1.56), we found a lower magnitude of the HR and a narrower confidence interval among obese women in sibling comparisons (HRobesity=1.10, 95%CI=0.94-1.27), but the upper limit of the 95%CI was still non-negligible, especially in moderate (obesity class II) (HR upper 95%CI=1.36) and extreme obese (obesity class III) (HR upper 95%CI=2.91) women. Nonetheless, any causal relationship is unlikely to be as strong as found in the meta-analysis. Future work is needed to explore the nature of the familial confounding and the potential risks associated with severe pre-pregnancy obesity (e.g. obesity class III).

In conclusion, there is an association between maternal pre-pregnancy overweight/obesity and ADHD in offspring, but this association is largely ascribable to unmeasured familial confounding, and not a strong causal relationship. Our findings highlight the importance of accounting for unmeasured familial confounders in risk factor studies of ADHD in offspring. Future studies need to elucidate the genetic and environmental origins of the unmeasured confounding and more studies with different methods and designs, in various populations, or focusing on sever maternal obesity are still needed to replicate and build upon our findings.

**Funding**

This work was supported by financial support from the Swedish Research Council (2018-02599) and through the ***S***wedish ***I***nitiative for Research on ***M***icrodata in the ***S***ocial ***a***nd ***M***edical Sciences (SIMSAM) framework grant no 340-2013-5867 and European Union’s Horizon 2020 research and innovation programme under grant agreement No 667302.

**Conflict of interest**

Dr Larsson has served as a speaker for Evolan and Shire and has received research grants from Shire; Dr Cortese reports receiving reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH), a non-profit organisation, Healthcare and the Canadian Alliance ADHD Resource (CADDRA) in relation to lectures that he delivered on ADHD; all outside the submitted work.

**KEY MESSAGES**

* Studies examining the effect of maternal pre-pregnancy overweight/obesity on risk of attention-deficit/hyperactivity disorder (ADHD) in offspring have only recently emerged and the findings are inconclusive.
* The causal status of the potential association between maternal pre-pregnancy overweight/obesity and risk of ADHD in offspring remain unclear.
* In a meta-analysis, we found a maternal pre-pregnancy overweight/obesity was associated with a higher risk of ADHD in offspring.
* Results from our family based quasi-experimental study suggested the observed association can be largely ascribed to unmeasured familial confounding, rather than a causal link.
* More studies with different methods and designs, in various populations, or focusing on sever maternal obesity are still needed to replicate and build upon our findings.

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