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MENTAL HEALTH

Maternal pre-pregnancy body mass index and offspring attention deficit hyperactivity disorder: a population-based cohort study using a sibling-comparison design

Qi Chen,[1]* Arvid Sjölander,[1] Niklas Långström,[1] Alina Rodriguez,[2,3,4] Eva Serlachius,[5] Brian M D'Onofrio,[6] Paul Lichtenstein[1] and Henrik Larsson[1]

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, [2]Department of Social Sciences–Psychology, Mid Sweden University, Östersund, Sweden, [3]Department of Epidemiology and Biostatistics, Imperial College London, London, UK, [4]Medical Research Council Social Genetic Developmental Psychiatry Centre, King's College London, London, UK, [5]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden and [6]Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN, USA

*Corresponding author. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Box 281, 17177 Stockholm, Sweden. E-mail: qi.chen@ki.se

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Background High maternal pre-pregnancy body mass index (BMI) is associated with increased risk of offspring attention deficit hyperactivity disorder (ADHD). However, the role of unmeasured familial confounding for this association remains unclear.

Methods We conducted a population-based cohort study via linkage of Swedish national and regional registers to investigate maternal pre-pregnancy BMI (underweight: BMI <18.5; overweight: $25 \leqslant$ BMI <30; obesity: BMI $\geqslant 30$) in relation to offspring ADHD. We followed 673 632 individuals born in Sweden between 1992 and 2000, with prospectively collected information on maternal pre-pregnancy BMI, until they received an ADHD diagnosis or ADHD medication, death, emigration or 31 December 2009. Hazard ratios (HRs) were estimated by Cox proportional hazards models. Stratified Cox proportional hazards models were applied to data on full siblings to control for unmeasured familial confounding.

Results At the population level, pre-pregnancy overweight/obesity was associated with increased risk of offspring ADHD ($HR_{overweight} = 1.23$, 95% CI = 1.18–1.27, $P = 0.01$; $HR_{obesity} = 1.64$, 95% CI = 1.57–1.73, $P = 0.01$), after adjustment for measured covariates. In full sibling comparisons, however, previously observed associations no longer remained ($HR_{overweight} = 0.98$, 95% CI = 0.83–1.16, $P = 0.82$; $HR_{obesity} = 1.15$, 95% CI = 0.85–1.56, $P = 0.38$).

Conclusions The results suggested that the association between maternal pre-pregnancy overweight/obesity and offspring ADHD could be ascribed to unmeasured familial confounding.

Keywords ADHD, maternal BMI, prenatal, confounding, sibling comparison

Introduction

Attention deficit hyperactivity disorder (ADHD) affects approximately 5% of children worldwide[1] and is associated with adverse health outcomes.[2–4] Despite a substantial heritability,[5] ADHD is also associated with several prenatal factors.[6,7] Although this has led to considerable interest in foetal programming hypotheses,[8–10] the role of unmeasured familial confounding remains unclear for these proposed risks.[11]

The period before pregnancy is a vital time window for the prevention of adverse pregnancy outcomes.[12] Overweight and obese women are at increased risk of insulin resistance, which can be further exacerbated by pregnancy-related metabolic alterations and result in many adverse perinatal and postnatal conditions.[13] Human studies[14,15] suggest that maternal pre-pregnancy overweight or obesity may influence offspring neurodevelopmental outcomes, including ADHD. One study found associations between pre-pregnancy overweight/obesity and teacher-rated ADHD symptoms among 12 556 school-aged children.[16] This finding was replicated in a study of 1714 pre-school children, demonstrating that offspring of overweight/obese mothers, as compared with offspring of normal-weight mothers, had higher risk of teacher-rated inattentive symptoms of ADHD, but not hyperactive-impulsive symptoms.[17]

In these studies, associations remained after controlling for measured covariates (e.g. maternal age at delivery, smoking during pregnancy, parental psychopathology), and may therefore indicate a potential causal effect. However, given that it is impossible to identify or accurately measure all the potential confounders, unmeasured confounding might also explain the observed associations. That is, pre-pregnancy obesity might represent a genetic predisposition rather than a causal risk factor for offspring ADHD.[18] Time-invariant family-wide environmental factors influencing both mothers and their children may also explain the observed associations.

An animal experiment[19] demonstrated a causal link between prenatal exposure to maternal obesity and hyperactivity in adult mice, but randomized trials are not always ethical or feasible in humans.[20] The sibling-comparison design represents an important alternative for causal inference in observational studies,[21–24] as it controls for genetic factors transmitted from mother to child that may contribute to both pre-pregnancy overweight/obesity and ADHD. This is because meiosis randomly distributes alleles of parents' genes across siblings during the process of recombination within the fertilized egg.[23] The sibling-comparison design also controls for time-stable environmental factors. Thus, the causal interpretation could be strengthened if the association at the population level remained when comparing siblings differentially exposed to maternal overweight/obesity during prenatal development. A substantial attenuation of the association, on the other hand, would indicate unmeasured familial confounding.

This study aimed to investigate the association between maternal pre-pregnancy BMI and offspring ADHD in a large longitudinal population-based sample, while controlling for measured covariates related to offspring and their mothers. Further, we compared biological full siblings to assess whether the association could be ascribed to unmeasured familial confounding.

Methods

Data source

We used data from a linkage between nine national or regional registers via the unique personal identification number (PIN) as follows: (i) The Medical Birth Register (MBR) contains data on more than 99% of births in Sweden since 1973;[25] (ii) The Multi-Generation Register supplies identifiers of biological relationships;[26] (iii) The National Patient Register (NPR) provides data on inpatient care since 1987 and outpatient visits to specialist (non-general practitioner) since 2001; each patient has one primary diagnosis and up to eight secondary diagnoses based on the International Classification of Diseases (ICD) (ICD-9 for 1987–96 and ICD-10 since 1997); (iv) The Prescribed Drug Register (PDR) contains data on drug identity [Anatomical Therapeutic Chemical (ATC) code] for all medication dispensed to the entire population in Sweden since 1 July 2005;[27] (v) The clinical Child and Adolescent Psychiatry database in the greater Stockholm region or county (Pastill) covers data on psychiatric diagnoses based on ICD-10 or the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR);[28] (vi) The database for health insurance and labour market study (LISA) in 2009 provides data on education level; (vii) The Population Register, (viii) Cause of Death Register and (ix) Migration Register were also used for the identifying study population.

The study was approved by the research ethics committee at Karolinska Institutet, Stockholm, Sweden.

Study population

A total of 894 444 individuals born in Sweden during 1992 and 2000 were identified from the MBR. We excluded those who had severe congenital malformation ($N = 32\,209$), were from multiple births ($N = 25\,302$), were stillborn ($N = 2767$), died before age 3 years or before 2001 ($N = 2613$), emigrated before age 3 years or before 2001 ($N = 18\,226$), lacked mother's identification number ($N = 250$) or received an ADHD diagnosis before age 3 years ($N = 47$). The remaining sample was composed of 813 030 eligible individuals (90.9% of the targeted population). Individuals with missing values

regarding maternal pre-pregnancy BMI ($N = 139\,398$) were also excluded, resulting in 673 632 individuals (82.9% of the eligible population) as the final study population. We further identified 272 790 full biological siblings nested within 130 060 families from this study population. Most families (91.0%) contributed two siblings, and the maximum number of siblings in a family was six. We also identified a sub-sample ($N = 260\,120$) consisting of the first- and second-born siblings from each family. This sample was used for a set of sensitivity analyses. All individuals were followed from age 3 years until a diagnosis of ADHD, death, emigration or 31 December 2009, whichever occurred first.

Exposure definition

Maternal weight and height were recorded by recall at the first antenatal clinic visit (around 10 weeks of gestation). Pre-pregnancy BMI was calculated as weight divided by squared height (kg/m^2) and classified into underweight (BMI <18.5), normal ($18.5 \leqslant$ BMI <25), overweight ($25 \leqslant$ BMI <30) and obese (BMI $\geqslant 30$), according to the WHO classification of BMI cut-offs.[29] The study population contained 20 354 (3.0%) individuals with underweight mothers, 451 220 (70.0%) individuals with normal-weight mothers, 148 888 (22.1%) individuals with overweight mothers and 53 170 (7.9%) individuals with obese mothers. Individuals with missing values for maternal pre-pregnancy BMI were more likely to have an ADHD diagnosis ($X^2 = 12.64$, $P < 0.001$) compared with individuals without missing values. Their mothers were more likely to be born outside Sweden ($X^2 = 3109.11$, $P < 0.0001$), with lower education ($X^2 = 856.64$, $P < 0.0001$), older at delivery ($t = -17.26$, $P < 0.0001$), smokers during pregnancy ($X^2 = 81.63$, $P < 0.0001$) and less likely to cohabit with child's father at childbirth ($X^2 = 221.57$, $P < 0.0001$).

Outcome definition

Individuals: with hyperkinetic disorder diagnoses (ICD-9: 314; ICD-10: F90) in the NPR ($N = 12\,282$; primary diagnosis: 86.8%; secondary diagnosis only: 13.2%); or ADHD (DSM-IV-TR: 314; ICD-10: F90) in the Pastill Register ($N = 2965$); or treated with ADHD medication [methylphenidate (N06BA04); amphetamine (N06BA01); dexamphetamine (N06BA02); or atomoxetine (N06BA09)] according to the PDR ($N = 14\,208$); were identified as ADHD cases. According to Swedish guidelines, ADHD medication should be reserved for patients where other non-pharmacological interventions have failed, which ensures that most prescriptions of ADHD medications were motivated by an ADHD diagnosis. The date of diagnosis was defined as the date of the first record in any registers, whichever came first. In total, we identified 17 380 unique individuals with ADHD from the three registers.

Measured covariates

Potential covariates, offspring and maternal demographic characteristics, were identified from different registers, including: offspring sex, birth order (first, second, third or fourth) and year of birth (1992–94, 1995–97 and 1998–2000); mother's country of birth (Sweden, other Scandinavian countries or other); maternal education ($\leqslant$9 years, 10–12 years or post-graduate education); maternal age at delivery ($\leqslant$19, 20–24, 25–29, 30–34 or $\geqslant$35 years); smoking during pregnancy (0, 1–9 or $\geqslant$10 cigarettes per day); and cohabitation with child's father at childbirth (yes or no).

Statistical analyses

Cox proportional hazards models were used to estimate hazard ratios (HRs) for the time to first-ever ADHD diagnosis, and robust standard errors were used to adjust the 95% confidence intervals (CIs) for the presence of familial clustering at the population level. Maternal underweight, overweight and obesity were all compared with normal weight. The Cox models were adjusted for all measured covariates mentioned above. Since perinatal offspring traits, such as gestational age and birthweight, might be on the causal pathway between maternal pre-pregnancy BMI and ADHD, we did not adjust for them.

Paired *t*-testing was used to examine the mean and the standard deviation (SD) of the difference in maternal BMI between discordantly exposed siblings. Stratified Cox proportional hazards models were used for sibling comparisons with a separate stratum for each set of full siblings. These analyses estimated the association between maternal pre-pregnancy BMI and offspring ADHD using within-mother variation in BMI. Siblings discordant for maternal pre-pregnancy BMI contribute with the main information, but siblings differentially exposed to any other covariates are also informative for the within-family analyses. The models were adjusted for the same covariates as in the adjusted models at the population level, except for mother's country of birth and highest maternal education, because these were constant within sets of siblings and thus already adjusted by the sibling-comparison design. We also assessed the studied association by pooling together pre-pregnancy overweight and obesity subgroups. In addition, we tested the robustness of our results using continuous maternal BMI as exposure.

We assessed the influence of non-random missingness of BMI and the potential effect modification by birth order on the studied associations. We also explored the potential confounding and modifying effects by different types of between-pregnancy variation in BMI (Normal-Normal, Normal-Overweight/Obesity, Overweight/Obesity-Normal and Overweight/Obesity-Overweight/Obesity). We performed additional sensitivity analyses to test the robustness of

our results in the restricted cohort and the generalizability of our results from siblings to the entire cohort.

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

Results

Offspring and maternal demographic characteristics were symmetrically distributed in the entire cohort and the sibling sample, except for birth order and year of birth (Table 1). Covariate analyses revealed that individuals exposed to pre-pregnancy overweight/obesity were less likely to be firstborn($P < 0.01$), and their mothers were more likely to be born outside Sweden ($P < 0.01$), with lower education ($P < 0.01$), older at delivery ($P < 0.01$) and smokers during pregnancy ($P < 0.01$), and were less likely to cohabit with the child's father at childbirth ($P < 0.01$) (data not shown).

At the population level, crude analyses suggested that maternal pre-pregnancy underweight, overweight and obesity were all associated with higher risk of offspring ADHD (Table 2). After adjustment for measured covariates, the associations for pre-pregnancy overweight and obesity were slightly attenuated but remained ($HR_{overweight} = 1.23$; $HR_{obesity} = 1.64$), whereas the association for pre-pregnancy underweight could not be observed (Table 2). We therefore focused on the effect of pre-pregnancy overweight and obesity in the subsequent sibling comparisons.

In the sibling sample, 19 814 families contained siblings discordant for maternal pre-pregnancy overweight/obesity (mean difference in BMI = 2.86, SD = 2.01, $t = 199.9$, $P = 0.01$). Among these families, 892 families contained siblings discordant also for ADHD. Within-sibling analyses showed that the observed associations at the population level were largely attenuated to null ($HR_{overweight} = 0.98$; $HR_{obesity} = 1.15$). The null effect within full siblings was replicated when overweight and obesity subgroups were pooled together (Table 3), and when continuous BMI was used as exposure ($HR_{continuousBMI} = 0.99$, 95% CI = 0.96–1.02, $P = 0.49$), highlighting the robustness of our results.

Sensitivity analyses

We conducted a series of sensitivity analyses to explore the validity of design assumptions[23] and the robustness of our results. First, we explored the influence of non-random missingness in pre-pregnancy BMI by replacing missing values with underweight, normal weight, overweigh or obesity in four separate models. In these models, the results were similar to those in the original analyses at the population level (data not shown), suggesting that bias due to non-random missingness had limited importance in the main results.

Second, to investigate the effect modification by birth order, we conducted analyses stratified on birth order in sibling pairs. Although more second-born were exposed to pre-pregnancy overweight/obesity compared with the firstborn individuals, the associations in firstborn siblings ($HR_{overweight} = 1.22$, 95% CI = 1.12–1.33, $P = 0.01$; $HR_{obesity} = 1.81$, 95% CI = 1.61–2.03, $P = 0.01$) were similar to those in second-born siblings ($HR_{overweight} = 1.29$, 95% CI = 1.18–1.41, $P = 0.01$; $HR_{obesity} = 1.77$, 95% CI = 1.58–1.97, $P = 0.01$), suggesting that birth order effects were of limited importance.

Third, using continuous BMI as exposure, we observed similar population level and within-sibling associations across subgroups of siblings whose mothers had different types of between-pregnancy variation in BMI (Table 4), suggesting that the confounding or modifying effects were of limited importance.

Fourth, most ADHD cases were identified via outpatient visits in the NPR from 2001 onwards. It was therefore possible that older siblings receiving a diagnosis earlier in life were not in the register or that younger siblings had not yet been diagnosed by the end of follow-up, resulting in misclassification of affected siblings. Therefore, we carried out additional within-sibling analyses in a restricted birth cohort born1994–98, consisting of 92 036 full sibling pairs nested in 46 018 families, with an average age difference of 2.35 (SD = 0.93) years. The analyses provided no evidence for increased risk of ADHD associated with either pre-pregnancy overweight ($HR_{overweight} = 0.86$, 95% CI = 0.64–1.16, $P = 0.32$) or obesity ($HR_{obesity} = 0.84$, 95% CI = 0.50–1.42, $P = 0.51$), consistent with the main results of sibling comparisons.

Finally, the adjusted associations among siblings analysed on their own ($HR_{overweight} = 1.26$, 95% CI = 1.19–1.35, $P = 0.01$; $HR_{obesity} = 1.77$, 95% CI = 1.63–1.93, $P = 0.01$) were comparable to those among the entire cohort (Table 2).

Discussion

Consistently with previous research,[17] we found that maternal pre-pregnancy overweight and obesity (but not underweight) were associated dose-dependently with increased risk of offspring ADHD after adjustment for measured covariates (e.g. offspring sex and birth order and maternal age at delivery). Sibling comparisons, on the other hand, remarkably attenuated the associations, suggesting that the association between maternal pre-pregnancy overweight/obesity and offspring ADHD may to a large extent be ascribed to unmeasured familial confounding. Future research needs to elucidate the nature of the familial confounding. In view of the evidence supporting a genetic overlap between overweight/obesity and ADHD,[30] for instance, via genetic variants related to the

Table 1 Demographic characteristics of offspring and their mothers

Covariates	Entire cohort[a] ($N = 673\,632$) N (%)	Full siblings[b] ($N = 272\,790$) N (%)
Offspring sex		
Male	344 176 (51.1)	139 949 (51.3)
Female	329 375 (48.9)	132 841 (48.7)
Birth order		
1st	275 617 (40.9)	99 268 (36.4)
2nd	251 226 (37.3)	117 795 (43.2)
3rd	102 251 (15.2)	38 171 (14.0)
⩾4th	44 527 (6.6)	17 556 (6.4)
Offspring year of birth		
1992–94	254 849 (37.8)	89 127 (32.7)
1995–97	217 959 (32.4)	107 160 (39.3)
1998–2000	200 824 (29.8)	76 503 (28.0)
Mother's country of birth		
Sweden	573 252 (85.1)	235 880 (86.5)
Denmark, Finland, Norway or Iceland	18 166 (2.7)	6377 (2.3)
Other	82 200 (12.2)	30 528 (11.2)
Maternal education		
⩽9 years	62 279 (9.4)	21 348 (8.0)
10–12 years	336 822 (50.9)	135 149 (50.3)
Postgraduate education	262 540 (39.7)	112 152 (41.7)
Maternal age at delivery (years)		
⩽19	9617 (1.4)	2442 (0.9)
20–24	105 187 (15.6)	44 214 (16.2)
25–29	245 508 (36.5)	108 657 (39.8)
30–34	209 710 (31.1)	85 430 (31.3)
⩾35	103 610 (15.4)	32 047 (11.8)
Smoking during pregnancy		
No cigarettes	547 584 (83.3)	238 130 (87.3)
1–9 cigarettes per day	71 140 (10.8)	22 786 (8.4)
⩾10 cigarettes per day	38 965 (5.9)	11 874 (4.3)
Cohabitation with child's father at childbirth		
Yes	614 608 (95.0)	266 140 (97.6)
No	32 033 (5.0)	6650 (2.4)

[a]In the entire cohort, 81 individuals missed data for sex, 11 for birth order, 14 for mother's country of birth, 11 991 for highest maternal education, 15 943 for smoking during pregnancy, and 26 991 for cohabitation status.
[b]In the full sibling sample, 5 individuals missed data for mother's country of birth and 4141 individuals missed data for highest maternal education. No other variables had missing data.

dopaminergic reward system,[31] we predict that the familial confounding may be genetic in origin.

In contrast to our findings, a recent animal study[19] demonstrated that offspring mice exposed to maternal diet-induced obesity were more active, as compared with unexposed mice. Although there is always a question of generalizability across species,[32] animal models offer full control of variables including genetic equivalence among animals, and thus a possibility to demonstrate causality. Clearly, the association between prenatal exposure to maternal obesity and behavioural disturbance in offspring needs further scrutiny.

There are alternative explanations (other than familial confounding) for the observed attenuated associations. First, even though several lines of research

Table 2 Hazard ratios for ADHD based on offspring exposed to different levels of maternal pre-pregnancy BMI

Exposure	Crude[a]		Adjusted[b]	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Pre-pregnancy normal weight	Reference		Reference	
Pre-pregnancy underweight	1.17 (1.08–1.28)	0.01	1.03 (0.94–1.12)	0.58
Pre-pregnancy overweight	1.31 (1.27–1.36)	0.01	1.23 (1.18–1.27)	0.01
Pre-pregnancy obesity	1.95 (1.86–2.04)	0.01	1.64 (1.57–1.73)	0.01

[a]$N = 673\,632$.
[b]$N = 620\,795$ adjusted for offspring sex, birth order, year of birth, mother's country of birth, highest maternal education, maternal age at delivery, smoking during pregnancy and cohabitation with child's father at childbirth.

Table 3 Hazard ratios for ADHD based on siblings exposed to high maternal pre-pregnancy BMI

Exposure	Full siblings[a]			
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Pre-pregnancy normal weight	Reference		Reference	
Pre-pregnancy overweight	0.98 (0.83–1.16)	0.82	0.98 (0.83–1.17)	0.84
Pre-pregnancy obesity	1.15 (0.85–1.56)	0.38		

[a]$N = 272\,790$, adjusted for offspring sex, birth order, year of birth, maternal age at delivery, smoking during pregnancy and cohabitation with child's father at childbirth.

Table 4 Hazard ratios for ADHD based on siblings of mothers with different patterns of variation in BMI

BMI category		Number of pairs	Difference in BMI	Population level analysis[a]		Sibling comparison[a]	
1st pregnancy	2nd pregnancy		Mean (SD)	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Normal	Normal	81 082	1.00 (0.84)	1.02 (1.00–1.05)	0.07	1.05 (0.97–1.13)	0.22
Normal	Overweight/Obese	14 924	2.89 (1.92)	1.05 (1.01–1.08)	0.01	1.00 (0.93–1.08)	0.97
Overweight/Obese	Normal	3600	2.49 (2.45)	1.01 (0.95–1.07)	0.79	0.85 (0.67–1.08)	0.17
Overweight/Obese	Overweight/Obese	30 454	1.92 (1.78)	1.06 (1.04–1.07)	0.01	0.97 (0.93–1.02)	0.24

[a]Adjusted for offspring sex and birth order.

indicate that the familial resemblance of ADHD is genetic in origin,[5] higher rates of misdiagnosis (i.e. false positives) in co-siblings of ADHD probands would also lead to attenuated estimates in sibling comparisons. Second, the sibling design does not implicitly control for time-varying confounders.[33,34] Failing to adjust for such confounders would, though not necessarily, invalidate unmeasured familial confounding as the main explanation for the observed results. Third, weight gain and weight loss between pregnancies may represent different biological processes (e.g. weight-regulatory system more effective for the protection against weight loss than weight gain[35]) and the impact of familial confounding may differ between the two types of between-pregnancy variation in BMI. However, sensitivity analyses provided little support for such an explanation, as similar results were observed for siblings discordant because of between-pregnancy weight gain (Normal-Overweight/Obesity) and weight loss (Overweight/Obesity-Normal). Fourth, discordant siblings might over-represent those with misclassifications of BMI due to measurement errors, which would also lead to attenuated within-sibling estimates.[34] Nevertheless, the true effect of high BMI is unlikely to be as prominent as previously suggested.

Our study has certain strengths. Sibling-comparison design controls for shared familial factors that are unlikely to be adequately measured or controlled in conventional observational studies. Further, the large nationwide and representative birth cohort with prospectively collected measures of exposure, outcome and covariates largely precluded recall bias.

This study has several limitations. First, as in all observational studies, we could not fully rule out residual confounding due to the lack of intact information on the exposure variable and potential

confounders, even though the dose-dependent associations at the population level were robust against bias from non-random missingness in maternal pre-pregnancy BMI.

Second, our sibling sample included 19 814 families with siblings discordant for maternal pre-pregnancy overweight/obesity and 892 families contained siblings discordant also for ADHD. These 892 families contributed with the main information in the sibling-comparison analyses, but in adjusted stratified Cox proportional hazards models, siblings discordant for any other covariate or length of follow-up are also informative for the within-family estimates. Despite the low magnitude of the HRs of the sibling-comparison analyses, we cannot completely rule out a causal effect of pre-pregnancy overweight/obesity. This is true especially for obesity, because the upper limit of the 95% CI was estimated to be 1.56 for pre-pregnancy obesity. Nonetheless, the association is unlikely to be as large as previously suggested.

Third, BMI might not represent an optimal proxy for overweight/obesity-related suboptimal metabolic conditions, indicating that future research needs to explore how more specific assessments of metabolic conditions, such as insulin resistance, relate to offspring ADHD. Given that we lacked repeated assessments of maternal pregnancy BMI across different trimesters, future research needs to explore the association between offspring ADHD and developmental trajectories of maternal body weight through pregnancy.

Fourth, the ascertainment of ADHD cases was predominantly based on the ICD-10 hyperkinetic disorder diagnosis or on prescribed medication unique for the treatment of ADHD and motivated by diagnosis. The ICD-10 definition of ADHD is stricter than that of DSM-IV-TR,[36] indicating that we most likely studied the more severe cases of ADHD. A previous study from our group showed that 70% of the twins with a national register-based ADHD diagnosis were identified as screen-positive for parent-rated ADHD.[37] Although our case identification strategies could not avoid false negatives (i.e. individuals with ADHD were not recorded in any registers) that would lead to null findings, bias due to false positives is unlikely.

Finally, it was not possible to classify ADHD cases according to the three DSM-IV-TR ADHD subtypes (i.e. combined, primarily hyperactive-impulsive and primarily inattentive types). This is a limitation, given that research indicates that maternal pre-pregnancy overweight/obesity is primarily associated with the inattentive component of ADHD.[17]

In conclusion, the association between maternal pre-pregnancy overweight/obesity and ADHD may to a large extent be ascribed to unmeasured familial confounding. These results need to be replicated in different samples and designs, and using more specific assessments of genetic and metabolic factors.

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Conflict of interest: None declared.

KEY MESSAGES

- Previous studies reported that maternal pre-pregnancy overweight/obesity might be associated with offspring ADHD. However, the role of unmeasured familial confounding for the association remains unclear.
- In line with previous research, we found that pre-pregnancy overweight/obesity was associated with increased risk of offspring ADHD after adjustment for measured covariates.
- Sibling comparisons showed remarkable attenuation of the previously observed associations, indicating the association could at least partially be ascribed to unmeasured familial confounding.

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