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Maternal prepregnancy body mass index and offspring attention-deficit/hyperactivity disorder: a quasi-experimental sibling-comparison, population-based design

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Abstract

Background—High maternal pre-pregnancy body mass index (BMI) has been associated with increased risk of offspring attention-deficit/hyperactivity disorder (ADHD). However, whether this effect is attributable to maternal or familial level confounds has been little examined.

Methods—The present study sought to examine these associations, utilizing data from the medical records of a health care system which treats 350,000 patients annually and a sibling-comparison design in a sample of 4,682 children born to 3,645 mothers.

Results—When examining the overall maternal effect, a linear association was observed between maternal pre-pregnancy BMI and child ADHD (b = .04, 95% confidence interval [95% CI] = .02 - .06, p = .0003), such that a one-unit (i.e., 1 kg/m^2) increase in pre-pregnancy BMI was associated with a 4% increase in the odds of ADHD ($exp\ b$ = 1.04). However, when the model was re-parameterized to take full advantage of the sibling-design to allow for the examination of both maternal and child-specific effects, the child specific pre-pregnancy BMI effect was not reliably different from zero (b = −.08, 95% CI = −.23 - .06, p = .24). In contrast, at the maternal-level, average pre-pregnancy BMI was a reliably non-zero predictor of child ADHD (b = .04, 95% CI = .02 - .06, p < .0001) with each one-unit increase in maternal pre-pregnancy BMI associated with a 4.2% increase in the odds of ADHD ($exp\ b$ = 1.04, 95% CI = 1.02 – 1.06).

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Conclusions—The association between maternal pre-pregnancy BMI and offspring ADHD may be better accounted for by familial or maternal confounds rather than a direct causal effect of BMI.

Keywords

ADHD; Maternal BMI; Quasi-experimental Design

While ADHD has substantial heritability of liability (Faraone et al., 2005), the interplay between genetic and specific environmental factors remains largely unknown. It is widely recognized that risk for ADHD is associated with early life developmental perturbations, including low birth weight (Pettersson et al., 2015), neurotoxicant exposures (Lee, Jacobs, & Porta, 2007; Zhu, Olsen, Liew, Niclasen, & Obel, 2014), maternal stress (Grizenko, Shayan, Polotskaia, Ter-Stepanian, & Joober, 2008: Rodriguez & Bohlin, 2005), and nutritional variations (Sinn, 2008).

Of particular interest is growing evidence that maternal obesity, and its potential link to metabolic syndrome or other non-communicable diseases, is a risk factor for neurodevelopmental outcomes in children (Krakowiak et al., 2012; Rizzo, Metzger, Burns, & Burns, 1991; Surén et al., 2014; Tanne, 2012). Several recent studies have reported an association between prenatal maternal adiposity and offspring ADHD, specifically. The first, an examination of over 12,000 school-aged children in Sweden, Denmark, and Finland, showed a risk of ADHD (i.e., odds ratio of 1.37-1.89) among offspring of mothers who were overweight or obese prior to pregnancy when compared to mothers of normal weight (Rodriguez et al., 2008). The same team followed a second cohort of 1700 Swedish mother-child pairs, finding that among offspring aged 5 years, maternal pre-pregnancy overweight and obesity were associated with 2-fold increase in risk for high levels of inattention symptoms (Rodriguez, 2010). These analyses adjusted for potential confounding factors, including maternal smoking, depressive symptoms, stressful life events, education, age, family structure, birth weight, gestational age, infant sex, family structure, maternal depressive symptoms, parental ADHD symptoms, and child overweight (Rodriguez et al., 2008; Rodriguez, 2010). In total, four studies have reported similar associations, with a typical effect size from 1.5 to 2.0-fold increase in risk of child ADHD diagnosis (Chen et al., 2014; Rodriguez et al., 2008) or symptoms (Buss et al., 2012; Rodriguez, 2010). Thus, prior work has provided initial support for the link between pre-pregnancy maternal overweight/obesity and childhood ADHD.

Various biologic mechanisms have been proposed to explain the possible link between maternal overweight/obesity and child ADHD, including alterations in the fetal steroid or hormonal environment (Baardman, Kerstjens-Frederikse, Berger, Bakker, Hofstra, & Plösch, 2013), dietary factors (Kang et al., 2014), and pro-inflammatory cytokines (Entinger et al., 2012; Oades, Myint, Dauvermann, Schimmelmann, & Schwarz, 2010). However, it is also possible that unmeasured confounds explain this association, as prior passive longitudinal designs precluded strong inferences. Other, unmeasured covariates still may explain the association (i.e., higher pre-pregnancy BMI may be associated with a variety of unmeasured factors that confer risk for ADHD). Fortunately, these effects can be estimated in human data using quasi-experimental designs (Lewis et al., 2013).

Only one prior study has utilized a quasi-experimental design to examine the association between prenatal maternal BMI (or overweight/obesity) and offspring ADHD. That study, a sibling-comparison design conducted on a Swedish sample of 272,790 full biological siblings nested within 130,060 families, utilized a fixed effects model and failed to replicate the association between maternal prenatal BMI and child ADHD. That suggested there may be unmeasured familial confounding factors which better explain the association between maternal overweight/obesity and child ADHD (Chen et al., 2014).

Importantly, however, the obesity rate in Sweden is substantially lower (i.e., approximately 18.6%; WHO, 2015) than that of the United States (i.e., approximately 34.9%; CDC, 2015), which limits generalizability. Thus, the sibling-comparison design utilized by Chen and colleagues (2014) requires replication in order to address important public health implications, such as the development of prenatal prevention programs directed toward reducing the incidence of ADHD, as well as to clarify whether research on transmission mechanisms should be pursued.

This study, therefore, tested the following inter-related questions: 1) Is maternal pre-pregnancy BMI associated with child ADHD even after control of maternal ADHD and demographic covariates? and 2) If an association between maternal pre-pregnancy BMI and offspring ADHD exists, does it withstand adjustment for unmeasured confounders through the use of a sibling-design? In contrast to the prior study by Chen and colleagues (2014), the present study utilized a “between-within effects model”. The key strength of such a design is that it allows for the partitioning of the overall BMI effect into between-mother versus between-child (within mother variation in BMI across siblings) contributions. Partitioning the data in this way provides a recognized, design-based approach for controlling for unmeasured variables that serve as potential familial or maternal-level confounds (e.g., D’Onofrio et al., 2012; D’Onofrio et al., 2008; Neuhaus & McCulloch, 2006; Rodgers, Cleveland, van den Oord, & Rowe, 2000).

Methods

Participants

De-identified data were extracted from electronic medical records of a large regional health care system in the upper Midwest of the United States of America. The patient-base is demographically representative of the service area, and is about 95% white (primarily northern-European descent). Variables extracted from the database were maternal age at delivery; maternal pre-pregnancy height and weight (used to calculate BMI); maternal age at measurement; maternal and child ADHD diagnosis; gestation duration; child gender; child age at last visit; and birth weight, and maternal ADHD diagnosis. Here, maternal ADHD diagnoses were ascertained from maternal medical records when the ICD-9-CM code was entered into the electronic medical record as a diagnosis which a physician was currently treating or had treated in the past. The initial dataset included all children 0–18 years of age seen between 1995 and 2013 (N=10,522).

From this population sample, the data set was restricted to children 5–12 years old. The 5–12- year-old age-range was selected as DSM-5 requires symptoms present by age 12 years

or earlier; thus, children past 12 years old were deemed to be no longer at risk. Additionally, we wanted to exclude cases of apparent remission, which may occur in 30–50% of adolescents (Langberg, Epstein, Altaye, Molina, Arnold, &Vitiello, 2008; Molina et al., 2009; for a review see Sagvolden et al, 2005). Further exclusions were applied. Children with at least two time points of a recorded diagnosis of ADHD (attention-deficit/hyperactivity disorder: *International Classification of Diseases, 9th Edition, Clinical Modification* [*ICD-9-CM*] codes 314.00 or 314.01; National Center for Health Statistics, 2002) were included as ADHD cases. Those with an ADHD diagnosis at one time-point were coded as ambiguous and were excluded (n=176). Also excluded were children with a diagnosis of autism spectrum disorder (ASD: *ICD-9-CM* code 299.00, as well as Asperger's syndrome or pervasive developmental disorder-not otherwise specified, PDD-NOS: ICD-9-CM code 299.80 or 299.81, respectively; National Center for Health Statistics, 2002), even if they had a comorbid ADHD diagnosis. For ASD, the health care system completes a universal screening for all children aged 18 to 24 months, and physicians complete a multidisciplinary evaluation upon screening positively. Families were excluded if mothers did not have at least one weight or body mass index (BMI) measurement prior to the pregnancy of the target child. All remaining children in the age range were included as control cases.

The final sample used in analyses consisted of 4,682 (N=187 with ADHD) children born to 3,645 different mothers. Among the 3,645 mothers, 75% (N = 2724) contributed a single child to the sample, while the remaining 25% (N = 921) contributed two or more children. Specifically, 2724 mothers contributed 1 child, 811 mothers contributed 2 children, 104 mothers contributed 3 children, and 6 mothers contributed 4 children.

Institutional and Ethical approvals—Marshfield Clinic Research Foundation (MCRF) institutional review board, which is responsible for the medical records, approved this study of de-identified clinical records.

Additional Measures & Covariates

Maternal Body Mass Index (BMI)—Maternal BMI within one year prior to pregnancy was calculated from height and weight measurements. Although pre-pregnancy BMI was used as a continuous predictor in analyses, standard BMI categories, as recommended by the World Health Organization, are noted for purposes of sample description as follows: Underweight: BMI < 18.5; Normal weight: BMI = 18.5-24.99; Overweight: BMI = 25–29.99; Obesity Class I: BMI = 30–34.99; Obesity Class II: BMI = 35–39.99; Obesity Class III: BMI ≥ 40.

Covariates—Covariates were child age at diagnosis, child gender, child gestational age, child birth order, maternal age at delivery, maternal ADHD diagnosis, and maternal weight gain during pregnancy. The maternal weight gain variable was limited by substantial variability with respect to when during gestation it was recorded (i.e., M = 19.99, SD = 10.83 weeks of gestation) and so was not a principal focus.

Data Analysis

A series of generalized estimating equations (GEE) were used to test study hypotheses regarding the association between pre-pregnancy BMI and child ADHD. GEE models accommodated both the dichotomous nature of the outcome (ADHD diagnosis; binominal distribution and logit link function) and the non-independence of observations (25% of mothers had two or more children in the dataset; the working correlation matrix was specified to have an exchangeable structure). An initial set of models tested the unique contribution of maternal pre-pregnancy BMI to child ADHD. We refer to these as aggregated models (Model 1) because this initial parameterization does not partition the pre-pregnancy BMI effect into separate child (within mother) and mother (between mother) components; and thus, does not separate effects that are familial or maternal (such as maternal ethnicity/race, SES, ADHD) from those that are specific to that child and that pregnancy—such as maternal BMI in that particular pregnancy.

In order to separate these effects, a second set of models adopted an alternative parameterization method that took advantage of the sibling design. The pre-pregnancy BMI value associated with each child was deviated from the mean pre-pregnancy BMI for each mother (i.e., within-family centering). This allows (a) maternal variation in BMI within the same mother across pregnancies, to be separated from (b) maternal variation in BMI across different women. In statistical terms, these models tested the unique contributions of child- and familial/mother-level pre-pregnancy BMI contributions to child ADHD. We refer to these as dis-aggregated models (Models 2 and 3) because this parameterization partitioned the pre-pregnancy BMI effect into separate child and mother-level components. In the disaggregated models, a statistically significant child-level pre-pregnancy predictor would be consistent with a child-specific association between pre-pregnancy BMI and ADHD that fully controls for unmeasured familial/mother-level confounds. A statistically significant mother-level pre-pregnancy predictor would be interpreted as indicating that the BMI-ADHD effect is associated with unmeasured familial- or maternal-level variables because pregnancy-specific BMI has been partitioned out. In Model 2, we included all families (including mothers who only contributed a single child to the sample) to ensure that any differences between aggregated and disaggregated results were due to differences in model parameterization (i.e., not sample size or sub-population differences). This approach also preserved statistical power by retaining all cases in the model. However, to ensure no effect of model selection, in Model 3, we repeated the disaggregated model approach while limiting the sample to those families who contributed multiple children to the dataset to further examine specificity.

Results

Sample Description

Table 1 provides a synopsis of demographic information for mothers and children, as well as the principal study predictor (i.e., maternal pre-pregnancy BMI), outcome (i.e., child diagnosis of ADHD), and covariates. In order to facilitate sample description, we also presented all study variables after grouping women into six BMI categories. As shown in Table 1, women in higher BMI categories prior to pregnancy gained less weight during

pregnancy, were slightly older, and had children with higher birth weights (Table 1)—all of which provided face validity to pre-pregnancy BMI measurements. Notably, women in higher BMI categories did not appear to exhibit higher rates of maternal ADHD and were not more likely to have contributed multiple children to the dataset (with the possible exception that women in the underweight category were more likely to only contribute a single child to the sample; Table 1).

Model 1: Total Sample: Aggregated Effect of Pre-Pregnancy BMI on Child Risk of ADHD

An initial GEE model was estimated to inform the functional form of the association between maternal pre-pregnancy BMI and child ADHD status. When both linear and quadratic (to examine a possible U-shaped relationship between maternal pre-pregnancy BMI and child ADHD) terms were included as predictors, neither was significant ($b = .05$, $p = .39$ and $b = -.01$, $p = .71$, respectively). The quadratic term was therefore omitted from subsequent models.

In the final linear model, the effect of BMI on child ADHD was reliably non-zero ($b = .03$, 95% confidence interval [95% CI] = .01 - .05, $p = .0021$). Exponentiating this coefficient indicated that each one-unit (i.e., 1 kg/m^2 or 2.2 lbs/m^2) increase in maternal pre-pregnancy BMI was associated with a 3% increase in the odds of ADHD ($exp\ b = 1.03$); a 10-unit increase in pre-pregnancy BMI (i.e., 10 kg/m^2 or 22 lbs/m^2) was associated with a 36% increase in the odds of offspring ADHD ($exp\ b = 1.36$). To provide context, for a woman at five feet, five inches tall and 140 lbs, a one-unit increase in pre-pregnancy BMI would be approximately 6 lbs, while a 10-unit increase would be approximately 60 lbs with such a change shifting a woman from a normal to obese level I category pre-pregnancy.

A second GEE model was estimated that added child and maternal covariates to the model, including maternal ADHD. The estimated coefficients are summarized in Table 2. Maternal age ($p < .0001$), maternal history of ADHD ($p < .0001$), child age ($p < .0001$), and child gender ($p < .0001$) were all associated with child ADHD, but child prematurity status ($p = .40$), child birth order ($p = .29$), and maternal weight gain during pregnancy ($p = .62$) were not. Notably, even with these covariates, maternal pre-pregnancy BMI continued to exert a unique and significant effect that was of similar magnitude with the inclusion of covariates ($b = .04$, 95% CI = .02 - .06, $p = .0003$).

To put these effects in context, consider the following. Being a boy instead of a girl was associated with a 246% increase (that is, more than tripling) in odds of being diagnosed with ADHD ($exp\ b = 3.46$, 95% CI = 2.47 – 4.85), maternal ADHD was associated with a 188% increase in odds of being diagnosed with ADHD ($exp\ b = 2.88$, 95% CI = 1.93 – 4.30), whereas a 10 unit increase in maternal pre-pregnancy BMI, equivalent to child born to a women whose pre-pregnancy BMI was in the obese I category (mean BMI = 32 kg/m^2) versus normal weight (mean BMI 22 kg/m^2), yielded a 46% increase in odds of child ADHD ($exp\ b * 10 = 1.46$, 95% CI = 1.19 – 1.80).

Model 2: Total Sample: Dis-Aggregated Effect of Pre-Pregnancy BMI on Child Risk of ADHD

In the next set of GEE models, we took advantage of the sibling design. All covariates were retained, but the single maternal pre-pregnancy BMI predictor was replaced by two terms: (1) a child-specific predictor that captures variance in BMI unique to that pregnancy and an (2) an average maternal pre-pregnancy BMI across pregnancies predictor (i.e., an average of maternal pre-pregnancy BMI across each of her own pregnancies for women with multiple children). Due to the use of within-family centering, these predictors were orthogonal and represented the unique contribution of child-specific (i.e., associated with a unique effect of pre-pregnancy BMI) versus general maternal effects (i.e., associated with an inference that BMI effects are due to unmeasured confounders, with the pregnancy-specific child effect removed).

Maternal average pre-pregnancy BMI was a significant predictor of child ADHD ($b = .04$, 95% CI = .02 - .06, $p < .0001$) with each one-unit increase in maternal pre-pregnancy BMI associated with a 4.2% increase in the odds of ADHD ($exp\ b = 1.04$, 95% CI = 1.02 – 1.06). However, and in contrast, the child specific pre-pregnancy BMI effect was not reliably non-zero ($b = -.08$, 95% CI = −.23 - .06, $p = .24$). The contributions of specific covariates were essentially unchanged from the previous model (seen by comparing coefficients in the first two columns of Table 2).

Model 3: Siblings Only: Dis-Aggregated Effect of Pre-Pregnancy BMI on Child Risk of ADHD

The prior results provide the best test of our hypothesis because they use the entire sample, maximizing error control. However, the ability to disaggregate the effects of child-specific versus maternal general pre-pregnancy effects was only possible because 25% of mothers contributed multiple children to the dataset. As a robustness check, we limited the final analysis exclusively to those families for whom two or more children were included in the dataset. Results were essentially unchanged. Again, maternal pre-pregnancy BMI was related to child ADHD ($b = .06$, 95% CI = .02 - .09, $p = .002$). Here, each one-unit increase in maternal pre-pregnancy BMI was associated with a 6.0% increase in the odds of ADHD ($exp\ b = 1.06$, 95% CI = 1.02 – 1.10), which is slightly higher than observed in the full sample. Also consistent, the child specific pre-pregnancy BMI effect was not reliably non-zero ($b = -.08$, 95% CI = −.22 - .05, $p = .22$). With the exception of child age, which was no longer significant in this reduced sample ($p = .16$), the contributions of specific covariates were similar in pattern or magnitude to the previous models (compare coefficients in the second and third columns of Table 2).

Magnitude of Differences in Pre-Pregnancy BMI across Siblings (Siblings only)

An implicit assumption of the dis-aggregated models is that there is meaningful variation in maternal pre-pregnancy BMI across pregnancies. For each of the 921 mothers who contributed two or more children to the dataset, we examined the largest and smallest pre-pregnancy BMI in the dataset. First, it was determined that there were similar differences between largest and smallest pre-pregnancy maternal BMI across pregnancies for families with children who were concordant for ADHD diagnosis (i.e., both children either had or did

not have a diagnosis of ADHD; M=2.4 lbs/m^2, SD=2.4) and those who were discordant for ADHD (i.e., one child had a diagnosis of ADHD and the other did not; M=3.3 lbs/m^2, SD=3.2, see Table 3). As a final sensitivity check, among families who contributed children who were discordant for ADHD, there was no statistically significant difference in maternal pre-pregnancy BMI for mothers of children without (M=30.45 lbs/m^2, SD=8.11) or with ADHD (M=29.53 lbs/m^2, SD=8.19; t(74)=1.78, p=.079).

Discussion

If pre-pregnancy maternal elevated BMI is part of the reason why children develop ADHD, this would be an important link in the etiological models for this condition. Although prior large population studies have attempted to control many covariates (Rodriguez et al., 2008, 2010), a strong additional inference for causality (or not) is provided by quasi-experimental designs (Lewis et al., 2013). Here we report only the second study to utilize such a design. The first such study (Chen et al., 2014) failed to support the BMI-ADHD hypothesis but was conducted in a population with low BMI and low obesity rates compared to the U.S. Our findings were similar to that prior sibling study and also failed to support the BMI-ADHD hypothesis.

First, like several prior reports (i.e., Chen et al., 2014; Rodriguez et al., 2008, 2010), the uncorrected models we reported here showed a robust association of maternal pre-pregnancy BMI with offspring ADHD even after accounting for a range of covariates that included, for the first time, maternal ADHD (itself, of course, a strong predictor of offspring ADHD). Crucially for our conclusions, the magnitude of risk that was associated with pre-pregnancy BMI was similar to previous population studies (i.e., a one-unit (i.e., 1 kg/m^2) increase in pre-pregnancy BMI was associated with a 4% increase in the odds of ADHD, including the Nordic studies (Rodriguez et al., 2008, Rodriguez, 2010), suggesting those overall effects are generalizable to a population with higher rates of obesity, such as ours. However, when models were re-parameterized to take advantage of the sibling design, we found the essentially same result as the prior study in this vein (Chen et al 2014): the increased risk for child ADHD that was attributed to pre-pregnancy BMI appears to be best accounted for by mother-level, not child- level, effects. That is, our study demonstrated that although the aggregate (overall) effect of maternal pre-pregnancy BMI to child ADHD effect was significant, the disaggregated, within mothers effect was not reliably non-zero, while the between mothers effect was. Put another way, according to tests of statistical significance, the effects are not pregnancy-specific as they would be if maternal BMI was exerting a causal effect. Some unmeasured 3rd variable may be accounting for the BMI-ADHD association. These results are consistent with Chen et al., 2014 who also used a sibling design in a sample of over 270,000 full biological siblings nested within 130,060 families.

Several other alternative explanations for the attenuated associations in the analyses of siblings are also possible and should be considered. For example, some prior work suggests that there are higher rates of misdiagnosis (i.e., false positives) among siblings of ADHD probands, which would lead to an attenuated effect (Biederman, 1991). Further, women with large changes in weight between pregnancies (i.e., substantial weight gain or weight loss) may have differing underlying biological processes (again, excess pro-inflammatory activity

is a ready hypothesis) than those who maintain a stable weight across pregnancies (Schwartz et al., 2003).

Importantly, it should be noted that while examinations of statistical significance suggest that the effect of maternal, pre-pregnancy BMI on child ADHD are not pregnancy-specific, an examination of the effect sizes present in this model are indicative of a possible inverse association between pre-pregnancy BMI and child ADHD in this sample. Specifically, with respect to the between-mother effect, with every unit of BMI increase, the odds of offspring ADHD increased by approximately 4%; however, with respect to the within-mother effect, with every unit of BMI increase there was a 9% decrease in the odds of offspring ADHD. While the broad confidence interval around this second parameter value precludes interpretation here, further examination of within-family effects will be important in conjunction with further examination of between-family effects.

The large, community-recruited, representative sample and prospective design largely precludes recall bias. While prior studies have also utilized such samples and designs, to our knowledge this was the first such study of its kind to be conducted utilizing data obtained within the United States. Although the sample was relatively homogenous with regard to race and ethnicity compared to the US population overall, the patterns of associations among obese categories and child and maternal characteristics were as expected, suggesting that this sample is similar to other US samples.

In addition to the cautions already noted, results should be considered in the context of other limitations. First, this was a retrospective chart review; gold-standard ADHD diagnostic assessments could not be verified and may have varied across providers. While recall bias is not particularly likely, a prospective design is needed for stronger conclusions. Second, BMI may not represent an optimal approximation for overweight/obesity, body fat composition, quality of diet/nutritional intake, or related health concerns, such as metabolic conditions. Direct observation of women prior to pregnancy would be necessary and to our knowledge such as costly undertaking has not yet been done in relation to ADHD in offspring. Future research may however be able to examine whether specific maternal pre-pregnancy conditions, such as high body fat, nutritional deficiencies, metabolic syndrome, and/or insulin resistance, relate to child diagnosis of ADHD. It is possible that these account for the fact that maternal BMI is a risk factor for offspring ADHD. Third, repeated measures of maternal weight at similar time points across the perinatal period were not available and there was significant variability with respect to when during gestation weight was obtained, as such, the association among weight gain during pregnancy and child ADHD were not able to be well-examined in the present study; maternal weight gain relative to pre-pregnancy BMI may be important (Rodriguez et al., 2008).

Also of note, unlike prior studies of children with ADHD, premature birth was not associated with child ADHD diagnosis. Thus, in this respect, this sample of children with ADHD may not be representative. However, weeks of gestation were included in all models as covariates and did not significantly alter the observed results.

A final limitation is that although there was significant change in maternal pre-pregnancy BMI across pregnancies in the present sample (mean=1.03, SD=3.32 or approximately 2.2 lbs/m^2), this change was lower than that observed by Chen and colleagues (2014; mean=2.86, SD=2.20 or approximately 6.3 lbs/m^2). Additionally, only a small subset (approximately 6.7%) of the present sample included mothers who contributed siblings who were discordant with respect to their ADHD status. Those who contributed discordant siblings had similar levels of variation between pregnancies (average BMI difference of 2.4 lbs/m^2, SD=2.4 between pregnancies) compared to those who contributed concordant siblings (3.3 lbs/m^2, SD=3.2). Thus, mothers who contributed concordant and discordant siblings appear to have similar levels of variation in BMI across pregnancies (Table 3). On the one hand, the fact that both we and Chen and colleagues (2014) reached the same conclusion about sibling effects (despite utilizing different analytical approaches, each with strengths and limitations) supports the robustness of our finding and theirs. On the other hand, it remains unclear whether either sample had sufficient variation between individual pregnancies to observe an individual effect on ADHD.

In conclusion, while maternal elevated BMI is clearly a risk factor for ADHD (in the sense that it statistically predicts greater odds of offspring ADHD diagnosis), it may not be a direct etiological factor. Our data suggest that the association between maternal pre-pregnancy overweight/obesity and child ADHD may be due to maternal or familial confounds that account for both maternal elevated BMI and child ADHD. Future work should examine what those confounds might be; we have offered several suggestions here.

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Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
ASD	Autism Spectrum Disorder
BMI	Body mass index
CDC	Centers for Disease Control
CI	Confidence Interval
GEE	Generalized Estimating Equations
ICD-9-CM	International Classification of Diseases, 9th Edition, Clinical Modification
M	Mean
MCRF	Marshfield Clinic Research Foundation
PDD-NOS	Pervasive Developmental Disorder, Not Otherwise Specified
SD	Standard Deviation

WHO World Health Organization

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Key Points

- High maternal pre-pregnancy BMI has been associated with increased risk of offspring ADHD.
- Whether this effect is attributable to maternal or familial level confounds has been little examined.
- This study reveals that the association between maternal pre-pregnancy BMI and offspring ADHD may be due to familial or maternal confounds.
- Future research should examine the nature of such potential familial or maternal confounds.

Table 1

Sample Description

	Total Sample (N = 4682)		Weight Categories I (N = 117)	II (N = 1874)	III (N = 1319)	IV (N = 727)	V (N = 390)	VI (N = 255)
	N	**M (SD)**	**M**	**M**	**M**	**M**	**M**	**M**
PrePreg Weight (Kg)[A]	4682	74.5 (18.8)	50.9	60.9	73.3	86.7	99.6	119.4
PrePreg BMI (Kg/m$^{2)}$ [A]	4682	27.6 (6.7)	17.6	22.3	27.2	32.3	37.2	44.9
Preg Wgt Change (Kg)[A]	4682	5.5 (7.3)	6.9	5.8	5.9	5.0	4.8	3.4
Mom Age (years)[A]	4682	27.1 (5.5)	24.9	26.9	27.2	27.1	27.6	28.9
Child Age (years)	4682	7.6 (1.8)	7.9	7.5	7.6	7.6	7.6	7.6
Child Gestation (weeks)	4682	38.2 (2.5)	38.0	38.3	38.3	38.2	38.0	38.1
Child Birth Weight (Grams)	4548	3379.2 (606.0)	3249.0	3331.5	3389.0	3428.3	3419.5	3538.2
	N	%	%	%	%	%	%	%
Maternal ADHD[B]	3645	8	9	7	8	8	9	11
Mom has > 1 child dataset[B]	3645	25	13	25	27	25	27	26
Child ADHD	4682	4	3	3	4	5	6	7
Child Gender (Male)	4682	49	45	49	50	50	49	52
Child Premature	4682	14	13	13	13	17	17	17
Child LBW	4548	8	9	8	8	10	12	7

Note: N = 3645 biological mothers for N = 4682 children; PrePreg – prior to pregnancy; A – for biological mothers who contribute more than one child to the dataset, this is an averaged value across children; B – this is a single value, including for biological mothers who contribute multiple children to dataset; I – Underweight (15 kg/m^2 ≤ BMI < 18.5 kg/m^2); II – Normal weight (18.5 kg/m^2 ≤ BMI < 25 kg/m^2); III – Overweight (25 kg/m^2 ≤ BMI < 30 kg/m^2); IV - Obese level I (30 kg/m^2 ≤ BMI < 35 kg/m^2); V - Obese level II (35 kg/m^2 ≤ BMI < 40 kg/m^2); VI - Obese level III (BMI > 40 kg/m^2); N – Sample size; M – Mean; SD – standard deviation; ADHD – attention deficit/hyperactivity disorder; Child Premature was defined as prior to 36 weeks of gestation; LBW – low birth weight (i.e., < 2500 grams).

Table 2

Synopsis of Regression Coefficients from GEE Models Predicting Child ADHD

	Sample – Approach		
	Total Sample – Aggregated (N = 4682)	**Total Sample – Disaggregated (N = 4682)**	**Sibling Subsample – Disaggregated (N = 1958)**
Predictor	b (95% CI)	b (95% CI)	b (95% CI)
PrePreg BMI	**0.04 (.02 - .06)** ***	—	—
PrePreg BMI (Child Deviation)	—	−0.09 (−.23 - .06)	−0.08 (−.22 - .05)
PrePreg BMI (Maternal Mean)	—	**0.04 (.02 - .06)** ***	**0.06 (.02 - .09)** **
Preg Wgt Change	−0.01 (−.03 - .02)	−0.01 (−.03 - .01)	−0.01 (−.04 - .03)
Maternal ADHD	**1.06 (.66 – 1.47)** ***	**1.07 (.66 – 1.47)** ***	**0.88 (.24 – 1.52)** **
Maternal Age	**−0.09 (−.13 - −.06)** ***	**−0.09 (−.13 - −.06)** ***	**−0.17 (−.23 - −.10)** ***
Child Age	**0.20 (.12 - .28)** ***	**0.19 (.11 - .27)** ***	0.11 (−.04 - .26)
Child Male	**1.24 (.90 – 1.58)** ***	**1.24 (.90 – 1.58)** ***	**1.15 (0.63 – 1.68)** ***
Child Premature	0.18 (−.24 – .59)	0.18 (−.23 – .59)	0.44 (−.28 – 1.16)
Child Birth Order	0.20 (−.17 −.58)	0.29 (−.11−.68)	0.36 (−.26 - .97)

Note:

* $p < .05$,

** $p < .01$,

*** $p < .001$;

N = 3645 biological mothers for N = 4682 children; PrePreg – prior to pregnancy; N – Sample size; M – Mean; SD – standard deviation; ADHD – attention deficit/hyperactivity disorder; Child Premature was defined as prior to 36 weeks of gestation; LBW – low birth weight (i.e., < 2500 grams)

Table 3

Synopsis of Difference between Largest and Smallest Maternal Pre-pregnancy BMIs for Mothers Contributing Concordant and Discordant Siblings

	Variable	Mean	SD	Minimum	Maximum
Concordant	BMI Average (kg/m^2)	27.2	6.2	16.7	61.6
(N=859)	BMI Diff. (kg/m^2)	2.4	2.4	0.0	15.7
Discordant	BMI Average (kg/m^2)	30.0	7.9	18.9	48.2
(N=62)	BMI Diff. (kg/m^2)	3.3	3.2	0.0	15.5

Note: Concordant—All siblings contributed by a mother either ADHD (attention-deficit/hyperactivity disorder) or non-ADHD; Discordant—Siblings contributed by a mother presented both with and without ADHD; BMI Average—Average maternal Body Mass Index across pregnancies; BMI Diff.—Average difference between largest and smallest maternal pre-pregnancy Body Mass Index