Published in final edited form as:

BJOG. 2016 December ; 123(13): 2094–2103. doi:10.1111/1471-0528.13909.

Gestational weight gain, pre-pregnancy body mass index, and offspring attention deficit hyperactivity disorder symptoms and behavior at age 10

SJ Pugh^a, JA Hutcheon^b, GA Richardson^{a,c}, MM Brooks^{a,d}, KP Himes^{e,f}, NL Day^{a,c}, and LM Bodnar^{a,c,e}

^aDepartment of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA.

^bDepartment of Obstetrics and Gynaecology, University of British Columbia, Vancouver, British Columbia, Canada.

^cDepartment of Psychiatry, School of Medicine, University of Pittsburgh, Pittsburgh, PA.

^dDepartment of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA.

^eDepartment of Obstetrics, Gynecology, and Reproductive Sciences, School of Medicine, University of Pittsburgh, Pittsburgh, PA.

^fMagee-Womens Research Institute, Pittsburgh, PA.

Abstract

Objective—To assess offspring attention-deficit hyperactivity disorder (ADHD) symptoms and emotional/behavioral impairments at age 10 in relation to maternal gestational weight gain (GWG) and pre-pregnancy body mass index (BMI).

Design and Setting—Longitudinal birth cohort from Magee-Womens Hospital, Pittsburgh, Pennsylvania (enrolled 1983-1986).

Population—Mother-infant dyads (n=511) were followed through pregnancy to 10 years.

Methods—Self-reported total GWG was converted to gestational-age-standardised z-scores. Multivariable linear and negative binomial regressions were used to estimate effects of GWG and BMI on outcomes.

Correspondence: Lisa M. Bodnar, PhD, MPH, RD, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, A742 Crabtree Hall, 130 DeSoto Street, Pittsburgh, PA 15261. 412.624.9032 (voice); lbodnar@pitt.edu.

Contribution of authorship

SJP, JAH, GAR, MMB, KPH, NLD, LMB designed the research. GAR and NLD provided essential materials. SJP did all analyses, wrote the manuscript, and had primary responsibility for the final draft. SJP, JAH, GAR, MMB, KPH, NLD, LMB critically reviewed drafts and approved the final manuscript

Disclosure of interests

None declared. The ICMJE disclosure of interest forms are available to view online as supporting information.

Details of ethics approval

This study was approved by the University of Pittsburgh Institutional Review Board (IRB #PRO14020264) on March 25, 2014.

Main outcome measures—Child ADHD symptoms were assessed with the Conners' Continuous Performance Test. Child behavior was assessed by parent and teacher ratings on the Child Behavior Checklist (CBCL) and Teacher Report Form, respectively.

Results—The mean(SD) total GWG(kg) was 14.5(5.9), and 10% of women had a pregravid BMI 30. Pre-pregnancy obesity (BMI of 30kg/m²) was associated with increased offspring problem behaviors including internalizing behaviors (adjusted β : 3.3 points, 95% CI: 1.7, 4.9), externalizing behaviors (adjusted β : 2.9 points, 95% CI: 1.4, 4.6), and attention problems (adjusted β : 2.3 points, 95% CI: 1.1, 3.4) on the CBCL, compared with normal weight mothers (BMI of 22 kg/m²). There were non-significant trends towards increased offspring impulsivity with low GWG among lean mothers (adjusted IRR: 1.2, 95% CI: 0.9, 1.5) and high GWG among overweight mothers (adjusted IRR: 1.7, 95% CI: 0.9, 2.8), but additional outcomes did not differ by GWG z-score. Results were not meaningfully different after excluding high-substance users.

Conclusions—In a low-income and high-risk sample, we observed a small increase in child behavior problems among children of obese mothers, which could have an impact on child behavior in the population.

Keywords

Gestational weight gain; maternal obesity; attention-deficit hyperactivity disorder; behavior

Introduction

Attention-deficit hyperactivity disorder (ADHD) is the most common developmental disability among children in the United States, affecting 7% to 9% of 5-17 year olds ¹. Annually, the United States spends an excess of \$42 billion dollars on medical treatment and lost wages ² related to ADHD. ADHD is diagnosed by a health-care provider if a child presents with at least 6 symptoms of inattention and hyperactivity/impulsivity in more than one setting (e.g. school, home, etc.)³. When diagnosis is not feasible due to the demanding protocol, characteristics of ADHD, such as impulsive behaviors, and co-morbid symptoms including somatic complaints and anxious/depressed feelings⁴ are often assessed by parent- and teacher-ratings⁵. The entirety of these characteristics results in functional impairments that limit a child's ability to learn and behave, contributing to lower academic achievement and decreased employment⁶. There is no cure for ADHD, and treatments vary in effectiveness⁷. Understanding potential preventive measures to reduce ADHD is a public health priority ⁸.

Biological evidence suggests maternal pre-pregnancy body mass index (BMI) and excessive weight gain (GWG) during pregnancy are potentially modifiable factors for offspring ADHD or related emotion/behavior disruptions^{9, 10}. High blood concentrations of pro-inflammatory cytokines and leptin are often found in both obese mothers and the developing fetus¹¹, which may contribute to over- and under-activation of a number of fetal neurodevelopmental processes¹²⁻¹⁴, including neuron proliferation, differentiation ¹⁵ and synapse formation ¹⁵. Animal studies have reported that offspring of mothers consuming a high-fat diet contributing to excessive weight gain during pregnancy had increased

circulating pro-inflammatory cytokines in the hypothalamus and hippocampus, where behavioral regulation systems are located¹⁶¹⁰.

Nevertheless, few studies have rigorously explored these associations in humans. A small body of evidence suggests that maternal obesity is associated with a modest increase in offspring problem behaviors^{17, 18} and an increased risk of learning disability diagnosis (including ADHD) in early childhood¹⁹. A single study examining GWG reported no relation with offspring problem behaviors²⁰. Moreover, the majority of studies assessed ADHD and behavior problems in children less than 6 years, yet the updated Diagnostic Statistical Manual-V increased the age range of an ADHD diagnosis to before 12 years²¹. Therefore, assessment of behavior later in childhood may capture more children affected by behavioral disruptions. Our objective was to assess offspring ADHD symptoms (inattention and impulsivity) and emotional/behavioral impairments at age 10 in relation to GWG and pre-pregnancy BMI while controlling for important confounders.

Methods

We used data from birth cohorts designed to study the effects of prenatal substance use on long-term offspring outcomes²². Women 18 years old were approached at a prenatal clinic at Magee-Womens Hospital in Pittsburgh, Pennsylvania from 1983-1986. Women were enrolled in these cohorts based on 1st trimester use of alcohol or marijuana. The alcohol cohort included women who drank 3 drinks per week and a random equal sample who drank <3 drinks per week. The marijuana cohort included women who smoked 2 joints per month and an equal sample who smoked <2 joints per month. These cohorts were combined for this analysis. There was 48% overlap in the alcohol and marijuana groups. From the pool of 1360 women screened for eligibility during the 1st trimester, 15% refused participation, and 763 women were followed through pregnancy and delivered a live-born singleton infant (Figure 1). The majority of women were low substance users during the first trimester (drank <3 drinks per week (n=508, 66%) or smoked <2 joints per month (n=516, 67%)).

The first and second prenatal assessments took place at a median of 18.7 weeks (IQR: 17.1, 20.7) and 31.1 weeks (IQR: 29.4, 33.1), respectively. Mother-child pairs were followed up at delivery [median 39 weeks (IQR: 38-40)], 8 months, 18 months, 3, 6, and 10 years postpartum. At each visit, children and mothers were assessed by separate trained interviewers who gathered data on maternal sociodemographic status, substance use, maternal psychological status, and offspring cognitive development. Our analysis focused on the 10-year postpartum visit to capture the most children with behavioral problems. Women provided informed, written consent and this study was approved by the University of Pittsburgh Institutional Review Board.

Women self-reported their pre-pregnancy weight and height at the first study visit. Pre-pregnancy BMI [weight (kg)/ height (m²)] was categorised as underweight (BMI <18.5 kg/m²), normal weight (BMI 18.5-24.9 kg/m²), overweight (BMI 25-29.9 kg/m²), or obese (BMI ≥ 30 kg/m²)²³. Mothers were asked at delivery, “How much total weight did you gain during this pregnancy?” Total GWG was converted to z-scores according to gestational age-standardised charts for normal weight women²⁴. We applied the normal weight z-score

charts to all women because we aimed to evaluate whether the association between GWG z-scores and outcomes varied by pre-pregnancy BMI.

At the 10-year follow-up visit, parents (or primary care-givers) and teachers assessed child behavior using the Child Behavior Checklist (CBCL) and the Teacher Report Form (TRF), respectively. Both scales have a high test-retest reliability (0.89 on the CBCL and 0.92 on the TRF)^{25, 26} and address the same child behavior and emotional problems. To best characterise impairments consistent with ADHD, we focused on internalizing behaviors (withdrawn behavior, somatic complaints, and anxious/depressed), externalizing behaviors (delinquent behavior and aggressive behavior), and attention problems. The internalizing and externalizing behavior summary scores and the individual score for the attention subscale were standardised based on the child's age and gender. A higher score indicates worse behavior problems^{25, 26}. We studied each score as a continuous variable and as a dichotomous variable (average behavior problems (<67) versus borderline clinically significant behavior problems (≥ 67))^{25, 26}.

Child ADHD symptoms were also assessed using an objective test: the Connors' Continuous Performance Test (CPT)²⁷. The CPT is a computerised task where various shapes in different colors are flashed across a screen and the child is instructed to respond only when a specified target appears. Attention is measured by omission errors, the number of times the child misses the target. Impulsivity is measured by commission errors, the number of times the child incorrectly responds to the target. Children were given 3 trials of the CPT, and the mean number of omission and commission errors were calculated.

At the first study visit during pregnancy, trained interviewers collected information on sociodemographic characteristics (i.e., maternal age, race, parity, employment, education, income, marital status) and the quantity and frequency of substance use during the year before pregnancy and during specific segments of the first trimester to calculate a more accurate depiction of first trimester use²⁸. At both prenatal study visits and at delivery, alcohol, marijuana, cigarette, and illicit drug use were collected and summarised as average daily volume, average daily joints, cigarettes per day, and illicit drug use (yes/no) for each trimester, respectively. We categorised each substance into overall pregnancy use to best capture non-users throughout pregnancy, users during the first trimester only, when many women do not know they are pregnant, and use throughout pregnancy. Maternal depression at the first study visit was measured using the Center for Epidemiological Studies Depression Scale (CES-D)²⁹ and anxiety was measured using the Spielberger's State-Trait Anxiety Personality Inventory (STAI)³⁰. The Home Observation for Measurement of the Environment (HOME) was administered to mothers or caretakers at 10 years postpartum to assess the quality and quantity of support for cognitive and social development in the home environment³¹. We studied the HOME scale as a continuous variable in models and as a dichotomous variable for descriptive statistics (under stimulated (<16) versus adequate stimulation (≥ 16)). Maternal intelligence was assessed at 10 years postpartum using the two-subtest version of the Wechsler Adult Intelligence Scale Full Scale (WAIS)³².

Statistical analysis

Student's t-tests and one-way ANOVAs were used to determine differences in child ADHD symptoms and behavior, GWG, and BMI by maternal characteristics. Pearson correlation coefficients were used to assess the strength of association between scales. Multivariable regression models were used to estimate beta coefficients or incidence rate ratios (IRR) and their corresponding 95% confidence intervals (CI) for associations between pre-pregnancy BMI categories and offspring behaviors. Linear regression was used for modeling internalizing, externalizing, and attention scores. Multivariable Poisson regression was used for the inattention score due to its skewed distribution. Negative binomial regression was used for modeling the impulsivity score, which had an over-dispersed distribution. Similar models were built for GWG z-scores as the main exposure.

To allow for flexible, non-linear relationships, we modeled the relation between maternal pre-pregnancy BMI and outcomes using splines. To select the best fitting spline, we compared restricted cubic spline terms with 3 knots at the 10th, 50th, and 90th percentiles and linear spline terms with 1 or 2 knots using Akaike information criterion (AIC) and Bayesian information criterion (BIC)³³. For all outcomes, we selected a linear spline term with 1 knot at the observed point of inflection at a BMI of 22kg/m². After model estimation, we used the 'xble' command in Stata to calculate adjusted coefficients and 95% CI for select BMI values compared with a BMI of 22kg/m² as the referent. Associations between GWG and behavioral outcomes did not deviate from linearity, so we categorised z-scores into 3 groups (<-1SD, -1 to +1SD, >+1SD) for ease of interpretation.

To test for effect modification between pre-pregnancy BMI and race, pre-pregnancy BMI and offspring sex, and GWG and pre-pregnancy BMI, statistical interaction terms were introduced into fully adjusted models. Effect modification was tested using an $\alpha = 0.05$ threshold based on the Wald p-values (linear regression) or likelihood ratio tests (Poisson and negative binomial regression). We built parsimonious models by adjusting for confounders that, if removed from the model, changed the effect estimate of the primary exposure by >10%³⁴. We included maternal race, parity, income, employment status, marital status, education, maternal intelligence, maternal depression, maternal anxiety, home environment stimulation, substance use, child gender, and pre-pregnancy BMI (in GWG models only) as potential confounders. Prenatal substance use variables were forced into models based on *a priori* decisions. Adjusted predicted behavior scores and ADHD symptom scores along with 95% CI were plotted with covariates set to population means.

We performed a sensitivity analysis by excluding high marijuana (>1 joint per day)³⁵, alcohol (>1 drink a day)³⁶, cigarette (≥ 20 cigarettes per day)³⁷, cocaine (any use), and illicit drug (any use) users during the 1st or 3rd trimester. Analyses were conducted in STATA, version 13.0, software³⁸.

Results

At delivery, there were 763 mother-child dyads. At the 10 year study visit, 636 (83%) pairs remained. We excluded records with incomplete data on pre-pregnancy weight and height (n=4), GWG (n=13), ADHD symptoms or behavioral assessments at age 10 (n=79), or other

covariates (n=29) (online appendix: Figure S1). A total of 511 mother-child pairs were used in the final analysis. Maternal GWG, pre-pregnancy BMI, maternal race, prenatal substance use, and child behaviors of interest did not differ between those with and without missing data (data available on request).

The mean (SD) pre-pregnancy BMI was 23.4 (5.7) kg/m² and the mean (SD) gestational weight gain in the cohort was 14.2 (5.9) kg. The majority of women at study enrollment were unmarried, unemployed, normal weight, had an income <\$500 a month (<\$1,400 per month in 2014³⁹) and were moderately depressed (Table 1). Over half of the women reported their race as Black. Most women reported no prenatal use of illicit drugs. At 10 years postpartum, mothers tended to provide a low stimulating home environment for their offspring and to have a below average IQ.

Parents rated 10% (n=49) and 12% (n=63) of children as having borderline clinically significant externalizing or internalizing behaviors, respectively. These respective values were 15% (n=77) and 8% (n=40) based on teacher-ratings. Only 5% (n=23) and 2% (n=11) of children were rated by both informants as having borderline clinically high externalizing and internalizing symptoms, respectively. The median (range) number of objective omission errors was 1 (0-6) and the median (range) number of commission errors was 2 (0-24). There was low to moderate correlation between parent and teacher ratings for externalizing ($r=0.33$), internalizing ($r=0.21$), and attention ($r=0.40$) scales. The correlation was also low between objective attention and impulsivity scales ($r=0.23$).

Maternal and child characteristics that were associated with child internalizing and externalizing behaviors and attention scores differed based on whether they were rated by a parent or teacher (online appendix: Table S1). Teacher ratings of behaviors tended to be higher among children of Black mothers, mothers providing a low stimulating home environment, mothers with below average IQ, and mothers with a monthly income <\$500 (<\$1,400 per month in 2014³⁹) compared with their counterparts. Parent-rated behaviors differed from teacher-rated behaviors in that they tended to be worse among children of White mothers, mothers with above average IQ, and mothers who used cigarettes during at least two trimesters. Apart from these differences, parent and teacher ratings of offspring behavior were not associated with maternal and child characteristics. There were fewer objective impulsivity errors among children of mothers with average or above IQ, but objective inattention errors did not differ by any maternal characteristics (online appendix: Table S1).

In bivariate analyses, maternal pre-pregnancy obesity was associated with ADHD symptoms and behaviors (online appendix: Table S2). Children of obese mothers scored 3 to 4 points worse on the parent-rated internalizing, externalizing, and attention scales, compared with children of normal weight mothers. However, there were generally no differences in behavior scores by GWG categories with the exception of teacher-rated internalizing behaviors (online appendix: Table S3).

Maternal race, parity, income, employment status, maternal intelligence, maternal depression, home environment stimulation, child gender, prenatal substance use (marijuana,

alcohol, cigarette, and illicit drug use), and pre-pregnancy BMI (GWG models only) met our definition of confounding in all models. After adjusting for confounders, maternal obesity was significantly associated with 4.9-, 4.2-, and 3.5-point increases in parent-rated offspring internalizing, externalizing, and attention scores, respectively, compared with children of normal weight mothers (online appendix: Table S4). When we examined objective measurements of offspring attention and impulsivity errors, we found that after confounder adjustment, maternal underweight was associated with 20% fewer offspring attention errors (adjusted IRR: 0.8, 95% CI: 0.6, 0.9) and maternal obesity was associated with 40% more impulsivity errors (adjusted IRR: 1.4, 95% CI: 1.0, 1.8), compared with children of normal weight mothers (online appendix: Table S4).

We observed a similar, but non-significant, trend for teacher-rated behavior problems. Using spline regression, we found that parent- and teacher-rated offspring internalizing, externalizing, and attention behavior problems tended to be lowest among mothers with pregravid BMI of 22 kg/m² and increased with both lower and higher BMI values (Figure 1; Table 2). For instance, a pregravid BMI of 28 kg/m² was associated with a 2.2-point (95% CI: 1.1, 3.4) increase in parent-rated and a 1.2 point (95% CI: -0.1, 2.5) increase in teacher-rated offspring externalizing problems, compared with a BMI of 22kg/m². Associations were similar for low BMI values, but were only borderline statistically significant for parent-rated scales.

There was a joint association between GWG and pre-pregnancy BMI on offspring impulsivity errors (likelihood ratio test p-value<0.005). Among lean mothers (BMI <25) with low GWG, children made 20% more impulsivity errors (adj IRR: 1.2, 95% CI: 0.9, 1.5) compared with GWG -1 to +1SD (Table 3). Among overweight mothers (BMI ≥25) with high GWG, children made 70% more impulsivity errors (adj IRR: 1.7, 95% CI: 0.9, 2.8, 3.2) compared with GWG -1 to +1SD (Table 3). Maternal GWG z-score was not associated with parent- or teacher-rated offspring behavior outcomes or objective measurements of offspring attention after confounder adjustment and the associations did not vary by pre-pregnancy BMI.

Neither maternal race nor child sex modified any of the relations above. Results were not meaningfully different after excluding high substance users (online appendix: Table S5-S7) or after the addition of other potential confounders (data available on request).

Discussion

Main Finding

In this longitudinal birth cohort followed to 10 years, we assessed characteristics of ADHD and co-morbid symptoms that contribute to functional impairments in children using tools that are consistent with those administered during an ADHD diagnostic evaluation⁴⁰. We found that maternal obesity was associated with more objectively-assessed offspring impulsivity errors, and both high and low pre-pregnancy BMI were associated with more offspring behavior problems. The results were generally consistent whether parents or teachers rated behaviors, but were mostly null on the objective scale, likely due to a limited variation in scores. Maternal GWG was associated with offspring impulsivity errors

depending on pre-pregnancy BMI. In contrast, GWG was not related to any other offspring ADHD symptoms or behavior problems. These relations remained after adjustment for factors including socioeconomic status and the postnatal home environment.

Strengths and limitations

Our findings may generalize only to pregnant populations with low socioeconomic backgrounds and higher rates of substance use. Nevertheless, our findings contribute information to the literature on an under-represented group, potentially at higher risk for offspring impairment associated with pre-pregnancy weight and weight gain. The compounding stressors associated with a lower socioeconomic status may contribute to a more susceptible environment for excess maternal weight to impact offspring cognitive development. These women were pregnant in the 1980's, a time when obesity was less common than today. However, there is no evidence that cognitive development or its association with obesity has changed over time.

An additional limitation is that we were not able to diagnose ADHD using gold-standard methodology; rather, we assessed attention and impulsivity, two of the core symptoms required for ADHD diagnosis. Additionally, we used two informants to assess emotional and behavioral symptoms often co-morbid in children with ADHD, although not part of the diagnostic criteria⁴¹. The low correlation observed between parent- and teacher-rated scales may reflect how a difference in the environment exacerbates different behaviors. Despite the low correlation, the overall relation with pre-pregnancy BMI and GWG was consistent across informants and tools. The use of multiple informants identifies a broader range of potential behavior problems than record-based diagnostic criteria and may overestimate the number of children with clinically significant behavioral problems. Another potential limitation of this study was unmeasured confounding from the home environment and shared genetic variants regulating both ADHD and maternal BMI. Although we used the HOME-SF, a widely employed and reliable tool, to assess the quality of the home environment, this questionnaire was administered at a single postnatal time point and might not adequately cover all areas of cognitive and environmental stimulation or exposures prior to 10 years, which may bias our findings away from the null.

The longitudinal nature of this study lends itself to attrition bias. However, the 83% retention rate at 10 years and the lack of difference in GWG, BMI, and other key variables between those with and without missing data at 10 years provides confidence that selection bias may not be a major concern. Additionally, this study was able to assess prenatal exposures and long-term offspring cognition, which contributes new information since most previous studies only assessed children younger than 6 years of age. Lastly, this study is limited by the reliance on self-reported pre-pregnancy weight, height, and total GWG, although it is difficult to predict the direction and magnitude of this bias⁴³.

A unique strength of this study is our use of gestational age-standardised GWG z-scores to classify weight gain. This classification allows us to separate the effect of weight gain from the effect of early gestational age at delivery, which is important when studying cognitive development and other outcomes related to preterm birth⁴⁴. We also evaluated non-linear relationships between BMI, GWG, and offspring behavior because our goal was to most

accurately describe underlying associations. Additionally, adjustment for prenatal substance use, socioeconomic factors, maternal psychological status, and home environment allowed us to address important confounding factors.

Interpretation

Our results relating BMI to subjectively-assessed offspring behaviors are consistent with those from an Australian cohort of 2,900 2-year-olds and their mothers, which found that for each 4-kg/m² increase in maternal pre-pregnancy BMI, there was a 0.5-point increase in externalizing problems as assessed using the Child Behavior Checklist¹⁷. In a Swedish cohort of over 1,000 pairs of mothers and their 5-year-old children, Rodriguez et al. (2010) reported that obese compared with normal weight mothers had a 2-fold increase in teacher-rated, but not parent-rated, attention problems as assessed by the Strengths and Difficulties Questionnaire. Additionally, in a European cohort, maternal overweight was associated with increased parent-rated externalizing problems in offspring 3-4 years of age⁴⁵. We observed larger effect sizes than these aforementioned studies, which may be due to our study of older children, in whom behavior problems may be more fully developed⁴⁶.

Two studies found no association between pre-pregnancy BMI and offspring behavior^{47, 48}. Chen et al. (2014) reported an increased risk of offspring ADHD diagnosis after 3 years of age among over 600,000 children of obese mothers, but the association was null after adjustment for familial confounding through a sibling analysis⁴⁷. This study highlights the importance of unmeasured confounding from the postnatal environment, a potential bias limiting previous studies. Our study, however, adjusted for a measure of the postnatal environment. Our findings may differ from Chen et al. (2014) because they ascertained ADHD diagnosis based on registry and medical record data. This captures only the most severe cases, while our study and previous studies assessed offspring behavioral symptoms consistent with ADHD, which may include a larger number of children with a range of symptoms.

Consistent with the only other study that we are aware of²⁰, we found no independent relation between maternal GWG and any offspring outcomes. However, we did observe a joint association between pre-pregnancy BMI and GWG on offspring impulsivity errors. Offspring of lean mothers with low GWG and offspring of overweight mothers with high GWG had a greater number of impulsivity errors, compared with their counterparts with average GWG. Excessive GWG may increase the already high concentrations of inflammatory markers present in the blood of obese women⁴⁹. Similarly, underweight women may have nutrient deficiencies that are exacerbated with low GWG. Both excessive inflammation and nutrient deficiency pathways may interfere with offspring brain development^{50, 51}. We may not have observed the same trend with attention errors because of the limited variation in the number of attention errors in this cohort.

Conclusions

In order to better understand the joint relation between maternal BMI and GWG with offspring ADHD, larger cohort studies with diverse, representative populations are needed. Future studies should also aim to assess offspring ADHD using a gold-standard diagnosis in

addition to behavior/emotion symptoms in late childhood to inform an inclusive group of affected children. The 3- to 4-point increase we observed in offspring externalizing and internalizing behavior scores among children of obese mothers compared with children of normal weight mothers may not be meaningful at an individual level, but may have a substantial impact on child behavior in the population. Preconception counseling to reduce weight before pregnancy may be an important step towards alleviating the familial and societal burden of ADHD. However, since nearly 50% of pregnancies are unplanned⁵², future studies should aim to assess modifiable factors in the postnatal period such as breastfeeding or early behavioral interventions in offspring to attenuate the adverse impact of maternal obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We wish to thank all parents and children for participating in the MHPCD study.

Funding

The following grants were received: R01HD072008, AA06390, AA06666, DA03874, DA03209

References

1. Akinbami L, Liu X, Pastor P, Reuben C. Attention Deficit Hyperactivity Disorder Among Children Aged 5-17 years in the United States, 1998-2009. 2011
2. Pelham WE, Foster EM, Robb JA. The economic impact of attention-deficit/hyperactivity disorder in children and adolescents. *Ambulatory pediatrics : the official journal of the Ambulatory Pediatric Association*. Jan-Feb;2007 7(1 Suppl):121–31. [PubMed: 17261491]
3. APA.. *Diagnostic and statistical manual of mental disorders*. 5th ed.. American Psychiatric Publishing; Arlington, VA: 2013.
4. Patel N, Patel M, Patel H. *Attention Deficit Hyperactivity Disorder/ Book 1*. 2012
5. Rowland AS, Lesesne CA, Abramowitz AJ. The epidemiology of attention- deficit/hyperactivity disorder (ADHD): a public health view. *Mental retardation and developmental disabilities research reviews*. 2002; 8(3):162–70. [PubMed: 12216060]
6. Birnbaum HG, Kessler RC, Lowe SW, Secnik K, Greenberg PE, Leong SA, et al. Costs of attention deficit-hyperactivity disorder (ADHD) in the US: excess costs of persons with ADHD and their family members in 2000. *Current medical research and opinion*. Feb; 2005 21(2):195–206. [PubMed: 15801990]
7. Attention Deficit Hyperactivity Disorder (ADHD). 2012. Pub ID: 12-3572 [cited; Available from: <http://infocenter.nimh.nih.gov/pubstatic/NIH%2012-3572/NIH%2012-3572.pdf>
8. [February 17, 2015] Leading Health Indicators: Mental Health. 2014. Available from: <https://www.healthypeople.gov/2020/leading-health-indicators/2020-lhi-topics/Mental-Health>
9. Tanda R, Salsberry PJ, Reagan PB, Fang MZ. The Impact of Prepregnancy Obesity on Children's Cognitive Test Scores. *Maternal and child health journal*. Feb; 2013 17(2):222–9. [PubMed: 22350633]
10. Grayson BE, Levasseur PR, Williams SM, Smith MS, Marks DL, Grove KL. Changes in melanocortin expression and inflammatory pathways in fetal offspring of nonhuman primates fed a high-fat diet. *Endocrinology*. Apr; 2010 151(4):1622–32. [PubMed: 20176722]
11. Catalano PM, Presley L, Minium J, Hauguel-de Mouzon S. Fetuses of obese mothers develop insulin resistance in utero. *Diabetes care*. Jun; 2009 32(6):1076–80. [PubMed: 19460915]

12. Tozuka Y, Kumon M, Wada E, Onodera M, Mochizuki H, Wada K. Maternal obesity impairs hippocampal BDNF production and spatial learning performance in young mouse offspring. *Neurochemistry international*. Oct; 2010 57(3):235–47. [PubMed: 20538025]
13. Niculescu MD, Lupu DS. High fat diet-induced maternal obesity alters fetal hippocampal development. *International journal of developmental neuroscience : the official journal of the International Society for Developmental Neuroscience*. Nov; 2009 27(7):627–33. [PubMed: 19695321]
14. Udagawa J, Hatta T, Hashimoto R, Otani H. Roles of leptin in prenatal and perinatal brain development. *Congenital anomalies*. Sep; 2007 47(3):77–83. [PubMed: 17688465]
15. Bouret SG. Neurodevelopmental actions of leptin. *Brain research*. Sep 2.2010 1350:2–9. [PubMed: 20399755]
16. Oades RD. Dopamine-serotonin interactions in attention-deficit hyperactivity disorder (ADHD). *Progress in brain research*. 2008; 172:543–65. [PubMed: 18772050]
17. Van Lieshout RJ, Schmidt LA, Robinson M, Niccols A, Boyle MH. Maternal pre-pregnancy body mass index and offspring temperament and behavior at 1 and 2 years of age. *Child psychiatry and human development*. Jun; 2013 44(3):382–90. [PubMed: 22983494]
18. Rodriguez A, Miettunen J, Henriksen TB, Olsen J, Obel C, Taanila A, et al. Maternal adiposity prior to pregnancy is associated with ADHD symptoms in offspring: evidence from three prospective pregnancy cohorts. *Int J Obes (Lond)*. Mar; 2008 32(3):550–7. [PubMed: 17938639]
19. Hinkle SN, Sharma AJ, Kim SY, Schieve LA. Maternal prepregnancy weight status and associations with children's development and disabilities at kindergarten. *Int J Obes (Lond)*. Jul 17.2013
20. Buss C, Entringer S, Davis EP, Hobel CJ, Swanson JM, Wadhwa PD, et al. Impaired executive function mediates the association between maternal pre-pregnancy body mass index and child ADHD symptoms. *PloS one*. 2012; 7(6):e37758. [PubMed: 22719848]
21. Association, AP. Diagnostic and statistical manual of mental disorders. 5th ed.. American Psychiatric Publishing; Arlington, VA: 2013.
22. Day NL, Richardson GA, Geva D, Robles N. Alcohol, Marijuana, and Tobacco: Effects of Prenatal Exposure on Offspring Growth and Morphology at Age Six. *Alcoholism: Clinical and Experimental Research*. 1994; 18(4):786–94.
23. World Health Organization. Physical Status: The use and interpretation of anthropometry. Switzerland: 1995.
24. Hutcheon JA, Platt RW, Abrams B, Himes KP, Simhan HN, Bodnar LM. A weight-gain-for-gestational-age z score chart for the assessment of maternal weight gain in pregnancy. *The American journal of clinical nutrition*. May; 2013 97(5):1062–7. [PubMed: 23466397]
25. Achenbach, T. Manual for the Child Behavior Checklist/4-18 and 1991 Profile. University of Vermont Department of Psychiatry; Burlington, VT: 1991.
26. Achenbach, T. Manual for the Teachers Report Form and 1991 profile. University of Vermont Department of Psychiatry; Burlington, VT: 1991.
27. Lindgren, SL,D. Pediatric assessment of cognitive efficiency (PACE). University of Iowa, Department of Pediatrics; Iowa City, IA: 1984.
28. Day NL, Robles N. Methodological issues in the measurement of substance use. *Annals of the New York Academy of Sciences*. 1989; 562:8–13. [PubMed: 2742287]
29. Radloff L. The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*. 1977; 1:385–401.
30. Speilberger, CD. Preliminary manual for the State-Trait Personality Inventory (STPI). University of South Florida; Tampa, FL: 1979.
31. Baker P, Mott F. National Longitudinal Study of Youth Child Handbook. 1989
32. Brooker BH, Cyr JJ. Tables for clinicians to use to convert WAIS-R short forms. *Journal of Clinical Psychology*. 1986; 42(6):982–6.
33. Kuha J. AIC and BIC: Comparisons of Assumptions and Performance. *Sociological Methods & Research*. Nov 1; 2004 33(2):188–229. 2004.

34. Greenland S. Modeling and variable selection in epidemiologic analysis. *American journal of public health*. Mar; 1989 79(3):340–9. [PubMed: 2916724]
35. Day NL, Richardson GA, Goldschmidt L, Robles N, Taylor PM, Stoffer DS, et al. Effect of prenatal marijuana exposure on the cognitive development of offspring at age three. *Neurotoxicology & Teratology*. 2011; 16(2):169–75. [PubMed: 8052191]
36. Day NL, Richardson GA. An analysis of the effects of prenatal alcohol exposure on growth: a teratologic model. *American journal of medical genetics Part C, Seminars in medical genetics*. May 15; 2004 127C(1):28–34.
37. Cornelius MD, Goldschmidt L, DeGenna N, Day NL. Smoking during teenage pregnancies: effects on behavioral problems in offspring. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco*. Jul; 2007 9(7):739–50. [PubMed: 17577803]
38. StataCorp.. *Stata Statistical Software: Release 13*. StataCorp LP; College Station, TX: 2013.
39. Consumer Price Index Calculator. 2014. [cited; Available from: <http://data.bls.gov/cgi bin/cpicalc.pl>]
40. French WP. Assessment and treatment of attention-deficit/hyperactivity disorder: part 1. *Pediatric annals*. Mar 1; 2015 44(3):114–20. [PubMed: 25806728]
41. Connor DF, Ford JD. Comorbid symptom severity in attention-deficit/hyperactivity disorder: a clinical study. *The Journal of clinical psychiatry*. May; 2012 73(5):711–7. [PubMed: 22697195]
42. Brunner Huber LR. Validity of self-reported height and weight in women of reproductive age. *Maternal and child health journal*. Mar; 2007 11(2):137–44. [PubMed: 17066316]
43. Lash TL. Heuristic thinking and inference from observational epidemiology. *Epidemiology*. Jan; 2007 18(1):67–72. [PubMed: 17149141]
44. Wilcox AJ, Weinberg CR, Basso O. On the pitfalls of adjusting for gestational age at birth. *American journal of epidemiology*. Nov 1; 2011 174(9):1062–8. [PubMed: 21946386]
45. Brion M-J, Zeegers M, Jaddoe V, Verhulst F, Tiemeier H, Lawlor DA, et al. Intrauterine effects of maternal prepregnancy overweight on child cognition and behavior in 2 cohorts. *Pediatrics*. Jan; 2011 127(1):e202–11. [PubMed: 21187310]
46. Vande Voort JL, He JP, Jameson ND, Merikangas KR. Impact of the DSM-5 attention-deficit/hyperactivity disorder age-of-onset criterion in the US adolescent population. *Journal of the American Academy of Child and Adolescent Psychiatry*. Jul; 2014 53(7):736–44. [PubMed: 24954823]
47. Chen Q, Sjolander A, Langstrom N, Rodriguez A, Serlachius E, D'Onofrio BM, et al. Maternal pre-pregnancy body mass index and offspring attention deficit hyperactivity disorder: a population-based cohort study using a sibling-comparison design. *International journal of epidemiology*. Feb; 2014 43(1):83–90. [PubMed: 24058000]
48. Antoniou EE, Fowler T, Reed K, Southwood TR, McCleery JP, Zeegers MP. Maternal pre-pregnancy weight and externalising behaviour problems in preschool children: a UK-based twin study. *BMJ open*. 2014; 4(10):e005974.
49. Sullivan EL, Grayson B, Takahashi D, Robertson N, Maier A, Bethea CL, et al. Chronic consumption of a high-fat diet during pregnancy causes perturbations in the serotonergic system and increased anxiety-like behavior in nonhuman primate offspring. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. Mar 10; 2010 30(10):3826–30. [PubMed: 20220017]
50. Antonow-Schlorke I, Schwab M, Cox LA, Li C, Stuchlik K, Witte OW, et al. Vulnerability of the fetal primate brain to moderate reduction in maternal global nutrient availability. *Proceedings of the National Academy of Sciences*. Feb 15; 2011 108(7):3011–6. 2011.
51. Wiggins RC, Fuller G, Enna SJ. Undernutrition and the development of brain neurotransmitter systems. *Life sciences*. Nov 19; 1984 35(21):2085–94. [PubMed: 6149444]
52. Finer LB, Zolna MR. Unintended pregnancy in the United States: incidence and disparities, 2006. *Contraception*. Nov; 2011 84(5):478–85. [PubMed: 22018121]

Figure 1.

Association between Pre-pregnancy Body Mass Index and Offspring Externalizing Behavior on the Parent-Rated Scale (Panel A) and Teacher-Rated Scale (Panel B), $n=511$ Adjusted predicted scores of parent- and teacher-rated externalizing behavior problems by pre-pregnancy body mass index. The solid lines represent the point estimates and dashed lines represent its 95% confidence bands. Predicted scores were estimated using linear regression and were set at the population average for maternal race, child sex, parity, income, employment, maternal depression, maternal intelligence, the home environment, and prenatal substance use (marijuana, alcohol, cigarette, and illicit drugs). Pre-pregnancy body mass index was modeled using a single knot ($BMI=22\text{kg/m}^2$) linear spline.

Table 1

Characteristics of the Maternal Health Practices and Child Development Cohort, Pittsburgh, PA (1983-1986) at Enrollment and 10 years Postpartum in Pittsburgh, PA (n=511)

	Overall N(%)
Enrollment or Delivery	
Maternal Age at Enrollment, mean(range)	23.1 (18-42)
Maternal Race	
White	250 (49)
Black	261 (51)
Marital Status	
Never Married	342 (67)
Married	169 (33)
Family Income (\$ per month)	
<500	311 (61)
500	200 (39)
Pre-Pregnancy Body Mass Index	
Underweight	73 (14)
Normal Weight	297 (58)
Overweight	92 (18)
Obese	49 (10)
Prenatal Alcohol use	
Never used	129 (25)
Drank 1 trimester	145 (28)
Drank 2 trimesters	237 (47)
Prenatal Marijuana use	
Never used	254 (49)
Smoked 1 trimester	125 (25)
Smoked 2 trimesters	132 (26)
Prenatal Cigarette use	
Never used	194 (38)
Smoked 1 trimester	44 (9)
Smoked 2 trimesters	273 (53)
Prenatal Illicit Drug use	
Used any	59 (11.5)
Maternal Depression Scale	
Not Depressed <16	143 (29)
Moderately Depressed 16	362 (71)
Child Sex	
Male	258 (51)
Female	253 (49)
10 years Postpartum	
HOME Stimulation Scale	

	Overall N(%)
Under stimulated <16	437 (85)
Stimulated 16	74 (15)
Maternal IQ	
Below Average 89	300 (59)
Above Average >89	211 (41)

Underweight (BMI <18.5 kg/m²); Normal weight (BMI 18.5-24.9 kg/m²); Overweight (BMI 25-29.9 kg/m²); Obese (BMI ≥30 kg/m²)

¹Includes school attendance; HOME: Home Observation for Measurement of the Environment

Adjusted Associations for Parent and Teacher-rated Offspring Behaviors by Pre-Pregnancy Body Mass Index (n=511)

	Maternal Rated: Internalizing β (95% CI) ¹	Maternal Rated: Externalizing β (95% CI) ¹	Maternal Rated: Attention β (95% CI) ¹	Teacher Rated: Internalizing β (95% CI) ¹	Teacher Rated: Externalizing β (95% CI) ¹	Teacher Rated: Attention β (95% CI) ¹
BMI (kg/m ²) ²						
18	1.3 (-1.1, 3.6)	2.1 (-0.1, 4.3)	0.9 (-0.7, 2.6)	2.6 (0.2, 5.0)	2.9 (0.5, 5.5)	1.2 (-0.7, 3.1)
20	0.6 (-0.5, 1.8)	1.1 (-0.1, 2.2)	0.5 (-0.4, 1.3)	1.3 (0.1, 2.5)	1.5 (0.2, 2.8)	0.6 (-0.4, 1.6)
22	Reference	Reference	Reference	Reference	Reference	Reference
24	0.8 (0.4, 1.2)	0.7 (0.4, 1.1)	0.6 (0.3, 0.9)	0.4 (-0.1, 0.8)	0.4 (-0.1, 0.8)	0.3 (-0.01, 0.7)
26	1.7 (0.8, 2.5)	1.5 (0.7, 2.3)	1.1 (0.5, 1.7)	0.7 (-0.2, 1.6)	0.8 (-0.1, 1.7)	0.7 (-0.01, 1.3)
28	2.5 (1.3, 3.8)	2.2 (1.1, 3.4)	1.7 (0.8, 2.6)	1.0 (-0.2, 3.1)	1.2 (-0.1, 2.5)	1.0 (-0.01, 1.9)
30	3.3 (1.7, 4.9)	2.9 (1.4, 4.6)	2.3 (1.1, 3.4)	1.4 (-0.3, 3.1)	1.6 (-0.2, 3.4)	1.3 (-0.01, 2.7)
32	4.1 (2.1, 6.2)	3.7 (1.8, 5.7)	2.8 (1.4, 4.3)	1.8 (-0.4, 3.9)	2.0 (-0.2, 4.3)	1.7 (-0.01, 3.3)
34	5.1 (2.6, 7.6)	4.6 (2.2, 6.9)	3.5 (1.7, 5.3)	2.2 (-0.5, 4.8)	2.5 (-0.2, 5.2)	2.1 (-0.02, 4.1)

¹ Adjusted for maternal race, child sex, parity, income, employment, maternal depression, maternal intelligence, the home environment, and prenatal substance use (marijuana, alcohol, cigarette, and illicit drugs)

² Pre-pregnancy body mass index modeled as a linear spline with a single knot at a BMI of 22kg/m²

Table 3

Adjusted Associations for Parent and Teacher-rated Offspring Behaviors and Objective Attention and Impulsivity by Gestational Weight Gain z-score (n=511)

Scales	GWG z-score <-1 SD	GWG z-score -1 to +1SD	GWG z-score >+1SD
	β^I (95% CI)	β^I (95% CI)	β^I (95% CI)
Parent-Rated			
Internalizing	-0.8 (-2.9, 1.4)	Reference	1.6 (-1.5, 4.8)
Externalizing	-0.4 (-2.5, 1.7)	Reference	1.8 (-1.2, 4.8)
Attention	-0.1 (-1.6, 1.5)	Reference	1.7 (-0.5, 3.9)
Teacher-Rated			
Internalizing	-1.8 (-4.0, 0.5)	Reference	0.1 (-3.1, 3.4)
Externalizing	-2.2 (-4.6, 0.1)	Reference	0.7 (-2.6, 4.1)
Attention	-1.2 (-2.9, 0.6)	Reference	-0.2 (-2.8, 2.4)
Objective			
	IRR ^I (95% CI)	IRR ^I (95% CI)	IRR ^I (95% CI)
Attention	1.1 (0.9, 1.3)	Reference	1.1 (0.8, 1.4)
Impulsivity			
Lean (<25kg/m ²)	1.2 (0.9, 1.5)	Reference	0.8 (0.6, 1.2)
Overweight (≥ 25 kg/m ²)	0.8 (0.6, 1.1)	Reference	1.7 (0.9, 2.8)

IRR- Incidence Rate Ratio; SD-Standard Deviation

^I Adjusted for maternal race, child sex, parity, income, employment, maternal depression, maternal intelligence, the home environment, pre-pregnancy body mass index, and prenatal substance use (marijuana, alcohol, cigarette, and illicit drugs)