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Maternal pre-pregnancy weight status and health care use for mental health conditions in the offspring

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ABSTRACT

Objectives: The objective of this study was to examine the relationship between pre-pregnancy maternal weight status and offspring physician visits for mental health conditions in childhood and adolescence.

Methods: We conducted a population-based retrospective cohort study of singleton infants born between the years of 1989 and 1993 using a linkage of the Nova Scotia Atlee Perinatal Database with administrative health data. Offspring were followed from birth to age 18 years. Maternal weight status was categorized according to WHO body mass index cutoffs. The number of physician visits for any mental health condition, mood, anxiety, and adjustment disorders, conduct disorder, and attention deficit hyperactivity disorder (ADHD) from age 0-18 years was determined from ICD codes in physician billings and hospital discharge abstract data. Compound Poisson regression adjusting for sociodemographics, maternal psychiatric disorders and smoking was used to model the association.

Results: In total, 38,211 mother-offspring pairs were included in the cohort. Within the first 18 years of life, offspring of mothers with obesity had significantly more physician visits for any mental health condition (adjusted incidence rate ratio [IRR] 1.21, 95% CI 1.14-1.28), mood, anxiety, and adjustment disorders (IRR 1.13, 95% CI 1.04-1.23), conduct disorder (IRR 1.16, 95% CI 1.17-2.11), and ADHD (IRR 1.44, 95% CI 1.19-1.74) compared to mothers of normal weight. Associations for mood, anxiety, and adjustment disorders and conduct disorder were strongest at 13-18 years.

Conclusions: Offspring of mothers with obesity appear to use health care for mental health conditions more frequently than offspring of normal weight mothers.

Key words: pregnancy, obesity, child, adolescent, mental disorders

INTRODUCTION

Pre-pregnancy obesity has been shown to have profound adverse consequences on infant health outcomes, including increased risk for birth injuries, preterm birth, low Apgar scores, respiratory distress syndrome, and macrosomia [1–4]. In childhood, offspring of mothers with obesity are at an elevated risk of chronic conditions such as obesity and asthma compared to offspring of mothers of normal weight [5, 6]. Previous research has also demonstrated an association between maternal obesity and neurodevelopmental outcomes of the child [5, 7–9]. Pre-pregnancy obesity is associated with increased risk of impaired cognitive performance [8], autism spectrum disorder [10], negative emotionality [11], and symptoms of attention-deficit hyperactivity disorder (ADHD) in school-aged children [11, 12]. A small number of studies have also shown maternal body mass index (BMI) to be positively associated with internalizing (e.g. anxiety or depression) and externalizing symptoms (e.g. aggressive behaviour) in the offspring [11, 13–15]. Previous studies were often limited in their ability to adjust for relevant confounders or were not population-based, which may have introduced selection bias [16]. Owing to the non-availability of mental health status assessment by validated instruments at the population level, we will use health care utilization for mental health conditions as a surrogate for offspring mental health. This information is recorded for all health care beneficiaries through administrative health data in Canada. Therefore, the objective of the present study was to examine the relationship between pre-pregnancy maternal weight status and offspring health care use for mental health conditions in a population-based sample in the Canadian province of Nova Scotia while controlling for relevant confounders.

METHODS

Study design and population

Our study was a population-based retrospective cohort study of women resident to the Canadian province of Nova Scotia who gave birth to singleton infants between January 1, 1989 and December

31, 1993. The offspring of women included in the cohort were followed to age 18 years. Information on the mothers and their children was obtained by linking the Nova Scotia Atlee Perinatal Database (NSAPD) with provincial administrative health data.

Data sources

The NSAPD collects information on all births to mothers who were resident to Nova Scotia since 1988. Extensive information on routine demographic variables, medical conditions, reproductive history, delivery events, and neonatal outcomes is recorded for each delivery. Trained coders enter these data from standardized clinical forms into the NSAPD. Nova Scotia uses a standard Prenatal Record in addition to forms completed at the time of the hospital delivery admission to document prenatal care and information relevant to care and medical research. The Reproductive Care Program of Nova Scotia administers the database, maintains the coding system, and ensures the quality, integrity and security of the data. Periodic abstraction and validation studies form an ongoing data quality assurance program and have shown that the data are accurate and reliable [17]. The Medical Services Insurance physician billing database documents diagnosis codes in ICD-9 format (one from 1989-1996; up to three after 1996) for each insured health service performed by a physician and paid for by the Nova Scotia provincial health care system. The Insured Patients Registry contains longitudinal information about each individual eligible for Nova Scotia health care services and was used to identify individuals in the cohort who left the province or died during the study period.

The linkage of the NSAPD with administrative health data was conducted by Health Data Nova Scotia based on the health card number. Prior to linkage, health card numbers were encrypted to ensure anonymity.

This study was approved by the IWK Health Centre Research Ethics Board (file #1015756), the Joint Data Access Committee of the Reproductive Care Program of Nova Scotia, and the data access

committee of Health Data Nova Scotia. All study procedures been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Exposure

The exposure variable, pre-pregnancy weight status as per WHO cutoffs (not overweight or obese: < 25 kg/m^2, overweight: 25 - < 30 kg/m^2, obese: ≥ 30 kg/m^2) [18], was obtained from the NSAPD and was based on maternal height and weight as reported by the mother at the first prenatal visit; underweight women were included in the "not overweight or obese" category. Maternal height was not routinely captured in the NSAPD before 2003 and was retroactively entered where available for women with pregnancies before that year. In cases where maternal height was not available, we estimated maternal BMI category from maternal weight based on data from 77,297 mothers for whom height and weight were recorded in the NSAPD from 2003-2015 (normal weight: < 68.0 kg; overweight: 68.0-76.6 kg; obese: ≥ 76.7 kg). The sensitivity of these weight-based categories was between 86 and 96%, and specificity was between 90 and 95% with the highest values observed for the obese category. Regression of common perinatal outcomes (gestational diabetes, mode of delivery, 5-min Apgar score <7, birth weight for gestational age, pre-eclampsia) based on imputed and recorded weight status showed that the effect estimates from the corresponding models did not differ by more than 10% with the imputation-based estimates generally being closer to the null than the complete case estimates. These findings support the accuracy and validity of the body weight-based categories.

Outcomes

The primary outcome of interest was offspring health care utilization for any mental health disorder as determined by the number of offspring outpatient physician visits that were coded with the mental health ICD Chapter (ICD-9, Chapter V); inpatient information was not considered in the present study. Secondary outcomes include offspring health care utilization for mood, anxiety, and adjustment

disorders (ICD-9: 296, 300, 308, 309, 311, 313), conduct disorder (ICD-9: 312), and ADHD (ICD-9: 314). All outcomes were measured across offspring ages 0 to18 years as well as in three age groups (pre-school [0-5 years], early childhood [6-12 years], and adolescence [13-18 years]).

Confounding variables

A directed acyclic graph was used to determine confounding variables (Figure 1), which included maternal age, area of residence (urban vs. rural, based on the second digit of the Canadian postal code), area-level income quintile at birth (Quintile of Adjusted Income per Person Equivalent, from Census of Canada information [19]), marital status (married/common-law vs. single/divorced/widowed), parity (1, 2, 3, or ≥ 4, including the current pregnancy), maternal psychiatric disorders during pregnancy (defined as any psychiatric condition diagnosed during pregnancy by a psychiatrist), and smoking in pregnancy (yes/no). Smoking during pregnancy was assessed at three timepoints (first prenatal visit, at 20 weeks, and on admission to the labour ward); any smoking at these times was considered smoking during pregnancy.

Statistical Analysis

Sociodemographic and clinical characteristics were summarized by maternal pre-pregnancy weight status and compared using analysis of variance and chi-squared test as appropriate. The association between maternal pre-pregnancy weight status and the number of physician visits for mental health conditions was estimated using zero-inflated negative binomial regression. Models were adjusted for maternal age, area of residence, area-level income quintile, marital status, parity, maternal psychiatric disorders during pregnancy, and smoking in pregnancy. Hot deck multiple imputation with five iterations was used to impute missing values of the confounding variables. We reported associations as incidence rate ratios (IRR) with 95% confidence intervals (CI). As the association between maternal weight status and mental health conditions in children and adolescents may differ between sexes,

analyses were also performed stratified by sex. The statistical software package R v3.3 was used to perform the statistical analyses [20].

RESULTS

A total of 48,790 singleton live births were recorded in the NSAPD between the years of 1989 and 1993. Information on birth weight and gestational age was available for 47,450 births. A total of 42,999 births could be successfully linked with administrative health data. We excluded 4788 offspring who were not insured for publicly funded health services in Nova Scotia for the first 18 years of life due to moving out of the province or death, yielding a final sample size of 38,211. In the complete case sample, 14.6% of mothers were classified as obese, 15.8% were classified as overweight, and 69.6% were normal weight. Table 1 reports the sociodemographic and clinical characteristics of the women and their offspring by pre-pregnancy weight status. Mothers with overweight or obesity were more likely than normal weight mothers to live in a rural area, be married or in a common-law relationship, be multi-parous, require a Caesarean section delivery, and have a large for gestational age offspring. Maternal pre-pregnancy weight, marital status, area-level income quintile, and smoking in pregnancy had 9.2%, 2.2%, 1.1%, and 4.1% missing information, respectively.

Table 2 shows that offspring of mothers with obesity have more physician visits (IRR 1.26, 95% CI 1.19-1.34) for any mental health condition during the first 18 years of life, as well as more visits for mood, anxiety, and adjustment disorders (IRR 1.16, 95% CI 1.07-1.25), conduct disorders (IRR 1.25, 95% CI 1.08-1.45), and ADHD (1.45, 95% CI 1.24-1.69), compared to offspring of mothers of normal weight in the adjusted models. There was no association between maternal overweight and offspring health care use for any of the outcomes. There was also no difference in service use for mental health conditions between the obesity and normal weight groups in the 0-5 years age range with the exception of ADHD. Within the 6-12- and 13-18-years age range, maternal obesity was statistically significantly associated with a higher number of physician visits for mood, anxiety, and adjustment disorders,

conduct disorder, and ADHD, but the magnitude of the association did not differ from those of the overall age group. In the sex-stratified (Tables S1 and S2) and complete case analyses (Table S3), associations remained consistent with the findings from the main analysis.

DISCUSSION

The present study found associations between maternal obesity with offspring mental health conditions including mood, anxiety, and adjustment disorders, conduct disorder, and ADHD, and expands on the existing studies on the topic by using a population-based sample and assessing offspring mental health through health care utilization for mental health conditions [11, 12, 14, 15, 21].

There is largely consistent evidence for an association of maternal obesity with offspring internalizing symptoms and mood or anxiety disorders, but the number of studies is limited [11, 13, 14, 21, 22]. The effect size in our study was fairly small with children of mothers with obesity having on average 16% more physician visits for mood, anxiety, and adjustment disorders during the first 18 years of life than children of mothers of normal weight. Our findings are difficult to compare to previous studies as we used health service use based on physician diagnostic codes from billing information, which are likely less sensitive and specific for the identification of mental health conditions compared to the validated diagnostic instruments used in previous studies. By contrast to previous studies, we did not find an association between maternal obesity and health services use for mood, anxiety, and adjustment disorders below six years of age since these symptoms are often not recognized and diagnosed at this age [23, 24].

We identified six studies that examined the relationship between maternal obesity and externalizing symptoms or externalizing disorders, most of which found significant associations [13–15, 21, 25, 26]. Of note, Brion and colleagues, using the Dutch Generation R study and the British Avon Longitudinal

Study of Parents and Children, failed to find consistent evidence for a relationship between maternal obesity and offspring externalizing problems [21]. The effect size for the outcome conduct disorder in our study was moderately strong in the 13-18 years group, with adolescent offspring of a mother with obesity having 57% more visits with an ICD code for conduct disorder than adolescents of a normal weight mother.

A link between maternal weight status and offspring ADHD has been examined in a number of studies [11–13, 27–29], most of which found a statistically significant association; however, one Swedish study found an association at the population level that vanished completely when sibling comparisons were used. Based on their findings, the authors suggested that unmeasured familial confounding explains the relationship [12]. The Swedish study was similar to ours in that they used population-based registry information and used physician diagnostic codes as the outcome. Since we did not have enough sibling-pairs with discordant maternal pre-pregnancy weight, we were unable to perform between-sibling comparisons in our cohort.

Several mechanisms for the association between maternal obesity and offspring mental health outcomes have been proposed, but the etiology remains largely unknown. Firstly, it has been suggested that obesity in pregnancy heightens the inflammatory state of the intrauterine environment due to increased secretion of adipokines and other pro-inflammatory mediators [30]. Obesity in pregnancy may also expose the fetus to lipotoxicity and oxidative stress [30–32], which may alter the programming and development of fetal neural circuitry [7, 32]. A number of pregnancy and obstetrical complications like gestational hypertension and gestational diabetes mellitus are more common in women with obesity [33] and have also been shown to be associated with neuropsychiatric outcomes in the offspring [34–37].

However, three studies that examined a potential mediation of the association between maternal obesity and offspring mental health by these conditions did not find an effect [13, 22, 38]. Other conditions that have been proposed as potential mediators include maternal stress during pregnancy [39], vitamin D deficiency [40], and the offspring's diet [41], physical activity [42], and weight status [43]. However, evidence on these associations is often conflicting and none of these factors have been formally examined yet as potential mediators of the relationship between maternal obesity and the child's mental health.

Strengths of the current study include its population-based design and large sample size, while most other studies were performed in smaller, selected samples. We were also able to follow individuals over a longer time period than most studies. However, there are also several limitations that should be acknowledged. The possibility of residual or unmeasured confounding poses the greatest threat to the validity of our findings. While we were able to control for a number of relevant confounders, there is the potential for residual confounding by socio-economic status or maternal mental health. The former was only available at the area-level, and the latter variable was limited in its potential to capture psychiatric conditions as evidenced by the low prevalence of 0.3% in the NSAPD. Confounding by unmeasured family factors or genetic factors is another possibility as demonstrated by the aforementioned ADHD study by Chen et al. [12]. However, other sibling and twin studies of similar associations still suggested a role of maternal pre-pregnancy weight. For example, an analysis from the Twins and Multiple Births Association Heritability Study in the UK found that even after taking into account genetic factors, children of mothers with obesity tended to show more externalizing behaviours than children of normal weight mothers [26]. Similarly, a US study of 30,000 sibling pairs showed that maternal obesity was associated with lower Intelligence Quotient scores compared to offspring of normal weight mothers [44].

By contrast to most other studies [14, 21, 22, 27], which used validated instruments to diagnose mental health conditions, we measured health service use for mood, anxiety, and adjustment disorders, conduct disorder, and ADHD based on ICD-9 codes from physician billings information. Since there are, to the best of our knowledge, no established case definitions for child and adolescent mental health conditions based on ICD codes in administrative data, we used counts of physician visits for the respective conditions as the outcome; this operationalization of the outcome may have a lower sensitivity for identifying mental health conditions as only parents of children with more severe symptoms may seek treatment. If this misclassification was non-differential (i.e. did not differ by maternal weight status), it would result in an attenuation of the association.

The exposure pre-pregnancy weight status was not measured but based on maternal self-report at their first prenatal visit. However, women gain relatively little weight in the first trimester [45], and in a setting where women are about to be weighed, self-report can be accurate [46, 47]. Self-report may have resulted in women underestimating their weight and over-estimating their height [48], which would have attenuated effect estimates due to the misclassification of women with overweight and obesity as normal weight. By using ICD codes from physician visits as a measure of mental health status, our findings are limited by diagnostic and coding accuracy and access to health care. Diagnoses from billing information may not accurately reflect mental disorders. In addition, only a small proportion of diagnostic codes were assigned by specialists, which may have resulted in both false positives and false negatives, especially for conditions that do not have objective diagnostic criteria or that are difficult to distinguish from developmentally occurring symptoms. Children who did not have readily available access to care or who did not seek medical care regarding mental health concerns would have been misclassified as not using health care for mental health conditions.

CONCLUSION

Offspring of mothers with obesity appears to use health care for mental health conditions more frequently than offspring of normal weight mothers. However, given the potential for residual confounding and uncertainty about a mechanism for this association, it is too early to suggest that weight loss before pregnancy can positively influence offspring mental health. Future research should use sibling and twin studies to further elucidate the role of family and genetic factors in the association between pre-pregnancy weight and neuropsychiatric conditions in offspring.

CONFLICT OF INTEREST DISCLOSURE

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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FIGURE

Figure 1: Directed acyclic graph with the hypothesized relationships between the maternal obesity and health care use for mental health conditions.

TABLES

Table 1: Sociodemographic and clinical characteristics of Nova Scotian women with a singleton birth between 1989 and 1993, stratified by pre-pregnancy weight status (complete cases, n=29,336).
Abbreviation: *SD* standard deviation
* based on a Canadian reference population [49]

	Normal weight n = 20,405 69.6%	**Overweight** n = 4637 15.8%	**Obese** n = 4294 14.6%	***P* value**
Maternal age [years] (mean, SD)	27.4 (5.1)	27.6 (4.9)	27.5 (4.8)	0.005
Married or common-law [%]	82.1	84.9	83.7	< 0.001
Rural Residence [%]	41.4	43.8	48.3	< 0.001
Area-Level Income [%]				< 0.001
Quintile 1 (lowest)	19.3	20.1	21.8	
Quintile 2	21.9	22.7	23.8	
Quintile 3	20.8	21.2	22.0	
Quintile 4	20.1	20.3	18.3	
Quintile 5 (highest)	18.0	15.7	14.1	
Parity [%]				< 0.001
1	46.1	42.7	40.9	
2	35.0	35.7	36.9	
3	13.7	15.2	15.1	
4+	5.2	6.4	7.1	
Smoking in Pregnancy [%]	29.9	28.9	28.6	0.143
Caesarean section [%]	17.3	19.9	27.3	< 0.001
Male infant [%]	50.8	50.2	50.2	0.651
Preterm birth [%]	4.9	4.5	4.9	0.434
Birth Weight for Gestational Age* [%]				< 0.001
Appropriate (10-90th percentile)	79.1	76.5	73.0	
Small (< 10th percentile)	11.6	7.9	7.0	
Large (> 90th percentile)	9.3	15.6	20.0	

Table 2: Incidence rates and incidence rate ratios with 95% confidence intervals for the association between pre-pregnancy weight status and physician visits for mental health conditions in the offspring (n=38,211). Models were adjusted for maternal age, area of residence, area-level income quintile, marital status, parity, maternal psychiatric disorders during pregnancy, and smoking in pregnancy.
Abbreviations: *ADHD* Attention Deficit Hyperactivity Disorder, *CI* confidence interval, *IR* incidence rate, *IRR* incidence rate ratio, *PY* person-years

	Unadjusted		**Adjusted**	
	IR (per 1000 PY)	IRR (95% CI)	IR (per 1000 PY)	IRR (95% CI)
Any Mental Health Disorder				
Normal Weight	8.42	Ref.	8.60	Ref.
Overweight	8.54	1.01 (0.96-1.08)	8.83	1.03 (0.97-1.09)
Obese	10.2	1.21 (1.14-1.28)	10.9	1.26 (1.19-1.34)
Mood, Anxiety, and Adjustment Disorders				
Normal Weight	2.99	Ref.	3.13	Ref.
Overweight	3.03	1.01 (0.95-1.08)	3.20	1.02 (0.96-1.09)
Obese	3.39	1.13 (1.04-1.23)	3.62	1.16 (1.07-1.25)
Conduct Disorder				
Normal Weight	0.697	Ref.	0.798	Ref.
Overweight	0.679	0.97 (0.87-1.09)	0.789	0.99 (0.88-1.10)
Obese	0.811	1.16 (1.00-1.34)	0.998	1.25 (1.08-1.45)
ADHD				
Normal Weight	3.11	Ref.	3.04	Ref.
Overweight	3.31	1.06 (0.92-1.23)	3.32	1.09 (0.95-1.26)
Obese	4.12	1.32 (1.14-1.54)	4.39	1.45 (1.24-1.69)

Table 3: Incidence rate ratios with 95% confidence intervals for the association between pre-pregnancy weight status and physician visits for mental health conditions in the offspring (n=38,211) by age. Models were adjusted for maternal age, area of residence, area-level income quintile, marital status, parity, maternal psychiatric disorders during pregnancy, and smoking in pregnancy.
Abbreviations: *ADHD* Attention Deficit Hyperactivity Disorder, *CI* confidence interval, *IRR* incidence rate ratio

	0-5 years		**6-12 years**		**13-18 years**	
	Unadjusted IRR (95% CI)	**Adjusted** IRR (95% CI)	**Unadjusted** IRR (95% CI)	**Adjusted** IRR (95% CI)	**Unadjusted** IRR (95% CI)	**Adjusted** IRR (95% CI)
Any Mental Health Disorder						
Normal Weight	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Overweight	0.95 (0.87-1.03)	0.97 (0.89-1.06)	1.02 (0.93-1.12)	1.04 (0.95-1.15)	1.03 (0.95-1.10)	1.03 (0.96-1.11)
Obese	1.03 (0.94-1.12)	1.07 (0.99-1.17)	1.30 (1.18-1.43)	1.37 (1.24-1.52)	1.20 (1.12-1.28)	1.24 (1.15-1.33)
Mood, Anxiety, and Adjustment Disorders						
Normal Weight	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Overweight	0.84 (0.71-1.00)	0.92 (0.78-1.08)	1.03 (0.91-1.16)	1.04 (0.92-1.19)	1.03 (0.95-1.11)	1.03 (0.96-1.11)
Obese	0.97 (0.69-1.38)	1.06 (0.85-1.33)	1.12 (0.98-1.29)	1.14 (1.00-1.29)	1.15 (1.06-1.24)	1.17 (1.08-1.27)
Conduct Disorder						
Normal Weight	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Overweight	0.92 (0.81-1.06)	0.95 (0.83-1.08)	0.96 (0.80-1.17)	0.98 (0.81-1.18)	1.15 (0.83-1.58)	1.13 (0.84-1.52)
Obese	0.97 (0.85-1.11)	1.03 (0.90-1.18)	1.24 (0.94-1.64)	1.37 (1.05-1.79)	1.52 (1.13-2.05)	1.57 (1.17-2.11)
ADHD						
Normal Weight	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Overweight	0.97 (0.76-1.23)	0.98 (0.77-1.24)	1.06 (0.90-1.26)	1.10 (0.93-1.31)	1.08 (0.90-1.30)	1.09 (0.91-1.31)
Obese	1.16 (0.92-1.45)	1.25 (1.00-1.56)	1.33 (1.11-1.58)	1.46 (1.22-1.74)	1.34 (1.11-1.61)	1.44 (1.19-1.74)