Maternal Metabolic Complications in Pregnancy and Offspring Behavior Problems at 2 Years of Age

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Abstract

Objectives Prenatal maternal metabolic problems such as pre-pregnancy adiposity, excess gestational weight gain, and gestational diabetes mellitus (GDM) are associated with an increased risk of psychopathology in offspring. We examined whether these exposures were linked to symptoms of emotional and behavioral problems in offspring at 2 years of age, or if associations were due to confounding variables.

Methods Data from 815 mother–child pairs enrolled at the Edmonton site of the Canadian Healthy Infant Longitudinal Development cohort were used to examine associations between gestational metabolic complications and scores on the externalizing and internalizing scales of the Child Behavior Checklist (CBCL-1½ to 5) at age two. Associations between maternal metabolic complications and offspring psychopathology were assessed before and after adjustment for gestational diet, socioeconomic status (SES), postpartum depression (PPD), prenatal smoking and breastfeeding.

Results Pre-pregnancy body mass index and GDM, but not gestational weight gain, predicted more offspring externalizing and internalizing problems. However, after adjustment for confounding variables, these associations were no longer statistically significant. Post-hoc analyses revealed that gestational diet accounted for unique variance in both externalizing (semi-partial $r_{diet} = -0.20$, $p < 0.001$) and internalizing (semi-partial $r_{diet} = -0.16$, $p = 0.01$) problems. PPD and SES also accounted for a similar amount of variance for both externalizing (semi-partial $r_{PPD} = 0.17$, $p < 0.001$; $r_{ses} = -0.11$, $p = 0.03$) and internalizing problems (semi-partial $r_{PPD} = 0.21$, $p < 0.001$; $r_{ses} = -0.14$, $p = 0.004$).

Conclusions for Practice Since the confounding effect of gestational diet persisted after adjustment for, and was similar in magnitude to, SES and PPD, future research should consider the impact of unhealthy prenatal diets on offspring neurodevelopment.

Keywords Child Behavior Checklist · Gestational diabetes mellitus · Obesity · Prenatal nutrition · Prenatal programming · Preschool

Significance

What is already known on the subject: Children exposed to maternal metabolic complications while in utero (e.g., maternal obesity, gestational diabetes mellitus) appear to be at an increased risk for emotional and behavioral problems later in life. However, no studies have examined whether maternal gestational diet confounds these associations.

What this study adds: Gestational diet plays an important role in links between metabolic complications during pregnancy and offspring behavioral problems. Further, the effect of gestational diet was similar in magnitude to socioeconomic disadvantage and postpartum depression, two well-known risk factors for offspring psychopathology.
Introduction

Emotional and behavioral problems affect up to 20% of children under 2 years of age (Skovgaard et al. 2007; von Klitzing et al. 2015) and predict an increased risk for psychopathology from pre-school age through adulthood (Masi et al. 2015; Moffitt et al. 2011). The identification of modifiable risk factors causally related to early behavioral problems is therefore of critical importance. The Developmental Origins of Health and Disease (DOHaD) hypothesis posits that prenatal and early postnatal adversity can increase disease susceptibility across the lifespan (Gluckman et al. 2008). Since major neural networks mediating emotion and behavior develop prenatally, fetal exposure to sub-optimal intrauterine conditions, such as those associated with excessive maternal adiposity and gestational diabetes mellitus (GDM), may increase the risk of psychiatric disorders later in life (Bale et al. 2010; Tau and Peterson 2010). Indeed, numerous observational studies have linked prenatal exposure to pre-pregnancy adiposity, excessive gestational weight gain (GWG), and GDM to emotional, behavioral, and cognitive problems in offspring, problems that may emerge as early as 2 years of age (Nomura et al. 2012; Rivera et al. 2015; Van Lieshout et al. 2012). Additionally, the effects of both elevated maternal pre-pregnancy body mass index (BMI) together with excessive GWG may further increase risk for neurodevelopmental problems in offspring relative to either exposure alone (Huang et al. 2014).

Despite this evidence, our knowledge of the clinical applicability of the DOHaD hypothesis to the prevention and amelioration of mental disorders in children remains limited. A major barrier to this is a widespread inability to adjust for known modifiable confounding variables that may impact the link between prenatal metabolic complications and offspring behavior problems, such as maternal diet and postpartum depression (PPD). Investigating the potential confounding effect of these variables would provide a more complete understanding of the mechanisms underlying the observed associations between metabolic complications and offspring behavioral problems and could provide potential targets for intervention.

Given this background, we used data from the Edmonton site of the Canadian Healthy Infant Longitudinal Development (CHILD) Cohort study to determine if (1) maternal pre-pregnancy adiposity, GWG, their interaction, and/or GDM were associated with offspring behavioral problems at 2 years of age, and (2) if these associations persisted after accounting for key confounding variables including gestational diet and PPD. This study extends previous research in this area by examining the confounding effect of maternal diet quality during pregnancy, a previously unstudied confounder of associations between maternal metabolic complications and offspring emotional and behavioral problems.

Methods

Sample

The CHILD study is a longitudinal birth cohort study, recruiting pregnant women in their second and third trimesters from the general population in four centres across Canada (see Subbarao et al. 2015 for study details). Mother–child dyads (n=815), of which 586 (72%) had complete outcome data on child behaviour at 2 years (Fig. 1), enrolled in the Edmonton (Alberta, Canada) sub-cohort of the CHILD study were examined. Edmonton was the only CHILD study site that examined behavioural outcomes in children. Each woman had only one child in this study. Enrollment for this study was carried out between 2008 and 2012. Women provided informed consent prior to inclusion in the study and at each study visit. Women participating in the study provided data at enrollment and at follow up visits occurring at 36 weeks gestation and at 3, 12, 24 and 36 months postpartum. At each visit, women completed questionnaires about family and child characteristics (see Supplemental Table e1). In the current study, we used data collected during pregnancy and from the 12, 24 and 36-month visits. Women were excluded if they were younger than 18 years old, could not speak or read English, if they delivered a multiple birth, had conceived via in vitro fertilization, their infant had a major congenital abnormality or was born preterm (before 35.5 weeks gestation; preterm

<table>
<thead>
<tr>
<th>Assessed for eligibility at the CHILD Edmonton Site (n=848)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not meet inclusion criteria (n=33)</td>
</tr>
<tr>
<td>Total recruited for Edmonton CHILD sub-cohort (n=815)</td>
</tr>
<tr>
<td>Did not complete the CBCL (n=229)</td>
</tr>
<tr>
<td>Behaviour outcome data at two-year follow-up n=586 of 815 (72%)</td>
</tr>
</tbody>
</table>

Fig. 1 Flow diagram of the sample of individuals with CBCL outcome data at 2 years of age
infants were excluded since the original CHILD study investigated the development of allergy and asthma and infants born prior to 35.5 weeks can have respiratory problems making the diagnosis of asthma difficult. See Supplemental e2 and Takaro et al. 2015 for details). CHILD study ethics approval was obtained from the University of Alberta Health Ethics Research Office (Pro00002099).

Pre-pregnancy Body Mass Index (BMI)

In the province of Alberta, perinatal clinical data is captured and recorded in the Alberta Perinatal Health Program (APHP) (Kaul et al. 2015) database, which collects clinical information from all hospital and registered midwife deliveries within the province (Donovan et al. 2015). A total of 727 (89%) of women had BMI data. Maternal pre-pregnancy BMI (weight in kg/height m^2) was calculated using pre-pregnancy weight extracted from medical charts (n = 350), retrospectively reported when the child was 3 years of age (if the prenatal record was not available (n = 117)) or estimated by weight obtained at 1 year after birth (n = 260) if neither were available. Maternal height was obtained from medical charts (n = 332) or obtained when the child was 1 year of age (n = 395). Azad et al. (2016) also used this method to obtain BMI. No significant differences between women with BMI calculated from prenatal chart weight (M\text{charts} = 25.8, SD = 5.28) vs. those that retrospectively self-reported their weight (M\text{self-report} = 25.2, SD = 4.95; p = 0.29) were observed. No differences were found between women with BMI calculated from chart weight and the women with BMI data estimated using a weight variable obtained at 1 year after birth (M\text{1-year} = 26.5, SD = 6.6) (p = 0.06). BMI was examined as both a continuous and a dichotomous variable using World Health Organization BMI cut-offs defined as normal; BMI = 18.5–24.9 kg/m^2 versus overweight/obese; BMI ≥ 25 kg/m^2 (WHO 2009). We decided ‘a priori’ to exclude women who were underweight (n = 18) because complications in these women and their offspring differ from those manifesting the adverse effects of overnutrition (Buss et al. 2012; Van Lieshout et al. 2013).

Gestational Weight Gain (GWG)

Maternal GWG was determined by subtracting pre-pregnancy weight from the last weight recorded on the prenatal chart before delivery (at an average gestational age of 37.1 weeks, SD = 2.93). GWG was retrospectively self-reported when the child was 3 years of age if GWG was unavailable from the prenatal chart (n = 15). Those that were retrospectively self-reported (M = 13.5, SD = 4.30) were not different from those with prenatal chart data (M = 15.1, SD = 6.50) (p = 0.36). GWG was examined as a dichotomous variable in keeping with the Institute of Medicine guidelines (recommended vs. excessive). A GWG of > 15 kg was considered excessive for individuals with a normal BMI, while excessive GWG for the overweight/obese category comprised overweight women (BMI = 25–29.99) with a GWG > 11 kg, and obese women (BMI > 30) with GWG > 9 kg (Rasmussen and Yaktine 2009).

Gestational Diabetes Mellitus (GDM)

GDM is screened for between 24 and 28 weeks gestation and is captured and recorded in the APHP (Kaul et al. 2015) database. The woman’s diagnosis of GDM was obtained from the pregnancy record completed by their perinatal health care provider. A total of 805 women (98%) had GDM data. Plasma glucose levels were determined using a 1-h 50 g glucose challenge test (DynaLife Testing 2014). 1-h oral glucose tolerance test plasma glucose levels above 7.8 mmol/L defined GDM status.

Emotional and Behavioral Problems (Primary outcome)

Symptoms of emotion and behavioral problems in offspring were reported by mothers at the 24 month follow-up visit using the 1½–5 year-old version of the Child Behavior Checklist [CBCL 1½–5] (On average, mothers completed the CBCL when their children were 2.02 years of age (SD = 0.32)). The CBCL 1½–5 is a validated, 99-item measure of child behavior that can be aggregated into internalizing and externalizing scales (Achenbach and Rescorla 2000). The internalizing scale (36-items) is comprised of emotionally reactive, anxious/depressed, somatic complaints and withdrawn subscales (Cronbach α = 0.89). The 24 item externalizing scale (Cronbach α = 0.92) consists of aggressive behavior and attention problems subscales. Internalizing and externalizing raw scores were examined as continuous outcomes to fully capture behavioral variability and maximize statistical power. Higher scores on each of the CBCL scales indicate more behavioural problems.

Confounding Variables

Confounding variables were chosen on an a priori basis if the literature suggested consistent associations with both our predictors (pre-pregnancy BMI, GWG, GDM) and child emotional and behavioral problems.

Maternal Gestational Dietary Quality

A food frequency questionnaire (FFQ) developed by the Fred Hutchinson Cancer Research Center was modified to reflect Canadian multi-ethnic food choices. This 175-item self-administered FFQ was completed by women (n = 699/815, 86%) at study enrolment (in the second and third trimester).
Women reported the average frequency and portion sizes of food consumed since becoming pregnant.

From this FFQ, the overall quality of maternal diet in pregnancy was determined using the Healthy Eating Index-2010 (HEI-2010), a dietary quality index designed to capture dietary habits in accordance with accepted Dietary Guidelines for adults (Guenther et al. 2014). The HEI-2010 has been validated in numerous populations including pregnant women (Guenther et al. 2013). The HEI-2010 is comprised of 12 components: total fruit, whole fruit, total vegetables, greens + beans, whole grains, dairy, total protein foods, seafood + plant proteins, fatty acids, refined grains, sodium and empty calories which includes consumption of solid fats, alcohol, added sugar. The final three components are foods to be consumed in moderation and are therefore reverse scored. Hence, higher scores on all subscales indicate better quality of diet. All 12 components are summed to yield an HEI total score variable with a maximum of 100, the highest quality diet measureable. The HEI total score was used in all analyses. In acknowledgement of the potential causal association between an unhealthy diet, higher BMI and GWG, we considered gestational diet as a confounding variable in our adjusted models. Since the pre-pregnancy BMI and GWG predictor variables consider weight prior to pregnancy; we argue that our measure of diet quality assessed during gestation could not be causally associated to these pre-pregnancy predictor variables. However, a higher BMI and greater GWG may be associated with poorer diet during gestation.

Socioeconomic Status

Socioeconomic status (SES) was assessed using the McArthur scale of subjective social status at the 12 month visit (Adler et al. 2000). This instrument uses a visual analogue scale that consists of two ladders with ten rungs each. Women are instructed to place an ‘x’ on the rung of the ladder indicative of their social standing relative to other citizens nationally, and then compared to individuals within their community. This scale has shown adequate reliability and has convergent validity with objective SES indicators. This scale also predicts health outcomes over and above objective measures of SES (Cundiff et al. 2013).

Maternal Postpartum Depression

The Center for Epidemiological Studies Depression scale (CES-D) is a self-reported 20-item scale that is a reliable and valid measure of depression during the postpartum period and beyond (Navarro et al. 2007). The total score was used to assess maternal depression at 12 months postpartum.

Maternal Smoking During Pregnancy

At enrollment (second and third trimester), women were asked if they smoked cigarettes (yes/no) at any time during pregnancy.

Breastfeeding Duration

Mothers were asked to report the age (in months) at which their child stopped any breastfeeding at the 24-month visit.

Statistical Analyses

Associations between our predictors and outcomes were examined using two separate statistical regression models. The first contained each predictor and each outcome separately (unadjusted models). We also investigated the interaction between BMI and GWG using the interaction term of a 2 × 2, between-subjects ANOVA in the unadjusted model. Our second, fully adjusted statistical models contained the variables in each of the first models plus all confounding variables. Pre-pregnancy BMI was also added as a confounder in the adjusted analysis for GDM. We conducted a post-hoc analysis to investigate the unique contribution of each variable in the fully adjusted models using semipartial correlations (Johnson and Wichern 2014). All statistical tests were 2-tailed and statistical significance was set at \( \alpha = 0.05 \). Data were analyzed using IBM SPSS version 23. All continuous data passed the statistical assumptions for regression models (e.g., normality tests). All associations are displayed as unstandardized beta (B) values that indicate for every one-unit change in the predictor, an \( x \) unit change is observed in the outcome (e.g., a one point increase in BMI would be associated with an \( x \) increase in behavioral problems).

To account for missing data, we examined both complete case and imputed data. Missing data for all variables were imputed using the fully conditional specification multiple imputation in SPSS 23. Since no significant differences between completed case and imputed data were observed, the results reported used complete data only.

Missing pre-pregnancy BMI data was associated shorter breastfeeding duration \([M = 6.0 (5.6) vs. 8.7 (5.6), p < 0.01]\), single or separated relationship status (OR 0.39, 95% CI 0.20–0.77), Caucasian ethnicity (OR 0.59, 95% CI 0.37–0.96) and younger age \([M = 29.6 (5.2) vs. 31.5 (4.3), p < 0.01]\). Missing GWG data also associated with single or separated relationship status (OR 0.4, 95% CI 0.25–0.77). The nine women missing GDM data did not differ from those for whom data were present. No significant differences were observed between women with and without any of our metabolic predictors and offspring internalizing and externalizing problems. Finally, women that did not complete...
the CBCL on their children were younger \([M = 29.6 (5.0)\) vs. \(31.5 (4.4), p < 0.01\)] of lower SES \([M = 6.2 (1.8)\) vs. \(6.6 (1.63), p < 0.01\)] and had fewer years of education \([M = 15.5 (2.9)\) vs. \(16.2 (2.6), p < 0.01\)].

**Results**

The mean pre-pregnancy BMI of the sample was 26.1 (SD = 5.7) and mean age was 31.5 years (SD = 4.52). Women with a BMI in the overweight/obese range had fewer years of education, a lower HEI-2010 score, shorter breastfeeding duration, were of lower SES, and a greater proportion had excessive GWG relative to women within the normal BMI category. Those diagnosed with GDM were older, had infants with a younger gestational age, were more likely to be Caucasian, and reported lower SES compared to those without GDM (Table 1). The offspring average raw externalizing score was 9.8 (SD = 6.8) and scores ranged from 0 to 39. The average internalizing score was 5.1 (SD = 4.9) and the range was 0–34.

For our unadjusted models, statistically significant associations were observed between pre-pregnancy BMI examined as both a continuous and dichotomous (normal vs. overweight obese) predictor and offspring externalizing symptoms \((BMI_{\text{continuous}}: B = 0.15, 95\% \text{ CI } [0.05; 0.26];\)
BMI dichotomous: \( B = 1.60, 95\% \text{ CI } [0.45; 2.74] \) and internalizing symptoms (BMI continuous: \( B = 0.09, 95\% \text{ CI } [0.02; 0.16] \); BMI dichotomous: \( B = 1.2, 95\% \text{ CI } [0.35; 2.0] \)) at 2 years of age. Neither excessive GWG nor the interaction between BMI and GWG were associated with offspring outcomes. GDM was associated with higher levels of externalizing (\( B = 2.56, 95\% \text{ CI } [0.41; 4.71] \)) and internalizing (\( B = 2.28, 95\% \text{ CI } [0.75; 3.81] \)) symptoms (Table 2) Statistically significant associations were no longer observed between BMI, GDM, and internalizing and externalizing behaviors following adjustment for confounders (Table 3).

A *post-hoc* examination of semi-partial correlations between all variables in the fully adjusted models revealed that total scores on the HEI-2010, PPD at 12 months, and SES each independently accounted for statistically significant associations between our predictors and internalizing and externalizing problems. Semi-partial correlations display the unique variance of an individual variable in the model in the outcome while removing the influence that all other variables have on this outcome. Total diet accounted for the most unique variance in externalizing problems (\( r_{\text{part,diet}} = -0.20, p < 0.01 \)). Additionally, PPD and SES also accounted for a significant amount of variance in externalizing problems (\( r_{\text{part,PPD}} = 0.17, p < 0.01 \), \( r_{\text{part,ses}} = -0.11, p < 0.05 \)). These variables, along with smoking in pregnancy accounted for internalizing problems (\( r_{\text{part,smoke}} = 0.12, p < 0.05 \)) (semi-partial correlation coefficients between HEI-2010 total, PPDs scores, SES and offspring behavior problems within the adjusted BMI model are shown, see Table 4 for both BMI and GDM models).

Component subscale scores of the HEI-2010 were then substituted into fully adjusted models *in place* of total diet quality (e.g., the empty calories subscale (calories from solid fats and added sugars) was substituted into the adjusted model in place of HEI-2010 total). The empty calories component retained statistically significant associations with externalizing (\( r_{\text{part,empty cal}} = -0.18, p < 0.01 \)) and internalizing (\( r_{\text{part,empty cal}} = -0.12, p < 0.05 \)) in both the BMI and GDM fully adjusted models. A sensitivity analysis that utilized a predictor variable of BMI calculated using only recorded pre-pregnancy weights (\( n = 467 \) participants) confirmed these findings (Supplementary Tables e3, e4 and e5).

### Discussion

Prior to adjustment for confounding variables, statistically significant associations were observed between maternal pre-pregnancy BMI, GDM, and offspring externalizing and internalizing symptoms at 2 years of age. However, these were no longer significant after adjustment for known confounding variables. Indeed, associations between BMI and offspring emotional and behavioral problems were accounted for by each of maternal diet, PPD, and SES. To our knowledge, this is the first study to show that the effect of pre-pregnancy adiposity and GDM on offspring emotional and behavioral problems may be accounted for by poor maternal pregnancy diet, PPD, and SES.

Previously published studies have reported associations between maternal metabolic complications of pregnancy (GDM, pre-pregnancy BMI and GWG) and offspring

<table>
<thead>
<tr>
<th>Predictors (B, 95% CI)</th>
<th>Externalizing</th>
<th>Internalizing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index(^a)</td>
<td>0.15 (0.05; 0.26)**</td>
<td>0.09 (0.02; 0.16)*</td>
</tr>
<tr>
<td>Body mass index (categorical)(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal–overweight/obese</td>
<td>1.6 (0.45; 2.74)**</td>
<td>1.2 (0.35; 2.0)**</td>
</tr>
<tr>
<td>Gestational weight gain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate vs. excess(^c)</td>
<td>0.79 (−0.78; 2.37)</td>
<td>0.33 (−0.75; 1.40)</td>
</tr>
<tr>
<td>Body mass index × gestational weight Gain(^d)</td>
<td>1.91 (NS)</td>
<td>0.10 (NS)</td>
</tr>
<tr>
<td>GDM(^e)</td>
<td>2.56 (0.41; 4.71)*</td>
<td>2.28 (0.75; 3.81)**</td>
</tr>
</tbody>
</table>

Unstandardized betas (B) indicate for every one-unit increase in the predictor, there is an x-unit increase in the outcome

\(^a\)\(p < 0.05; \)\(^*\)\(p < 0.01\)

\(^a\)Continuous BMI (Of women that completed the CBCL, 569/586 (94%) also had BMI data)

\(^b\)Normal versus overweight (BMI 25–29.9) Obese (BMI > 30)

\(^c\)GWG was calculated separately for normal, overweight and obese BMI categories as per IOM guidelines: adequate = 11–15 kg for normal BMI, < 6 kg for overweight, < 4 kg for obese; excessive ≥ 15 kg for normal, > 11 kg for overweight, > 9 kg for obese

\(^d\)BMI (normal vs. overweight/obese) by GWG (adequate vs. excessive), \( F \) statistics shown from 2×2 between subjects ANOVA

\(^e\)For the GDM model, of the women that completed the CBCL, 582/586 (99%) had GDM data
behavior problems in young children (Nomura et al. 2012; Robinson et al. 2012; Van Lieshout et al. 2012). Most of this prior work has linked metabolic complications in pregnancy to delayed cognitive development (Pugh et al. 2015), autism spectrum disorders (Li et al. 2016) and externalizing problems including hyperactivity and inattention despite adjustment for confounders (Ornoy et al. 2015; Rodriguez 2010). However, to our knowledge, none contained data on maternal diet quality during pregnancy and few have assessed PPD using a validated scale.

Post-hoc analyses revealed that maternal diet quality, PPD, and SES each accounted for a significant amount of unique variance in offspring behavioral problems in fully adjusted models. However, overall maternal diet and particularly empty calories accounted for a significant amount of variance in both internalizing and externalizing problems. This supports previous findings that diet is linked to better offspring neurodevelopment outcomes (Bolduc et al. 2016; Nyaradi et al. 2013) and is similar to the results of large cohort studies that examined associations between diet in pregnancy and offspring externalizing problems at age 5 and 6 years (Jacka et al. 2013; Steenweg-de Graaff et al. 2014). However, these studies did not examine the role that gestational diet played in the associations between maternal BMI or GDM and offspring behavior.

Poor gestational diet, accounted for a significant amount of variance in offspring behaviour problems, even in the presence of well-known risk factors for offspring psychopathology such as SES and PPD. Moreover, the magnitude of the effect of poor maternal diet was similar to these established contributors to behavioral problems in early childhood. Therefore, future studies investigating the mental health and neurodevelopment of offspring exposed to maternal metabolic complications in-utero should adjust for maternal diet quality.

Further, we investigated the subscales of the HEI-2010 to determine if the effect of overall diet was driven by any dietary components in particular. Our finding that much of the effect of overall diet was driven by the empty calories scale of the HEI-2010 (e.g., calories from solid fats, added
Table 4  

Table 4  Post-hoc analyses of semi-partial correlations accounting for the associations between BMI, GDM and offspring behaviour problems at 2 years of age

<table>
<thead>
<tr>
<th>Model</th>
<th>Semi-partial correlation coefficients (r_s, p-value)</th>
<th>Externatizing</th>
<th>Internalizing</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (continuous)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal diet</td>
<td>−0.20 (&lt;0.01)</td>
<td>−0.16 (&lt;0.01)</td>
<td></td>
</tr>
<tr>
<td>Empty caloriesa</td>
<td>−0.18 (&lt;0.01)</td>
<td>−0.12 (&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>0.17 (&lt;0.01)</td>
<td>0.21 (&lt;0.01)</td>
<td></td>
</tr>
<tr>
<td>SES</td>
<td>−0.11 (&lt;0.05)</td>
<td>−0.14 (&lt;0.01)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>0.04 (N.S.)</td>
<td>0.12 (&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>−0.08 (N.S.)</td>
<td>−0.09 (N.S.)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.06 (N.S.)</td>
<td>0.03 (N.S.)</td>
<td></td>
</tr>
<tr>
<td>GDM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal diet</td>
<td>−0.20 (&lt;0.01)</td>
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<td>−0.08 (N.S.)</td>
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<td></td>
</tr>
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<td>BMI</td>
<td>0.05 (N.S.)</td>
<td>0.03 (N.S.)</td>
<td></td>
</tr>
<tr>
<td>GDM</td>
<td>0.07 (N.S.)</td>
<td>0.07 (N.S.)</td>
<td></td>
</tr>
</tbody>
</table>

Semi-partial correlations are used to display the unique variance that each individual variable in the fully adjusted model accounts for in the outcome while removing the influence that all other variables have on this outcome. (e.g., the unique variance that maternal diet accounts for in offspring behavioural problems while accounting for all other variables in the model).

aThe HEI-2010 (maternal diet) component that remained significant when added to the fully adjusted model in place of HEI-total.

sugar), is supported by studies in rodent models which have shown that high-fat diets can contribute to altered neurotransmitter signaling, neuroendocrine dysregulation and inflammation (Golan et al. 2005; Sullivan et al. 2015). These effects appear to be mediated by epigenetic alterations in offspring mesocorticolimbic dopamine systems (Vucetic et al. 2010). Indeed, chronically low dopamine levels developing in response to hypomethylation of the promoter region of the dopamine transporter gene could produce an increased propensity of reward seeking behaviors in order to restore homeostatic dopamine balance (Vucetic et al. 2010). Epigenetic alterations occurring in response to maternal high fat diets could therefore potentially be involved in the development of behaviour problems in humans.

The results of this study should be interpreted with the following limitations in mind. First, the observational nature of this study limits causal inference. Second, whether our measurement of diet quality specifically measures nutrition during pregnancy or longer-term dietary habits (e.g., before pregnancy, or across a woman’s whole life) that may influence offspring neurodevelopment is unclear. Third, these associations may be due to confounders of links between dietary quality and our outcomes. Fourth, although we adjusted for breastfeeding duration, we cannot rule out the possibility that child postnatal diet outside of breastfeeding contributes to these findings, because we did not have access to these data. However, Jacka et al. (2013) did adjust for child diet and found that maternal prenatal diet retained significant associations with offspring externalizing problems. We also were unable to adjusted for exclusive breastfeeding. Fifth, we only had reports on offspring from a single informant (the child’s mother). Sixth, a subset of our maternal weight values were not obtained from prenatal charts, therefore, although these values were not different from prenatal chart weights, they may be subject to response bias. Finally, we did not have the capacity to control for genetic factors potentially influencing maternal behaviors including dietary choices. However, the CHILD study is in the process of obtaining and analysing genetic data, providing opportunities to consider these factors in future research.

In order to further advance the field, future observational studies should attempt to examine other potentially modifiable confounders of associations between metabolic complications during pregnancy and offspring neurodevelopmental outcomes including maternal physical inactivity. These studies could also examine the interactions between metabolic complications and behavioral lifestyle factors (e.g., nutrition, physical inactivity) to further elucidate the impact of these exposures on offspring neurodevelopment. Future studies should also investigate these associations using larger more diverse sample sizes. Studies should also examine more specific components of offspring behavior problems (e.g., impulsivity, reward sensitivity). Ongoing randomized controlled trials of maternal lifestyle interventions could also be utilized to investigate the impact of maternal lifestyle on offspring brain and behavior. If improving diet prenatally is shown to benefit offspring neurodevelopment, these interventions could have immense public health potential (Van Lieshout and Krzeczkowski 2016).

Our data suggest that associations between maternal metabolic complications during pregnancy and offspring behavior problems are accounted for by SES, PPD and maternal diet. Since numerous studies have observed moderate to strong continuity between behavior and emotion problems in early childhood and adult psychopathology, the examination of modifiable risk factors for emotional and behavioral problems is integral to the prevention and/or amelioration of mental disorders across the lifespan. Given the significant preventive promise of the DOHaD hypothesis, future studies should attempt to determine if optimizing maternal diet during pregnancy could be utilized to improve offspring neurodevelopment, in addition to its other well-known benefits for women and children.
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Compliance with Ethical Standards

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