



Short Communication

Prenatal maternal mental health symptoms predict infant leptin at birth

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ABSTRACT

Childhood obesity can be predicted by metabolic signaling at birth. Understanding what exposure factors, such as prenatal mental health, predict metabolic signaling at birth are important for understanding the etiology of childhood metabolic dysregulation. Drawing on data from the Born in Bradford (BiB) multi-ethnic birth cohort in the United Kingdom ($N = 2962$ dyads), this study examined associations between maternal prenatal mental health symptoms and infant leptin and adiponectin. We tested whether total maternal prenatal symptoms as well as specific symptom subscales forecasted infant cord blood levels of leptin and adiponectin. We found that higher total maternal mental health symptoms and somatic symptoms, specifically, predicted lower infant cord blood leptin. We did not find evidence that maternal prenatal mental health symptoms predicted adiponectin. Together, our findings suggest that maternal mental health symptoms may become biologically embedded through infant metabolic changes via leptin.

1. Introduction

Childhood obesity affects more than 18% of children in the United States (Hales et al., 2018) and costs the health care system billions of dollars (Kompaniyets et al., 2020). In recent years, researchers have established that childhood obesity can be predicted by metabolic signaling at birth (Chaoimh et al., 2016; Mantzoros et al., 2009) and that differences in metabolic regulation start almost instantly after a child is born (Gruszfeld et al., 2016). As such, determining prenatal exposure factors that contribute to metabolic markers at birth is important for understanding the etiology of childhood metabolic dysregulation.

Research on infant metabolic proteins, termed adipocytokines, is an emerging area. Metabolic proteins, such as leptin and adiponectin, are secreted by adipose tissue and signal energy availability (Ahima, 2006). Leptin acts on hypothalamic pathways in the brain by both activating catabolic neuronal circuits to inhibit appetite and increase energy expenditure and dampening anabolic neuronal circuits responsible for stimulating appetite and inhibiting energy expenditure, depending on energy intake (Stofkova, 2009). Generally, higher leptin in infancy predicts more adaptive outcomes, including higher birthweight, lower Body Mass Index (BMI) in childhood, and slower weight gain between birth and 2 months of age (Chaoimh et al., 2016; Mantzoros et al., 2009). Adiponectin is anti-inflammatory and inversely associated with leptin and Body Mass Index (BMI) (Matsubara et al., 2002). Higher adiponectin is also associated with improved insulin sensitivity and metabolic

regulation (Stofkova, 2009; Kadowaki and Yamauchi, 2005). Fetal adiponectin likely contributes to fetal growth both in utero and postnatally in the first years of life (Mazaki-Tovi et al., 2005, 2011; Fasting et al., 2009), but this research is limited. While there is limited research regarding adiponectin, its association with leptin (Matsubara et al., 2002) suggests it may also be important in early metabolic health.

One exposure factor that may predict infant metabolic signaling is prenatal maternal mental health symptoms. The fetal programming hypothesis states that a stimulus or insult during gestation, such as exposure to maternal prenatal mental health symptoms, can have health implications for offspring (Barker, 1998; Beydoun and Saftlas, 2008), including metabolic and obesity-related disorders (Entringer et al., 2012). Prenatal mental health symptoms are common, with an estimated 12% of pregnant people experiencing depression (Woody et al., 2017) and 15% experiencing clinical levels of anxiety (Dennis et al., 2021). Additionally, between one third to more than one half of pregnant individuals report mild to moderate stress (Loomans et al., 2013). Consequently, prenatal mental health is considered a significant public health issue (Sherbourne et al., 2001).

Two relevant biological processes that may transmit metabolic risk to the infant from maternal mental health symptoms include activation of the pregnant person's Hypothalamic Pituitary Adrenal (HPA) axis (Davis et al., 2007; O'Donnell and Meaney, 2017), and chronic, low grade inflammation (Christian, 2012; Gumusoglu and Stevens, 2019). Aberrant patterns in both processes are observed in pregnant individuals experiencing mental health symptoms (Lahti-Pulkkinen et al., 2020; Seth et al., 2016). Briefly, maternal-placental-fetal hormones and pro-inflammatory cytokines play crucial roles during gestation in cell division and

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migration, and tissue formation, which likely affects the structure and function of fetal biological systems (Entringer et al., 2012; Barouki et al., 2012). This complex signaling between the pregnant person and fetus is sensitive to neurobiological changes associated with maternal mental health symptoms, consistent with evolutionary biology theory (Barouki et al., 2012; Gluckman et al., 2011). Environmental signals during gestation prepare fetuses for the environments they will enter. In regards to metabolism, exposure to mental health symptoms should plausibly prepare the infant for an environment where basic nutritional needs may not be met (Entringer, 2013). Lower levels of leptin at birth, for instance, are associated with a higher weight gain between the ages of 0 and 2 (Chaoimh et al., 2016; Mantzoros et al., 2009), an adaptive trait for infants who may not receive adequate nutrition. But while adaptive in the shorter term, there are also adverse consequences. A higher weight gain between the ages of 0 and 2 predicts both child and adult obesity and metabolic disorders (Druet et al., 2012).

The fetal programming literature focuses on stress, depression, and anxiety during pregnancy (Beydoun and Saftlas, 2008; Davis et al., 2007; Kingston and Tough, 2014; Leis et al., 2014). However, researchers have called for further investigation of associations between other mental health symptom domains experienced during pregnancy, such as somatic symptoms, and infant health (Nylen et al., 2013). Somatic symptoms refer to medically unexplainable physical symptoms that often co-occur with mental health disorders (Simon et al., 1999). An uptick in somatic symptoms, such as sleep disruption, changes in appetite, and fatigue, across pregnancy is expected (Kelly et al., 2001). However, somatic symptoms may be more indicative of mental health challenges rather than “normal aches and pains” associated with pregnancy (Nylen et al., 2013; Kelly et al., 2001), and are less studied. For instance, higher stress is associated with migraines and sleep disturbances in pregnancy (Williams et al., 2010). Therefore, a more nuanced understanding of distinct symptoms with regard to fetal programming effects is crucial for identifying underlying biobehavioral pathways and capturing mental health symptoms that may otherwise be obscured.

Drawing on data from a large-scale multi-ethnic birth cohort in England, the current exploratory study examined associations between maternal prenatal mental health symptoms and infant adipocytokines at birth. We tested whether total maternal prenatal symptoms as well as specific symptom subscales forecast differences in cord blood levels of leptin and adiponectin to provide initial data on potential contributors to infant metabolic profiles.

2. Method

2.1. Born in Bradford cohort study

The Born in Bradford (BiB) Birth Cohort study (Wright et al., 2013) was established to investigate child morbidity and mortality in Bradford, United Kingdom (UK). About 20% of the half-million residents are of South Asian ethnicity (majorly Pakistani) and urban communities in Bradford are among the poorest in the UK. Between March 2007–November 2010, 12,453 pregnant women with 13,776 pregnancies between 26- to 28-weeks’ gestation were recruited to participate. Enrollment rates were high, with 80% of approached women agreeing to participate. The National Health Service Research Ethics Committee (protocol no:06/Q1202/48) granted ethical approval and participants provided written informed consent. Questionnaires were administered in the participant’s preferred language (i.e., English, Urdu, or Mirpuri).

The present study examines a subset of participants from the larger project who provided complete data on prenatal maternal mental health symptoms at baseline (26–28 weeks’ gestation), and cord blood leptin and/or adiponectin ($N = 2962$ dyads for leptin models, $N = 1059$ for adiponectin models). All cases with maternal mental health symptoms and cord blood data were included. Independent subjects t-tests revealed that mothers with full data compared to those with missing data were slightly older ($M = 28.7$ vs. 27.9 years), but had similar rates of infant sex

type, cohabitation status, and income (Table 1).

2.2. Measures

2.2.1. Maternal prenatal mental health symptoms

The 28-item General Health Questionnaire (GHQ) assesses psychological symptoms (Goldberg and Hillier, 1979). The four subscales include: somatic (e.g., “have you recently been getting any pains in your head?”), social (e.g., “have you recently felt that you are playing a useful part in things?”), anxiety (e.g., “have you recently been getting scared or panicky for no good reason?”), and depressive symptoms (e.g., “have you recently felt that life is entirely hopeless?”). The GHQ is completed on a 4-point Likert scale (1 = *better than usual* to 4 = *worse than usual*). This measure has been validated in adult outpatient clinic settings and has shown high internal reliability, $\alpha = 0.86$ (Banks, 1983). This measure also demonstrates high internal reliability in our sample, $\alpha = 0.90$. Higher scores correspond to worse symptomology.

2.2.2. Infant cord blood adipocytokines

Cord blood samples were taken at birth and refrigerated at 4 °C in ethylenediamine tetraacetic acid (EDTA) tubes. Within 12 h of collection, samples were spun and frozen at –80 °C. The Glasgow Royal Infirmary Department of Biochemistry measured leptin and adiponectin using enzyme-linked immunosorbent assays (Wright et al., 2013; West et al., 2014).

2.2.3. Covariates

Child sex and BMI at birth; and maternal ethnicity, and race were recorded from maternal and child medical records. Maternal age, household income, and cohabitation status were assessed by self-report. Household income was quantified as an income decile relative to all United Kingdom’s incomes in 2007. Adipocytokine levels differ by sex and BMI (Lönnerdal and Havel, 2000), as well as age and race/ethnicity (Ambrosius et al., 1998). The extent to which prenatal mental health symptoms can affect offspring biology may differ by income (Gajaria and Ravindran, 2018) or cohabitation status (Sexton et al., 2012). Therefore, we covaried for these variables.

2.3. Data analysis plan

To investigate associations between maternal prenatal mental health symptoms and infant cord blood leptin and adiponectin, we performed multivariate linear regressions. We ran models by the total GHQ score,

Table 1
Descriptive statistics for study variables.

Variable	<i>M</i>	<i>SD</i>	Range
Cord Blood Leptin (ng/mL)	10.05	9.19	0.15–47.04
Cord Blood Adiponectin (ng/mL)	32.11	12.88	3.40–71.63
Maternal Mental Health			
Total	51.25	10.71	28.00–83.37
Somatic	14.17	3.87	7.00–25.84
Social	15.05	2.32	7.00–22.33
Anxiety	13.66	4.64	7.00–27.49
Depression	8.31	2.29	7.00–16.55
Income	2.54	2.03	1.00–10.00
Mother Age (Years) ⁺	27.95	5.60	15.00–44.17
Infant BMI	13.31	1.34	8.92–22.17
Sex (Child)			
Male	51.50%		
Female	48.50%		
Ethnicity			
White-British	37.10%		
Pakistani-British	41.50%		
Cohabitation Status			
Lives with Baby’s Father	83.00%		

⁺ Current sample significantly differed from those with incomplete data for this variable, $p < .001$.

and four GHQ subscale scores for each adipocytokine, resulting in ten regression models. The GHQ subscale scores enable us to explore more specific dimensions of psychopathology symptoms for adults. In each model, we covaried for child sex, maternal age at birth, ethnicity, cohabitation status, BMI at birth, and income.

3. Results

3.1. Maternal prenatal mental health symptoms as a predictor of cord blood leptin

We ran a series of multivariate linear regression models to determine if maternal prenatal mental health symptoms predicted cord blood leptin. Here, we found that total maternal prenatal mental health symptoms predicted lower infant cord blood leptin ($B_{\text{Mental Health Total}} = -0.03$, $SE = 0.02$, $p = .040$). To explore if certain dimensions of maternal mental health symptoms predicted leptin, we ran a series of models with the GHQ symptom subscales as the independent variables. Somatic symptoms significantly predicted lower leptin ($B_{\text{Somatic}} = -0.08$, $SE = 0.04$, $p = .042$). Anxiety symptoms marginally predicted lower leptin ($B_{\text{Anxiety}} = -0.06$, $SE = 0.03$, $p = .069$), however social and depressive symptoms did not (Table 2, Supplementary Material).

3.2. Maternal prenatal mental health symptoms as a predictor of cord blood adiponectin

We ran a series of multivariate linear regression models to determine if maternal prenatal mental health symptoms predicted cord blood adiponectin. Total maternal mental health symptoms did not predict infant adiponectin ($B_{\text{Mental Health Total}} = 0.01$, $SE = 0.04$, $p = .831$). None of the symptom subscales predicted infant adiponectin. (Table 2, Supplementary Material).

Table 2
Abbreviated main effect regression models predicting infant adipocytokines.

Predictor	B	SE	t	p	sr ²
Leptin by GHQ-Total Symptoms					
Intercept	7.55	0.60	12.57	.000	
GHQ-Total	-0.03	0.02	-2.05	.040	-.04
Leptin by GHQ-Somatic Subscale					
Intercept	7.49	0.60	12.46	.000	
GHQ-Somatic	-0.08	0.04	-2.04	.042	-.04
Leptin by GHQ-Social Subscale					
Intercept	7.56	0.60	12.53	.000	
GHQ-Social	-0.09	0.07	-1.37	.169	-.02
Leptin by GHQ-Anxiety Subscale					
Intercept	7.56	0.60	12.56	.000	
GHQ-Anxiety	-0.06	0.03	-1.82	.069	-.03
Leptin by GHQ-Depression Subscale					
Intercept	7.61	0.61	12.55	.000	
GHQ-Depression	-0.09	0.07	-1.31	.189	-.02
Adiponectin by GHQ-Total Symptoms					
Intercept	30.28	1.53	19.81	.000	
GHQ-Total	0.01	0.04	0.21	.831	.01
Adiponectin by GHQ-Somatic Subscale					
Intercept	30.24	1.53	19.77	.000	
GHQ-Somatic	-0.06	0.10	-0.64	.525	-.02
Adiponectin by GHQ-Social Subscale					
Intercept	30.28	1.53	19.81	.000	
GHQ-Social	0.15	0.17	0.90	.367	.03
Adiponectin by GHQ-Anxiety Subscale					
Intercept	30.28	1.53	19.80	.000	
GHQ-Anxiety	0.02	0.08	0.19	.852	.01
Adiponectin by GHQ-Depression Subscale					
Intercept	30.15	1.54	19.58	.000	
GHQ-Depression	0.15	0.17	0.88	.381	.03

4. Discussion

The purpose of this exploratory study was to investigate associations between maternal prenatal mental health symptoms and infant cord blood leptin and adiponectin. We found that higher maternal total mental health symptoms during pregnancy and specifically, somatic symptoms, predicted lower infant leptin. Maternal prenatal mental health symptoms did not predict adiponectin.

This is the first study to our knowledge to investigate and identify associations between higher maternal prenatal mental health symptoms and lower infant leptin at birth, and with the benefit of a large, diverse sample. Low leptin in infants is thought to contribute to risk for Type 2 diabetes and obesity (Stocker and Cawthorne, 2008). In fact, researchers have proposed that leptin supplementation for infants may decrease the risk of developing an adverse metabolic phenotype (Stocker and Cawthorne, 2008). Here, we also found that maternal somatic symptoms predicted lower leptin in infants. In adults, a depressive profile with somatic symptoms is associated with abnormal leptin signaling (Milaneschi et al., 2017), however this has yet to be demonstrated in pregnant individuals. Given the positive correlation between maternal and fetal leptin (Walsh et al., 2014), it is plausible that the biologic signaling associated with maternal somatic symptoms may also affect infant leptin. This transmission likely occurs via HPA axis activation and chronic low grade inflammation (Davis et al., 2007; O'Donnell and Meaney, 2017; Christian, 2012; Gumusoglu and Stevens, 2019; Lahti-Pulkkinen et al., 2020; Seth et al., 2016), however, future research is needed to further explore underlying mechanisms.

Although this area of research is limited, our findings raise the possibility that maternal prenatal mental health symptoms may predict differences in infant leptin, which is an emerging important marker of child health risk. If replicated with additional research, metabolic risks associated with exposure to maternal prenatal mental health symptoms could potentially be mitigated (e.g., supplementation) or targeted preventatively (e.g., early childhood obesity intervention programs).

We did not find evidence that maternal prenatal mental health symptoms predicted infant adiponectin. The importance of adiponectin is better established in adulthood, where it is inversely associated with BMI, but is less clear in infancy (Mantzoros et al., 2009; Matsubara et al., 2002; Arita et al., 2012). It is possible that programming effects on adiponectin may not appear until later in development. Alternatively, biological changes associated with maternal prenatal mental health symptoms may not affect infant adiponectin levels. Cortisol is thought to be the mechanism through which maternal mental health symptoms can affect the fetus (Godfrey and Barker, 2001; Kapoor et al., 2006; Davis and Sandman, 2010), but is only associated with leptin (Wabitsch et al., 1996), not adiponectin (Weber-Hamann et al., 2007), in adults. Therefore, it is possible that maternal prenatal mental health symptoms may not act on fetal biological pathways that affect adiponectin.

Our findings have several limitations. First, the underlying biological mechanism is unclear. Our results only indicate associations, and do not reveal causal pathways. Our study was exploratory and hypothesis generating in nature, but we recognize the risk of Type 1 error as a limitation to these analyses. Future research is certainly needed to replicate these findings. Another limitation is that our sample is comprised of individuals living in Bradford, UK. Universal health care and social programs in the UK may overcome some of the challenges related to health care accessibility that would compound infant health challenges, potentially making our findings less generalizable countries with fewer social welfare resources. At the same time, the BiB birth cohort is one of the most ethnically and socioeconomically diverse large-scale birth cohorts in the world, likely capturing experiences beyond those of exclusively White, middle-upper class families who comprise the majority of English-language developmental research (Grosser et al., 2016). Additionally, our analyses assessed maternal mental health symptoms dimensionally, as opposed to utilizing clinical-cut off scores. While future research should certainly examine differences in infant

leptin and adiponectin between clinical and non-clinical parent groups, dimensional approaches capture experiences of individuals with sub-threshold symptoms. Finally, maternal mental health symptoms were assessed between 26 and 28 weeks of gestation. We do not yet know if mental health symptoms experienced in other prenatal periods are associated with infant leptin or adiponectin, or if the 26–28 week window represents a sensitive period for infant leptin. Lastly, we were unable to control for maternal BMI during or pre-pregnancy or for any mental health care services received.

Importantly, there are notable exceptions to associations between higher leptin and more adaptive outcomes in adult samples (Castro-Rodriguez et al., 2020; Clapp and Kiess, 1998), such that we caution the interpretation of our findings. In adults, low leptin indicates a deficiency (Montague et al., 1997) and high levels indicate potential leptin resistance (Myers et al., 2012), both of which are associated with adverse health effects. Additionally, in one infant study, higher leptin predicted higher insulin and Interleukin (IL)-10, and a higher risk of developing asthma in infants of obese mothers (Castro-Rodriguez et al., 2020). Higher fetal leptin has also been associated with higher fetal fat mass (West et al., 2014; Clapp and Kiess, 1998; Lepercq et al., 2001). While our findings held covarying for infant BMI, we likely did not capture nuances of metabolic signaling in the context of obesity during pregnancy. Future research is certainly needed to assess associations found here in higher risk pregnancies (e.g., gestational diabetes, obesity). Additionally, as mentioned above, we were unable to covary for maternal BMI variables.

The future research opportunities in this area remain ample. First, greater clarity surrounding the later health correlates of leptin in cord blood is needed, including systematic reviews of existing research. While much of the literature suggests that higher leptin forecasts better infant and child outcomes (Chaoimh et al., 2016; Mantzoros et al., 2009), there are exceptions as discussed above (West et al., 2014; Castro-Rodriguez et al., 2020; Clapp and Kiess, 1998; Lepercq et al., 2001), making our findings difficult to contextualize. Similarly, the literature on infant adiponectin and its implications for child health outcomes is scarce. Further work should also investigate mental health symptom dimensions not assessed here, such as neurodevelopmental disorder symptoms (e.g., hyperactivity) and psychosis-spectrum symptoms.

To our knowledge, this study is the first to investigate associations between maternal prenatal mental health symptoms and infant adipocytokines. We found that prenatal maternal mental health symptoms predicted infant leptin, but not adiponectin. Our findings contribute to an important emerging area of the literature, especially in terms of understanding fetal programming effects of maternal mental health symptoms during pregnancy.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bbih.2021.100317>.

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