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Associations of maternal weight status prior and during pregnancy with neonatal cardio-metabolic markers at birth: The Healthy Start Study

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Abstract

Background—Maternal obesity increases adult offspring risk for cardiovascular disease; however the role of offspring adiposity in mediating this association remains poorly characterized.

Objective—To investigate the associations of maternal pre-pregnant body mass index (maternal BMI) and gestational weight gain (GWG) with neonatal cardio-metabolic markers independent of fetal growth and neonatal adiposity.

Methods—A total of 753 maternal-infant pairs from the Healthy Start study, a large multi-ethnic pre-birth observational cohort were used. Neonatal cardio-metabolic markers included cord blood glucose, insulin, glucose-to-insulin ratio (Glu/Ins), total and high-density lipoprotein cholesterol (HDL-c), triglycerides, free fatty acids and leptin. Maternal BMI was abstracted from medical records or self-reported. GWG was calculated as the difference between the first pre-pregnant

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CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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weight and the last weight measurement before delivery. Neonatal adiposity (percent fat mass) was measured within 72 hours of delivery using whole body air displacement plethysmography.

Results—In covariate adjusted models, maternal BMI was positively associated with cord blood insulin (p=0.01) and leptin (p<0.001) levels and inversely associated with cord blood HDL-c (p=0.05) and Glu/Ins (p=0.003). Adjustment for fetal growth or neonatal adiposity attenuated the effect of maternal BMI on neonatal insulin, rendering the association non-significant. However, maternal BMI remained associated with higher leptin (p<0.0011), lower HDL-c (p=0.02) and Glu/Ins (p=0.05), independent of neonatal adiposity. GWG was positively associated with neonatal insulin (p=0.02), glucose (p=0.03) and leptin levels (p<0.001) and negatively associated with Glu/Ins (p=0.006). After adjusting for neonatal adiposity, GWG remained associated with higher neonatal glucose (p=0.02) and leptin levels (p=0.02) and lower Glu/Ins (p=0.048).

Conclusions—Maternal weight prior and/or during pregnancy is associated with neonatal cardio-metabolic makers including leptin, glucose, and HDL-c at delivery, independent of neonatal adiposity. Our results suggest that intrauterine exposure to maternal obesity influences metabolic processes beyond fetal growth and fat accretion.

Keywords

Maternal obesity; Pregnancy; Cardio-metabolic risk; Leptin

INTRODUCTION

Offspring of obese mothers have greater risk of adult obesity, diabetes and cardiovascular disease (CVD) later in life[1]. However, it is not clear whether the increased risk for future diabetes and CVD conferred by exposure to maternal obesity is completely mediated by development of obesity in the offspring. It is also not clear whether these associations are present very early in life, i.e., among neonates, which would lend additional support to the fetal programming component of the developmental overnutrition hypothesis[2–4].

In studies on adolescents, maternal pre-pregnant BMI was associated with offspring lipid and inflammatory markers; however these associations were largely mediated by offspring adiposity[5]. In contrast, offspring BMI in an adult cohort (mean age 23.8 yrs) did not completely mediate the association between maternal pre-pregnant BMI and offspring risk of developing type 2 diabetes[6]. During infancy, there are currently only a limited number of studies that have investigated maternal obesity associations with offspring neonatal cardio-metabolic outcomes, with somewhat contradictory results. In a cohort of 121 singleton term pregnancies, neonatal fat mass and percent body fat did not mediate the association between maternal pre-pregnant BMI and neonatal estimated insulin resistance[7]. Consistent with these results, infant fat mass at birth was not a significant predictor of offspring insulin resistance in cohort of 67 young adults (23 years of age) delivered to lean and obese mothers[8]. In contrast, a prospective cohort of 248 mother-offspring pairs reported that infant ponderal index mediated the relationship between obese pregnancies and cord blood plasma glucose-to-insulin ratio and insulin concentrations[9].

Given that maternal obesity is associated with infant fat mass at delivery[10–12]; it is important to determine whether offspring size and adiposity are factors that mediate the association between maternal weight status prior and during pregnancy with offspring cardio-metabolic markers of future risk[5,13]. Cross-sectional data in population-based studies during pregnancy and early development will further our understanding fetal programming of obesity and improve our ability to design and implement appropriate primordial prevention intervention studies.

MATERIALS AND METHODS

Population

Data used in this analysis were obtained from the Healthy Start study, a longitudinal, pre-birth cohort of ethnically diverse pregnant women and their offspring in Colorado. Women 16 years or older and who were less than 24 weeks gestation were recruited from the University hospital obstetric clinics from 2009–2014. Women were excluded if they were expecting multiple births, had a previous stillbirth or preterm birth prior to 25 weeks gestation, had pre-existing diabetes, asthma managed with steroids, cancer, or had a serious psychiatric illness. All participants provided written informed-consent before enrolling. The Healthy Start study was approved by the Colorado Multiple Institutional Review Board and is registered as an observational study at clinicaltrials.gov as NCT02273297.

The eligible cohort for this analysis included 1,012 mother-infant dyads that delivered between March 2010 and August 2014, had a gestational age ≥ 37 weeks, and complete neonatal body composition (fat mass, fat-free mass, and fat mass percent) measured within 3 days following delivery. The analytical data set included 753 mother-infant dyads with complete data on all variables of interest. The 753 mother-infant dyads in the present analysis were similar to the 1,012 participants from the eligible cohort with regards to maternal age, pre-pregnant BMI, observed gestational weight gain, income, race-ethnicity, gravidity, smoking, mode of delivery, infant sex, gestational age at birth and birth weight (Supplementary Table 1).

Assessment of Neonatal Cardio-Metabolic Outcomes

Infant metabolic markers were measured in cord blood drawn at the time of delivery and processed by the University of Colorado Clinical and Translational Sciences Institute (CCTSI) Core Lab. Insulin (μU/mL) in serum and plasma was measured using radioimmunoassay (EMD Millipore Corporation, Billerica, MA). Glucose (mg/dl), cholesterol (mg/dl), HD-cL total (mg/dl), non-HDL-c (mg/dl), triglycerides (mg/dl), and free fatty acids (μmol/l) were measured using manufacture prepackaged enzymatic kits and the AU400e Chemistry Analyzer (Olympus America, Center Valley, PA). Cord serum leptin levels were determined by ELISA (Alpco, Salem, NH). We calculated insulin sensitivity as the ratio of neonatal glucose and insulin as described previously[9,14,15].

Assessment of Infant Birth Weight and Adiposity

Birth weight was abstracted from delivery medical records. Neonatal body composition, including body mass (g), fat mass (g), fat-free mass (g), and percent fat mass (%FM) was

measured within 72 hours of delivery using whole body air displacement plethysmography (PEA POD, Life Measurement, Inc.)[16,17]. The PEA POD technique uses a two compartment model to estimate fat mass (i.e. adipose tissue) and fat-free mass (i.e. bone, water, and non-bone mineral protein). At least two PEA POD measurements were collected for each neonate by trained clinical research personnel. The measure of neonatal adiposity in this analysis was calculated as %FM using the average of the two closest fat mass and body mass measurements.

Assessment of Maternal Pre-Pregnant BMI and GWG

Maternal pre-pregnant BMI was calculated from pre-pregnancy weight (kg) divided by height squared (m^2). Maternal height was recorded at the first in-person interview, by clinic staff using stadiometry. Maternal pre-pregnant weight was collected through medical record abstraction or self-reported at first visit (89.8% and 10.2% respectively). Pre-pregnant BMI was categorized as defined as normal weight (NW, pre-pregnant BMI < 25 kg/m^2), overweight (OW, pre-pregnant BMI 25–30 kg/m^2) and obese (Ob, pre-pregnant BMI >30 kg/m^2). GWG was calculated for the entire pregnancy as the difference between the pre-pregnant weight measurement and the last weight measurement before delivery.

Maternal and Infant Covariates

Gestational age of the infant was based on clinical assessment at the first prenatal visit and ultrasound examination. Maternal fasting glucose were measured during late gestation and processed by the CCTSI. Maternal age at delivery was calculated by subtracting maternal date of birth from infant delivery date. Household income, maternal education, maternal smoking during pregnancy, number of previous pregnancies as well as maternal race and ethnicity were obtained from study-specific questionnaires.

Statistical Analysis

Descriptive statistics were generated for maternal and infant characteristics by maternal pre-pregnancy BMI (NW, OW, and Ob). Differences across the categories of maternal BMI were tested using analysis of variance (ANOVA) for continuous variables. For categorical characteristics, Cochran-Mantel-Haenszel tests were used to test for associations between the outcomes and the predictors. The row mean score differ statistic was used if the outcome variable was ordinal and the predictor was not. The correlation statistic was used if both outcome and predictor were ordinal. The general association statistic was used if neither outcome nor predictor were ordinal. For continuous characteristics, partial F tests were used to compare means between pre-pregnant BMI categories. Multivariable linear regression models were used to evaluate the effects of pre-pregnant BMI and GWG on each neonatal cardio-metabolic outcome with subsequent adjustment for covariate groups. The base model (Model 1) assessed the association of maternal exposures, BMI and GWG, with neonatal cardio-metabolic outcomes, after adjusting for maternal and infant covariates including: offspring gestational age and sex, maternal age, gravidity, race/ethnicity, pre-pregnancy BMI (when GWG was examined) and GWG (when maternal BMI was explored), smoking throughout pregnancy and household income. Model 2 included all terms in Model 1 and additionally adjusted for birth weight. Finally, model 3 included all terms in Model 1 as well as adjusting for neonatal %FM. We interpreted birth weight (Model 2) or neonatal %FM

(Model 3) as mediators of the relationship between maternal exposure and neonatal outcomes when the significance (p-value) of the association between maternal BMI/GWG and neonatal outcomes was attenuated and/or became no longer significant once infant birth weight or neonatal adiposity were included in the model. We did not correct for multiple testing as we treated each outcome being tested as representing a separate family of null hypotheses[18]. The analysis presented in this study was based on large observational cohort (N=753) with available data. The study was not specifically powered for this analysis. All data presented met the assumptions of the statistical tests and the analyses were conducted using the plyr[19], car[20], and lsmeans[21] packages implemented in the R statistical language, version 3.1.1[22] using R-Studio, version 0.98.501[23].

RESULTS

Table 1 presents maternal and neonatal characteristics by pre-pregnancy BMI category. Obese mothers were less likely to be non-Hispanic white (39%; $p<0.001$), more likely to be nulliparous ($p<0.001$) and to have given birth by caesarian section ($p=0.025$). Furthermore, obese mothers were more likely to come from households with a combined income of less than $20,000 per year (30%, $p<0.001$) and a higher pre-delivery fasting glucose levels ($p<0.001$). Offspring of obese mothers had significantly higher birth weight ($p=0.006$), %FM ($p<0.001$), cord blood insulin ($p=0.038$) and leptin levels ($p<0.001$), as well as significantly lower glucose/insulin ratios ($p=0.005$) and non-HDL-c levels ($p=0.005$).

Table 2 presents the associations of continuous measures of pre-pregnant BMI and GWG with neonatal cardio-metabolic markers. Maternal pre-pregnant BMI and GWG were positively and independently associated with neonatal insulin ($p=0.010$, $\beta=0.01$ and $p=0.016$, $\beta=0.09$; respectively) and neonatal leptin ($p<0.001$, $\beta=0.71$ and $p<0.001$, $\beta=0.37$; respectively). After adjusting for neonatal adiposity, the above relationships were attenuated and became non-significant for cord blood insulin, but remained significant for leptin levels ($p<0.001$, $\beta=0.51$ and $p=0.015$, $\beta=0.22$; respectively). We also found that maternal pre-pregnant BMI, but not GWG, was negatively associated with HDL-c ($p=0.019$, $\beta=-0.11$) while GWG, though not pre-pregnant BMI, was positively associated with neonatal glucose ($p=0.026$, $\beta=0.27$), both independent of neonatal adiposity. Finally, both pre-pregnant BMI and GWG were negatively and independently associated with neonatal glucose-to-insulin (Glu/Ins) ratio ($p=0.003$, $\beta=-0.14$ and $p=0.006$, $\beta=-0.13$; respectively) and these associations remained significant after adjusting for neonatal adiposity ($p=0.050$, $\beta=-0.09$ and $p=0.048$, $\beta=-0.09$; respectively).

DISCUSSION

In this pre-birth cohort, we found that maternal over-weight or obesity prior to pregnancy and/or increased weight gain during pregnancy were associated with several cord blood cardio-metabolic markers in the offspring including higher insulin, glucose and leptin levels and lower HDL-c and the ratio of glucose-to-insulin. With the exception of the associations with cord blood insulin, these relationships were independent of neonatal adiposity. Our data extend what is known about maternal obesity and offspring cardio-metabolic outcomes in children[5] and adults[13] and provide novel evidence that maternal weight prior and/or during

pregnancy is associated with neonatal cardio-metabolic outcomes including leptin, glucose, Glu/Ins and HDL-c at delivery. Importantly, our data also demonstrate that exposure to maternal obesity *in utero* may increase future cardio-metabolic risk independent of fetal growth and fat accretion, possibly through mechanisms resulting in programmed insulin and leptin resistance.

Studies examining the impact of maternal obesity on circulating levels of neonatal insulin and glucose are limited and present conflicting evidence. In a cohort of 53 lean and 68 obese pregnancies evaluated at elective caesarian delivery, Catalano *et al.* reported that neonates delivered to obese mothers had greater glucose and insulin concentrations and higher estimated insulin resistance, even after adjusting for neonatal adiposity (assessed based on the sum of skinfolds)[7]. In contrast, Lou *et al*. reported that maternal glucose tolerance and fetal ponderal index mediated the association between maternal obesity and lower cord plasma glucose-to-insulin ratios and elevated insulin concentrations[9]. In our study, the relationship of maternal weight with neonatal insulin was largely explained by increased fetal growth and adiposity, suggesting, as expected, that offspring insulin blood levels are associated with fat mass. Nevertheless, we observed a positive association between GWG and neonatal glucose levels, independent of fetal growth and adiposity. We also found that maternal glucose levels prior to delivery were significantly higher in obese mothers suggesting that at least part of the association between maternal weight and neonatal glucose levels may be the result of increased glucose transfer across the placenta from obese mothers to their offspring[24–26]. Moreover, higher maternal weight status prior to and during pregnancy were each associated with a lower glucose to insulin ratio in the cord blood, independent of neonatal adiposity. Glucose to insulin ratio is a marker of insulin resistance in older children[27] and adults[28]. In models additionally adjusting for mode of delivery the results and parameter estimates were generally consistent with those presented in Table 2, although the association between maternal obesity and neonatal insulin and glucose was slightly attenuated. Taken together, our results suggest a programmed propensity for insulin resistance in offspring of obese mothers that is already apparent at birth. We are currently exploring this hypothesis in mechanistic studies using infant mesenchymal stem cells collected from the umbilical cord from a sample of Healthy Start participants.

Lipoprotein abnormalities, including low plasma concentrations of HDL-c and its major protein component, apolipoprotein A-I (apo A-I), are documented CVD risk factors in adults[29–31]. Previous studies in children[5] and adults[13] have reported that the association between maternal obesity and abnormal offspring lipid outcomes are largely explained by offspring adiposity. During infancy, the contribution of offspring adiposity to associations between maternal weight status and neonatal lipid profiles have produced conflicting results. In a cohort of 98 mothers, maternal obesity and fetal macrosomia were associated with offspring lipid and lipoprotein abnormalities including hypertriglyceridemia and reduced HDL cholesterol[32]. These authors also report that fetal macrosomia without maternal obesity was not found to affect cord blood lipid and lipoprotein patterns[32]. Similarly, Kelishadi *et al*. reported that neonatal anthropometerics did not mediate the association of pre-pregnant BMI ≥ 25 with elevated cord triglycerides and with apoB in a cohort of 442 vaginally delivered maternal-infant pairs[33]. Our analyses demonstrate neonatal non-HDL cholesterol

was significantly lower in obese pregnancies and that maternal pre-pregnant BMI was negatively associated with neonatal HDL-c, independent of fetal growth and adiposity. To our knowledge, this is the first report to show that maternal obesity during early pregnancy is negatively and independently associated with neonatal HDL-c at delivery. Collectively, these results reflect the possible interactions between maternal weight status during pregnancy and placenta cholesterol transport and/or fetal cholesterol metabolic pathways that contribute to lower neonatal HDL-c at delivery and may increase offspring CVD risk during adulthood.

Neonatal leptin has been suggested as a possible biomarker of future fetal programming[34], given the known effects of leptin on brain development[35], appetite control[36], and other critical metabolic pathways[37]. Large-scale population studies have documented that measures of maternal obesity are positively associated with neonatal leptin levels[38,39] and that neonatal leptin concentrations are positively correlated with infant birth weight[40]. An important observation made in this study revealed that increased cord blood leptin levels were associated with maternal BMI and GWG, independent of fetal growth and neonatal fat mass. The mechanisms linking maternal obesity to elevated neonatal leptin concentrations in humans remain unclear, as current data suggest that elevated circulating leptin *in utero* may originate from both fetal and placental tissues[41]. Other studies have shown elevated cord blood leptin concentrations in infants of women with Type 1 diabetes and gestational diabetes as compared with control pregnancies not complicated by diabetes[42], even after controlling for differences in birth weight, suggesting a direct influence of maternal hyperglycemia on neonatal leptin levels. It is possible that fetal exposure to maternal diabetes and/or obesity may lead postnatally to increased insulin secretion and adiposity in the infant despite the rising plasma leptin concentrations, which are unable to control the release of insulin and subsequent weight gain[43]. Based on our results, we hypothesize leptin resistance as a result of *in utero* exposure to maternal obesity and/or diabetes may manifest in the postnatal life as an inability of rising plasma leptin concentrations to suppress insulin secretion and weight gain, and/or to regulate appetite in the central nervous system (CNS)[44].

The strengths of this study include a large, well characterized cohort of ethnically diverse mothers with pre- and perinatal records in combination with infant cardio-metabolic outcomes and neonatal body composition (PEA POD)[16,17] measured at the time of delivery Furthermore, given that neonatal body composition changes significantly in the first days of life, we limited out analyses to newborns that were measured using PEA POD in the first 72 hours after birth. The limitations of this study include self-reported assessment of maternal pre-pregnant weight in a subset of participants (10.2%). Importantly, in a study that evaluated 5,040 pregnant and non-pregnant women taking part in the National Health Examination Survey between 2003–2006, self-reported pre-pregnancy weight was reported to be valid markers of maternal weight status prior to pregnancy[45]. Nevertheless, if mothers under-reported their pre-pregnancy weight status, this bias would likely result in underestimating the true associations between maternal BMI and neonatal cardio-metabolic outcomes at birth. Given that umbilical cord lipid measures are higher in umbilical vein (from mother) than the umbilical artery (from fetus)[46], an additional limitation of this study was that we did not discriminate venous from arterial blood in the umbilical cord blood

sample. We did however adjust our analyses for, maternal age, gravidity, race/ethnicity, smoking throughout pregnancy and household income, as well as offspring gestational age and offspring sex which are factors that can affect lipids and hormones at the time of delivery. Additional adjustment of the models by mode of delivery did not change the final results. Finally, we were not able to directly measure neonatal insulin resistance and used cord blood glucose to insulin ratio as an indirect marker of neonatal insulin sensitivity.

In conclusion, our results demonstrate that maternal weight prior and/or during pregnancy is associated with several cardio-metabolic markers of future risk in the offspring, already present at birth. Specifically, we found that maternal weight prior and/or during pregnancy is associated with higher neonatal leptin, glucose, Glu/Ins and lower HDL-c at delivery, and these associations were independent of neonatal adiposity. We interpret these alterations to suggest that *in utero* exposure to maternal obesity results in programmed insulin and leptin resistance, a hypothesis that needs further testing in mechanistic studies. Nevertheless, these findings lend additional support to the notion that primordial prevention of cardio-metabolic disease should start during the prenatal period.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Healthy Start cohort according to categories of maternal pre-pregnancy BMI

	Normal Weight	Overweight	Obese	P-value
Maternal Characteristics				
n (%)	405 (53.3)	200 (26.3)	155 (20.4)	
Maternal Age (years)	27.5 (6.4)	27.5 (6.1)	27.5 (5.6)	0.926
Pre-pregnancy BMI (kg/m^2)	21.5 (2.0)	27.1 (1.4)	36.1 (5.9)	**<0.001**
Observed GWG (kg)	15.4 (5.4)	14.1 (6.5)	10.5 (8)	**<0.001**
Fasting Glucose (mg/dl)	76.4 (7.5)	79.4 (7.5)	81.8 (11.6)	**<0.001**
Race/Ethnicity, (%)				**<0.001***
Hispanic	68 (17.0)	64 (32.2)	54 (35.1)	
Non-Hispanic white	247 (61.8)	97 (48.7)	54 (39.0)	
Non-Hispanic black	55 (13.8)	28 (14.1)	10 (19.5)	
Non-Hispanic other	30 (7.5)	10 (5.0)	60 (6.5)	
Gravidity, n (%)				**<0.001***
First pregnancy	221 (55.2)	134 (67.3)	119 (77.3)	
Not first pregnancy	179 (44.8)	65 (32.7)	35 (22.7)	
Maternal Smoking Status, n (%)				0.422*
No Smoking in pregnancy	364 (91.0)	185 (93.0)	137 (89.0)	
Smoking during pregnancy	36 (9.0)	14 (7.0)	17 (11.0)	
Household income, n (%)				**<0.001****
$20,000 or less	45 (11.2)	30 (15.1)	46 (29.9)	
$20,001 to $40,000	43 (10.8)	28 (14.1)	31 (20.1)	
$40,001 to more	231 (57.8)	101 (50.8)	44 (28.6)	
Missing or Unknown	81 (20.2)	40 (20.1)	33 (21.4)	
Infant Characteristics				
Gestational age at birth (weeks)	39.6 (1.1)	39.5 (1.1)	39.4 (1.1)	**0.007**
Birth weight (g)	3257.3 (389)	3309.9 (451.5)	3362.5 (451.3)	**0.006**
Fat Mass (%)	8.7 (3.7)	9.0 (3.7)	10.1 (4.1)	**<0.001**
Glucose (mg/dl)	81.4 (20.6)	82.5 (18.2)	82 (19.9)	0.645
Insulin (uIU/mL)	8.7 (6.6)	9.0 (4.9)	10.0 (6.3)	**0.038**
Glucose/Insulin Ratio	13 (7.8)	11.9 (7.0)	11.0 (7.1)	**0.005**
HDL-c (mg/dl)	26.3 (7.5)	26.2 (6.5)	25.0 (7.6)	0.095
Non-HDL-c (mg/dl)	61 (25.1)	57.9 (15.6)	55.4 (16.4)	**0.005**
Triglycerides (mg/dl)	49.1 (40.5)	47.9 (51)	42.4 (23.2)	0.12
Free Fatty Acids (uEq/L)	290.9 (140)	302.8 (163.8)	270.2 (142.1)	0.313
Leptin (ng/ml)	14.3 (13.2)	17.5 (15.8)	21.5 (21.2)	**<0.001**
Offspring Sex, n (%)				0.633*

	Normal Weight	Overweight	Obese	P-value
Female	197 (49.2)	94 (47.2)	69 (44.8)	
Male	203 (50.7)	105 (52.8)	85 (55.2)	
Mode of delivery, n (%)				**0.025***
Not Caesarean	322 (80.5)	155 (77.9)	106 (69.7)	
Caesarean	78 (19.5)	44 (22.1)	46 (30.3)	

1 Mean ± SD (all such values),

(*) notes row mean score test and

(**) notes general association test.

Table 2

Pre-pregnant BMI and GWG associated with infant cardio-metabolic outcomes at birth

Cord Blood Outcome	Maternal Exposure	Model 1				Model 2			Model 3		
		n	β	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value
Glucose	Pre-pregnant BMI	726	0.18	(−0.05, 0.42)	0.129	0.17	(−0.07, 0.42)	0.163	0.19	(−0.05, 0.44)	0.115
	GWG	726	0.26	(0.03, 0.49)	0.026	0.25	(−0.01, 0.49)	0.042	0.27	(0.04, 0.51)	0.024
Insulin	Pre-pregnant BMI	695	0.1	(0.02, 0.18)	0.01	0.07	(−0.01, 0.14)	0.092	0.07	(−0.01, 0.15)	0.074
	GWG	695	0.09	(0.02, 0.17)	0.016	0.05	(−0.02, 0.13)	0.179	0.07	(−0.01, 0.14)	0.082
Glucose/Insulin Ratio	Pre-pregnant BMI	695	−0.14	(−0.23, −0.05)	0.003	−0.09	(−0.09, −0.19)	0.053	−0.09	(−0.19, −0.01)	0.05
	GWG	695	−0.13	(−0.22, −0.04)	0.006	−0.07	(−0.17, 0.02)	0.112	−0.09	(−0.18, −0.01)	0.048
HDL-c	Pre-pregnant BMI	625	−0.09	(−0.18, −0.01)	0.05	−0.12	(−0.22, −0.03)	0.011	−0.11	(−0.21, −0.02)	0.019
	GWG	625	0.04	(−0.05, 0.13)	0.369	0.01	(−0.09, 0.10)	0.903	0.02	(−0.07, 0.12)	0.627
Non-HDL-c	Pre-pregnant BMI	686	−0.16	(−0.42, 0.11)	0.239	−0.18	(−0.44, 0.09)	0.2	−0.19	(−0.45, 0.08)	0.176
	GWG	686	0.18	(−0.08, 0.44)	0.177	0.16	(−0.11, 0.42)	0.251	0.15	(−0.11, 0.42)	0.25
Triglycerides	Pre-pregnant BMI	675	0.01	(−0.50, 0.51)	0.984	0.13	(−0.38, 0.64)	0.624	0.06	(−0.46, 0.56)	0.82
	GWG	675	−0.08	(−0.57, 0.41)	0.757	0.07	(−0.44, 0.57)	0.792	−0.03	(−0.53, 0.47)	0.9
Free Fatty Acids	Pre-pregnant BMI	652	−0.09	(−1.94, 1.76)	0.925	0.2	(−1.70, 2.10)	0.838	0.4	(−1.49, 2.30)	0.677
	GWG	652	−1.07	(−2.91, 0.78)	0.258	−0.77	(−2.67, 1.12)	0.423	−0.76	(−2.62, 1.10)	0.42
Leptin	Pre-pregnant BMI	639	0.71	(0.51, 0.90)	<0.001	0.57	(0.38, 0.76)	<0.001	0.51	(0.33, 0.69)	<0.001
	GWG	639	0.37	(0.18, 0.56)	<0.001	0.24	(0.05, 0.43)	0.013	0.22	(0.04, 0.40)	0.015

Model 1: Adjusted for offspring gestational age, offspring sex, maternal age, gravidity, race/ethnicity, pre-pregnancy BMI, smoking throughout pregnancy and household income; **Model 2:** Model 1 + offspring birth weight; **Model 3:** Model 1 + offspring fat mass