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Placental Weight Mediates the Effects of Prenatal Factors on Fetal Growth: the Extent Differs by Preterm Status

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Abstract

Elevated pre-pregnancy body mass index (BMI), excessive gestational weight gain (GWG), and gestational diabetes (GDM) are known determinants of fetal growth. The role of placental weight is unclear. We aimed to examine the extent to which placental weight mediates the associations of pre-pregnancy BMI, GWG, and GDM with birthweight-for-gestational age, and whether the relationships differ by preterm status. We examined 1035 mother-infant pairs at birth from the Boston Birth Cohort. Data were collected by questionnaire and clinical measures. Placentas were weighed without membranes or umbilical cords. We performed sequential models excluding and including placental weight, stratified by preterm status. We found that 21% of mothers were obese, 42% had excessive GWG, and 5% had GDM. 41% were preterm. Among term births, after adjustment for sex, gestational age, maternal age, race, parity, education, smoking and stress

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during pregnancy, birthweight-for-gestational age z-score was 0.55 (0.30, 0.80) units higher for pre-pregnancy obesity vs. normal weight. It was 0.34 (0.13, 0.55) higher for excessive vs. adequate GWG, 0.67 (0.24, 1.10) for GDM vs. no DM, with additional adjustment for pre-pregnancy BMI. Adding placental weight to the models attenuated the estimates for pre-pregnancy obesity by 20%, excessive GWG by 32%, and GDM by 21%. Among preterm infants, GDM was associated with 0.67 (0.34, 1.00) higher birthweight-for-gestational age z-score, but pre-pregnancy obesity and excessive GWG were not. Attenuation by placental weight was 36% for GDM. These results suggest that placental weight partially mediates the effects of pre-pregnancy obesity, GDM and excessive GWG on fetal growth among term infants.

Keywords

pre-pregnancy BMI; gestational weight gain; gestational diabetes; placental weight; fetal growth; birth weight z-score

Introduction

Elevated pre-pregnancy body mass index (BMI), excessive gestational weight gain (GWG), and gestational diabetes (GDM) are known determinants of fetal growth. (1-4) The mechanisms and mediation role of placental weight for these relationships are unclear. Women with GDM pass excess glucose across the placenta which contributes to fetal overgrowth.(5) Larger placentas are associated with higher pre-pregnancy body mass index (BMI), excessive GWG, and GDM. (6-9) Thus, placental size may be an important mediator between pre-pregnancy BMI, GWG, GDM and increased fetal growth. Placental weight has also been linked with adult diseases including hypertension and cardiovascular disease (10), suggesting that the influences of the placenta during fetal life may have long-term effects. To our knowledge, there are no prospective studies in humans that examine the mediation of placental weight on the association between these prenatal factors and fetal growth.

Furthermore, both placental and fetal growth are closely correlated to gestational age. The placenta size increases until late in gestation, supporting on-going fetal growth,(9) but preterm infants miss the final weeks of intra-uterine growth. In addition, infants born preterm are smaller at birth than fetuses of the same gestational age that remain in utero and deliver at term. (11). Thus, infants born preterm may have different intra-uterine growth patterns. It is important to evaluate whether the association of prenatal factors and placental weight with fetal growth differs between term and preterm infants.

The objectives of this study were to examine the extent to which placental weight mediates the well-established association between prenatal factors (pre-pregnancy BMI, GWG, GDM) and birth weight-for-gestational age and BMI at birth; and whether these relationships differ by term and preterm births. To address these objectives, we analyzed data from the Boston Birth Cohort, a large, multi-ethnic, inner-city cohort of mother-infant pairs enrolled postpartum at the Boston Medical Center.

Methods and Procedures

Study Population

The study population and data collection methods are described elsewhere (12). Briefly, The Boston Birth Cohort was initiated in 1998 and recruitment is ongoing at the Boston Medical Center (BMC), a large urban hospital serving a multi-ethnic inner-city population.

The Boston Birth Cohort was originally designed to study adverse birth outcomes, particularly preterm births. The inclusion criteria of the parent study are as follows: Any woman admitted to the Labor and Delivery floor at BMC who delivered a singleton live infant and met our case (gestational age <37 weeks or birth weight <2,500 grams) or control (gestational age ≥ 37 weeks with birth weight ≥ 2,500 grams) criteria was eligible (13). Multiple gestation pregnancies, pregnancies resulting from in-vitro fertilization, deliveries resulting from maternal trauma and newborns with major birth defects were excluded. This study was approved by Institutional Review Board (IRB) at the Children's Memorial Hospital (CMH) and Boston University Medical Center (BUMC).

Mother-infant pairs were recruited 24 to 72 hours postpartum. After obtaining written informed consent, we conducted a face-to-face maternal interview using a standardized questionnaire. We also reviewed maternal and infant medical records using a standardized abstraction form to obtain clinical data including prenatal care, ultrasound findings, placental weight, placental pathology reports, laboratory reports, pregnancy complications, labor and delivery course, and birth outcomes (infant gender, gestational age, birth weight and birth length).

This report focused on mothers aged 18-34 years. There were 3857 women aged 18-34 years at childbirth. We excluded 55 women with pre-existing diabetes before pregnancy and 2,767 due to missing values of placental weight (n=1338), GWG (n=525), both placental weight and GWG (n=904). This left 611 term births and 424 preterm births, totaling 1035 mother-infant pairs for analysis. We compared included and excluded participants and found no differences in pre-pregnancy BMI, weekly GWG (100g/week), GWG per 2009 Institute of Medicine (IOM) guidelines, parity and smoking during pregnancy (Online Supplemental Table 1). Among term births, the mothers included in this report were more likely to report “very stressful” as the amount of stress in life during pregnancy than those excluded (23.6% vs. 17.9%). Among preterm births, the mothers included were more likely to identify themselves of black race (55.4% vs. 48.9%), and to have an education of high school or above (74.5% vs. 67.4%) (Online Supplemental Table 1). The included infants had slightly lower birth weights and BMI in both term and preterm births and lower birth weight-for-gestational-age z-score in term births compared to those excluded.

Main Predictors of Offspring Weight Status at Birth

Pre-pregnancy Obesity—Maternal pre-pregnancy BMI (kg/m^2) was calculated by pre-pregnancy weight and height obtained by self-report during the maternal postpartum interview, and categorized as underweight (<18.5), normal (18.5-24.9), overweight (25.0-29.9), and obese (≥ 30.0).

Gestational weight gain—GWG was calculated as the difference between the final measured weight prior to delivery abstracted from the medical record and self-report of pre-pregnancy weight. We categorized GWG into inadequate, adequate and excessive GWG as defined by IOM in 2009 (14). Specifically, “adequate” weight gain describes a gain of 28-40 pounds for an underweight women (BMI <18.5 kg/m²), 25-35 pounds for a women of normal weight (BMI 18.5-24.9 kg/m²), 15-25 pounds for an overweight women (25.0-29.9 kg/m²), and 11-20 pounds for an obese women (BMI ≥ 30.0 kg/m²). Those below and above the corresponding range were classified as “inadequate” and “excessive” respectively. Because GWG categories are based on total GWG, it may not adequately reflect the time for gestational weight gain and the velocity of GWG, especially for mothers who deliver premature. We also calculated a weekly GWG (100g/ week) as a continuous measure by the formula: weekly GWG (100g/week) =10*GWG (kg)/gestational age (weeks). But, of note, since weight gain is not linear across pregnancy, weekly GWG also has its limitations.

Gestational Diabetes—We abstracted presence or absence of GDM from the medical record. The diagnosis of GDM was based on clinician's interpretation of the results of standard glucose tolerance testing during pregnancy. We excluded participants with a pre-pregnancy history of diabetes mellitus because they may have different pattern of pre-pregnancy BMI and GWG.

Placental Weight—Placental weights were abstracted from medical records from pathology reports. Obstetricians chose to send placentas to pathology at the time of delivery for various reasons including prematurity, intrauterine growth restriction, concern for chorioamnionitis or abruption, maternal drug and/or alcohol use, hypertensive disorders including chronic and pregnancy induced hypertension, and perinatal depression. Placentas were fixed in formalin for 1-2 days, membranes and umbilical cord removed, and then weighed on a digital scale. We classified placental weight into three groups: low, medium and high, based on sex- and gestational age-specific tertiles of placental weights. We compared the mother-infant pairs with placental data vs. those without, and found that there were no differences in infant sex, maternal age, weekly GWG, GWG per 2009 IOM guidelines, and maternal education in term and preterm births. Compared to mothers without placenta weights, those with placental weights were more likely to identify themselves of black race and have infants born earlier with lower birth weights and birth weight-for-gestational age z-scores in both term and preterm births. Mothers of term births with placenta weights were more likely to report their lives as “very stressful” during pregnancy (22.9% vs. 17.5%), more often nulliparous (49% vs. 40.5%) and more were smokers during pregnancy (22.7% vs. 17.0%) compared with mothers of term births without placenta weights. And mothers of preterm births with placental weights were more often obese (22.0% vs. 15.8%) and had infants of lower BMI at birth compared to mothers of preterm births without placental weight (online supplemental Table 2).

Main Outcomes of Weight Status at Birth

Our measures of weight status at birth were birth weight-for-gestational age z-score (“fetal growth”) and BMI at birth. We abstracted clinical measure of birth weight (grams) and birth length (cm) from the medical record. We estimated birth weight-for-gestational age z-score

based on sex-specific U.S. national reference data. (15) Birth weight-for- gestational age z-score reflects the percentile rank of an infant's birthweight in the reference population of same sex and gestational week. For example, a female infant born at a gestation age of 37 weeks with a z-score of 1.96 is heavier than 97% and lighter than 2% of the reference population of females born at 37 weeks gestation. BMI was calculated as birth weight (kg)/ birth length² (m²). We used BMI at birth, given that the new World Health Organization (WHO) growth charts use BMI-for-age from 0 to 2 years. (16)

Definitions of Major Covariates

Maternal socio-demographic factors including age, race/ethnicity, and education level, smoking history during pregnancy and the amount of life stress during pregnancy (not stressful, average, or very stressful) were obtained by self-report during the maternal postpartum interview and included as covariates because these factors are known to influence fetal growth. (7, 17, 18)

Infant factors including sex and gestational age at birth were abstracted from the medical record. We determined gestational age at delivery from maternal report of last menstrual period (LMP) and early ultrasound (< 20 weeks). If the estimate of gestational age from the ultrasound differed by > 7 days than that predicted by maternal report of last menstrual period, then we used the ultrasound assessment. If there was no ultrasound and no known date of LMP, we used clinician report of gestational age based on Dubowitz physical exam findings. Preterm was defined as gestational age <37 weeks, and term as ≥ 37 weeks.

Statistical Analysis

First we compared maternal and infant characteristics between included and excluded participants (online supplemental Table 1), between those with and without placental data (online supplemental Table 2) and between term and preterm births (Table 1), using t-test for continuous variables and Chi-square tests for categorical data. Next, we used ANOVA F-tests or t-tests to compare placental weight, birth weight-for-gestational age zscore and birth weight measures among groups of main exposures and covariates in term and preterm births separately (Table 2).

We used multivariable linear regression to evaluate the relationship between pre-pregnancy BMI, GWG, GDM, placental weight and outcome measures, including birth weight-for-gestational age z-score (Table 3), and BMI at birth (Table 4) with stratification by gestational age (preterm vs. term).

We performed sequential models by excluding and including placental weight to evaluate a possible mediation effect of placental weight on prenatal factors and birthweight measures. First we looked at sex-adjusted models for each predictor (Model 1). Next we adjusted for covariates of *a priori* interest including demographics and factors which may influence fetal growth such as maternal smoking and stress during pregnancy (Model 2). Then we added placental weight in the models to examine the extent to which placental weight mediates the relationship between pre-pregnancy BMI, GWG, GDM and birth weight outcomes, without adjustment for pre-pregnancy BMI (Model 3). Next, we examined the associations of GWG

and GDM with birth weight outcomes after adding pre-pregnancy BMI as an additional confounder (Model 4), and then evaluated the mediation effect of placental weight (Model 5). Finally we performed a grand model with all covariates and predictors to assess the association between placental weight and fetal growth measures with adjustment for other three predictors (Model 6). Weekly GWG was used in Model 6. As mediator (placental weight in this paper), it should predict outcome in a model controlling for predictors of interest. All linear regression models were performed for term and preterm births separately.

Finally, we used locally weighted nonparametric smoothing plots (SAS LOESS, SAS Institute, Cary, NC, USA) to graphically examine the relationship of sex- and gestational-age specific placental weight levels (low, medium and high) with birth weight outcomes across pre-pregnancy BMI and GWG, in term and preterm births (Figure 1 and 2). All analyses were performed with SAS 9.1 software (SAS Institute Inc) and Empower(S) (www.empowerstats.com).

Results

Study population

The characteristics of 1035 mother-infant pairs are presented in Table 1. 41% were preterm with gestational ages ranging from 22.7 to 36.9 weeks. The mean maternal age (years) was 26.3 ± 4.7 in term births and 26.5 ± 4.7 in preterm births. The majority of mothers identified themselves as black and Hispanic (51.4% and 24.1% among term births and 55.4% and 18.6% among preterm births). 63.4% and 65.8% reported completion of high school or less; 23.6% and 27.6% characterized their life as “very stressful” during pregnancies; 21.8% and 28.5% of women smoked during pregnancy among term and preterm births respectively. 20% and 21.9% of mothers were obese (pre-pregnancy BMI $\geq 30.0 \text{ kg/m}^2$), 48.3% and 33.5% had excessive GWG per 2009 IOM guidelines, and 5.1% and 5.7% had GDM among term and preterm births, respectively. Compared to preterm infants, term infants had higher mean placental weight (475 ± 138 vs. 349 ± 122 g), birth weight (3168 ± 655 vs. 1972 ± 722 g) and BMI (kg/m^2) at birth (12.8 ± 1.9 vs. $10.6 \pm 2.0 \text{ kg/m}^2$), and similar birth weight-for-gestational age z-score (-0.54 ± 1.26 vs. -0.56 ± 0.83) (Table 1).

Table 2 revealed that male infants had higher weight status at birth (birth weight, birth weight-for-gestational age z-score and BMI at birth) than females born at term, and male infants had a higher mean birth weight than females born preterm. Obese mothers had greater mean placental weight and measures of offspring weight status at birth than normal weight mothers among term births only. Mothers with excessive GWG and GDM had greater mean placental weight and measures of weight status at birth in both term and preterm infants, compared to mother with adequate GWG and without GDM. Mothers who smoked during pregnancy had infants with lower mean birth weight and birth weight-for-gestational age z-score compared to non-smoking mothers in term births (Table 2).

Associations of Prenatal Factors and Placental Weight with Birth Weight-for-Gestational Age Z-score

Among term births, birth weight-for-gestational age z-score was 0.55 units higher for pre-pregnancy obesity vs. normal weight (95% CI 0.30, 0.80) with adjustment for infant sex, gestational age, maternal age, education, race, parity, smoking and life stress during pregnancy (Table 3, Model 2). With adjustment for pre-pregnancy BMI and other covariates, birth weight-for-gestational age z-score was 0.34 units (0.13, 0.55) higher for excessive vs. adequate GWG and 0.67 units higher (0.24, 1.10) for GDM vs. no DM (Model 4). Adding placental weight to the models attenuated the estimates for pre-pregnancy obesity by 20% (Model 2 and 3), excessive GWG by 32%, and GDM by 21 %, suggesting a 20-30% mediation effect of placental weight (Table 3, Model 4 and 5). With adjustment for pre-pregnancy BMI, GWG, GDM and other covariates, birth weight-for-gestational age z-score was 0.82 units (0.64, 1.00) higher for high vs. medium placental weight (Model 6).

Among preterm infants, GDM ($\beta=0.67$, 95% CI 0.34, 1.00, Table 3, Model 4) and high placental weight (0.55, 0.41, -0.69, Table 3, Model 6) were associated with higher birth weight-for-gestational age z-score; but pre-pregnancy obesity [0.05, -0.15 to 0.24, Table 3, Model 2] and excessive GWG [0.06, -0.13 to 0.25, Table 3, Model 4] were not. Attenuation by placental weight was 36 % for GDM among preterm births (Table 3, Model 4 and 5). We did not find associations between pre-pregnancy obesity and GWG (categories or continuous measures) and birth weight-for-gestational age z-score.

Low placental weight was associated with lower birth weight-for-gestational age z-score in both term [-0.63, -0.81 to -0.44] and preterm infants [-0.58, -0.72 to -0.43] (Table 3, Model 6).

Associations of Prenatal Factors and Placental Weight with BMI at Birth

We found similar associations for prenatal factors, placental weight and BMI at birth (Table 4). Among term births, after adjustment for infant sex and other covariates, BMI (kg/m^2) at birth was 0.7 (95% CI 0.3, 1.1) higher for infants born to obese mothers vs. mothers with normal weight (Model 2). After additional adjustment for pre-pregnancy BMI, BMI at birth was 0.5 (0.2, 0.9) higher for excessive vs. adequate GWG, and 1.0 (0.3, 1.6) higher for GDM vs. no DM (Model 4). Adding placental weight to the models attenuated the estimates for pre-pregnancy obesity by 14% (Model 2 and 3), excessive GWG by 20%, and GDM by 20% (Model 4 and 5).

Among preterm births, GDM was associated with 0.9 (95% CI 0.1, 1.7) higher BMI at birth, but pre-pregnancy obesity (-0.2, -0.7 to 0.2) and excessive GWG (0.1, -0.3 to 0.5) were not. However, a GWG of 100 grams per week was associated with 0.1 higher BMI at birth (95% CI 0.03, 0.2) (Table 4, Model 4). Attenuation by placental weight was 33% for GDM and 30% for weekly GWG in preterm births (Table 4, Model 4 and 5).

Similarly, high placental weight was associated with higher BMI at birth in both term (0.9, 95% CI 0.6, 1.2) and preterm infants (0.9, 0.5, 1.3), and low placental weight was associated with lower BMI at birth in both term (-0.7, -1.1, -0.4) and preterm infants (-0.7, -1.1, -0.3)

compared to medium placental weight with adjustment for pre-pregnancy BMI, weekly GWG, GDM and other covariates (Model 6).

Graphic Analysis of Prenatal Factors, Placental Weight and Weight Status at Birth

Smoothing plots showed that infants with the highest tertile of placental weight had consistently higher birth weight-for-gestational age z-scores and BMIs at birth than infants with placental weights in the middle tertile, which were consistently higher than infants with the lowest tertile of placental weight in both term and preterm births, with adjustment for infant sex and other covariates (Figure 1 and 2).

Discussion

In this study we found that maternal obesity, excessive GWG, and GDM were associated with greater birth weight-for-gestational age z-score (fetal growth) and BMI at birth among term births. Adding placental weight in the models substantially attenuated these relationships, suggesting that placental weight may partially mediate the association of maternal obesity, excessive GWG, and GDM with fetal growth and BMI at birth. Among preterm births, we found a positive association between GDM and birth weight-for-gestational age z-score and BMI at birth which was also partially mediated by placental weight. Finally, we found that placental weight was a strong predictor of birth weight-for-gestational age z-score and BMI at birth after controlling for pre-pregnancy BMI, GWG and other covariates in both term and preterm births. This study improved our understanding of the role of the placenta in fetal growth, a complex process that involves multiple maternal and fetal factors.

The prevalence of pre-pregnancy obesity (21%), excessive GWG (42%) and GDM (5%) in our cohort was similar to others (19-21). Previous studies reported that offspring of mothers with pre-pregnancy obesity, excessive GWG and GDM are larger at birth; our results confirmed previous findings. (4, 22, 23) Unlike other studies, we were able to examine the associations between prenatal factors and fetal growth and BMI at birth in term and preterm births separately. We found that pre-pregnancy obesity and excessive GWG were associated with birth weight-for-gestational age z-score and BMI at birth among term births, but not among preterm infants. It is possible that other adverse risk factors that contribute to preterm birth also impact fetal growth. For example, intrauterine inflammation is thought to induce preterm birth as well as poor fetal growth (24, 25) As placental and other pathologies are more prevalent and pronounced in the preterm group, these adverse factors may have obscured any effect of maternal obesity and excessive GWG on fetal growth in preterm births. Finally, it is also possible that effects of maternal obesity and GWG are most influential during the period of most rapid fetal growth (third trimester). Third trimester growth is shortened among infants born preterm.

Similar to other studies, we found that placental weight correlated with weight status at birth. (6, 7) To our knowledge, our study is the first to test the hypothesis whether, and to what extent, placental weight mediates the relationship between other known pre- and perinatal predictors of fetal growth and birth weight outcomes. Our findings suggest that placental weight partially mediates the effect of pre-pregnancy BMI, GWG and GDM on

fetal growth. Excessive GWG and GDM may represent a state of intrauterine over-nutrition, where the placental supply of maternal nutrients is too abundant, leading to a larger placental and subsequently larger infant. Our interpretation is biologically plausible. Placental size is correlated with capacity for nutrient transfer and increases steadily throughout gestation.(26) In animal studies of sheep, enlarged placentas by diet manipulation produced larger lambs.(10) In horses, where size differs by breed, when fertilized embryos from smaller breeds are implanted in larger breeds, the placental and fetal weights are larger than if the embryos remained in the smaller breed. This demonstrates that placental weight and surface area can enhance fetal size. (26) In human epidemiologic studies, maternal diet and energy intake can affect placental size.(26-28) For example, women who fast during Ramadan during the last trimester have smaller placentas. (27) Taken together, previous animal and epidemiologic studies suggest that maternal nutrition may influence fetal growth via placental weight.

There is growing evidence that the placenta plays a key role in fetal programming of cardiometabolic diseases.(10) In addition to nutrient transport, the placenta also plays a key role in production of hormones which can influence intra- and extra-uterine growth. (28) For example, progesterone and placental lactogen promote maternal glucose delivery;(26) insulin-like-growth factor II promotes fetal growth;(29) and 11 β -hydroxysteroid dehydrogenase type 2 inactivates glucocorticoids.(28) These endocrine functions may play a role in fetal programming of future metabolic diseases.(28) Future examination of placental hormones in larger sample may help elucidate the role of placenta in fetal programming.

Despite the close correlation known between placental size and fetal growth, the mediation effect of placental weight on the associations between these prenatal factors and fetal growth is partial (20%-36%), not complete. This is also evident by the positive associations of maternal obesity, GWG and GDM with greater fetal growth after controlling for placental weight in term births, where the effect estimations should go to 0 if the mediation is complete. Thus, other pathways that do not involve placental weight are yet to be identified. Secondly, we simplify our assumption in one way direction of maternal-placenta-fetal unit in this study. Since fetal growth can influence placental growth (30), and this may account for the partial mediation found in this study. Thirdly, placental weight is but one of several physical parameters that may predict outcomes, including placental thickness, width, length and cord placement position. Placental size may also increase due to remodeling from a prior injury. Thus, caution is needed when using placenta weight alone to reflect placental function as a determinant of fetal growth. Our epidemiologic findings provide the basis for future studies to further investigate the roles of placenta in mediating the effects of prenatal factors on fetal growth.

Strengths of this study include its multiple pre- and perinatal factors, measures of placental weight, as well as a wide range of potential known confounders of preterm birth and fetal growth among a relatively large number of women. In particular, we were able to adjust for smoking status and stress during pregnancy, known factors that can restrict fetal growth via placental insufficiency. (7, 31) Also, our cohort had a large number of preterm births to evaluate outcomes in term and preterm infants separately.

Limitations include our clinical measures of placental weight. Placentas were sent to pathology for a variety of clinical indications and only the mother-infant pairs with placental weights were examined for this study, which may lead to a higher prevalence of placental pathologies (inflammation, vascular pathology etc) or smaller placental weight in the analysis sample than in study participants as a whole. Thus the findings cannot be generalized to all mother-infant pairs in the cohort or to pregnant women in general. The direction of the effect of selection bias is not obvious. The function of placentas in this sample was likely to be lower due to placental pathologies, which may have underestimated the mediation effect of placenta weight in general. However, we can't exclude the possibility that certain placental pathology may lead to a more substantial mediation effect of maternal factors on fetal growth. Second, the study participants included had relatively lower social economic status (SES) and greater prevalence of prematurity compared to those excluded, which may also limit generalizability of our findings. Thus we performed our analysis with stratification by preterm status, and adjusted for SES factors. In the context of these limitations, our findings may be viewed as hypothesis-generating. The study of obesity in this unique population is designed to bring general insight to our understanding of pregnancy. Confirmation studies of larger sample sizes with inclusion of women with placentas that are more representative of general populations are needed. Thirdly, pre-pregnancy BMI was calculated from self-reported height and weight. Because women tend to under-report their weight by up to 2.5 kg(32), our calculated BMIs may be systematically low. The misclassification of some women from higher BMI category to the lower group could bias our findings toward the null. Fourth, we did not have paternal BMI, a covariate that may influence birth weight status. However, a previous study reported that paternal BMI was not associated with placental and birth weight after adjustment for maternal factors.(7) Finally, we used clinical assessment of recumbent birth length which tend to systematically over-estimate length and underestimate BMI by a reliably predictable amount (regression equation: research-standard length= 95.3% of the clinical measurement + 1.88 cm). (33) Since clinical assessment and research-standard measures of length were highly correlated ($R^2 = 0.98$),(33) the use of clinical measures should not change the associations we found.

Conclusion

In this U.S. urban multi-ethnic birth cohort, we found that placental weight is a strong predictor of fetal growth, and appears to partially mediate the effect of maternal obese, GDM and excessive GWG on fetal growth and BMI at birth among term infants, and mediate the effects of GDM on fetal growth and BMI at birth among preterm infants. Our findings suggest that the placenta serves as intermediary between maternal conditions of over nutrition and offspring obesity, and therefore may serve a critical role in fetal programming of subsequent metabolic diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Mesman I, Roseboom TJ, Bonsel GJ, Gemke RJ, van der Wal MF, Vrijkotte TG. Maternal pre-pregnancy body mass index explains infant's weight and BMI at 14 months: results from a multi-ethnic birth cohort study. *Arch Dis Child*. 2009; 94:587–95. [PubMed: 19332418]
2. Ludwig DS, Currie J. The association between pregnancy weight gain and birthweight: a within-family comparison. *Lancet*. 2010; 376:984–90. [PubMed: 20691469]
3. Oken E, Taveras EM, Kleinman KP, Rich-Edwards JW, Gillman MW. Gestational weight gain and child adiposity at age 3 years. *Am J Obstet Gynecol*. 2007; 196:322 e1–8. [PubMed: 17403405]
4. Schaefer-Graf UM, Heuer R, Kilavuz O, Pandura A, Henrich W, Vetter K. Maternal obesity not maternal glucose values correlates best with high rates of fetal macrosomia in pregnancies complicated by gestational diabetes. *J Perinat Med*. 2002; 30:313–21. [PubMed: 12235720]
5. Hillier TA, Pedula KL, Vesco KK, et al. Excess gestational weight gain: modifying fetal macrosomia risk associated with maternal glucose. *Obstet Gynecol*. 2008; 112:1007–14. [PubMed: 18978099]
6. Hindmarsh PC, Geary MP, Rodeck CH, Kingdom JC, Cole TJ. Factors predicting ante- and postnatal growth. *Pediatr Res*. 2008; 63:99–102. [PubMed: 18043501]
7. L'Abée C, Vrieze I, Kluck T, Erwich JJ, Stolk RP, Sauer PJ. Parental factors affecting the weights of the placenta and the offspring. *J Perinat Med*. 2011; 39:27–34. [PubMed: 20954852]
8. Taricco E, Radaelli T, Nobile de Santis MS, Cetin I. Foetal and placental weights in relation to maternal characteristics in gestational diabetes. *Placenta*. 2003; 24:343–7. [PubMed: 12657507]
9. Teasdale F. Gestational changes in the functional structure of the human placenta in relation to fetal growth: a morphometric study. *American Journal of Obstetrics and Gynecology*. 1980; 137:560–568. [PubMed: 7386550]
10. Thornburg KL, O'Tierney PF, Louey S. Review: The placenta is a programming agent for cardiovascular disease. *Placenta*. 2010; 31(Suppl):S54–9. [PubMed: 20149453]
11. Weiner CP, Sabbagha RE, Vaisrub N, Depp R. A hypothetical model suggesting suboptimal intrauterine growth in infants delivered preterm. *Obstet Gynecol*. 1985; 65:323–6. [PubMed: 3883260]
12. Kumar R, Ouyang F, Story RE, et al. Gestational diabetes, atopic dermatitis, and allergen sensitization in early childhood. *J Allergy Clin Immunol*. 2009; 124:1031–8. 4. [PubMed: 19733904]
13. Wang X, Zuckerman B, Pearson C, et al. Maternal cigarette smoking, metabolic gene polymorphism, and infant birth weight. *Jama*. 2002; 287:195–202. [PubMed: 11779261]
14. Institute of Medicine. *Weight Gain During Pregnancy: Reexamining the Guidelines*. Washington (DC): National Academies Press (US); 2009.
15. Oken E, Kleinman KP, Rich-Edwards JW, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. *BMC Pediatrics*. 2003; 3:6. [PubMed: 12848901]
16. Child growth standard. [accessed 11/30/2011] http://www.who.int/childgrowth/standards/bmi_for_age/en/index.html
17. Steyn K, de Wet T, Saloojee Y, Nel H, Yach D. The influence of maternal cigarette smoking, snuff use and passive smoking on pregnancy outcomes: the Birth To Ten Study. *Paediatr Perinat Epidemiol*. 2006; 20:90–9. [PubMed: 16466427]
18. Li J, Olsen J, Vestergaard M, Obel C, Baker JL, Sorensen TI. Prenatal stress exposure related to maternal bereavement and risk of childhood overweight. *PLoS One*. 2010; 5:e11896. [PubMed: 20689593]

19. Chu SY, Kim SY, Bish CL. Prepregnancy obesity prevalence in the United States, 2004-2005. *Matern Child Health J.* 2009; 13:614–20. [PubMed: 18618231]
20. Chu SY, Callaghan WM, Bish CL, D'Angelo D. Gestational weight gain by body mass index among US women delivering live births, 2004-2005: fueling future obesity. *Am J Obstet Gynecol.* 2009; 200:271, e1–7. [PubMed: 19136091]
21. Lawrence JM, Contreras R, Chen W, Sacks DA. Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999-2005. *Diabetes Care.* 2008; 31:899–904. [PubMed: 18223030]
22. Dietz PM, Callaghan WM, Sharma AJ. High pregnancy weight gain and risk of excessive fetal growth. *Am J Obstet Gynecol.* 2009; 201:51, e1–6. [PubMed: 19576373]
23. Nohr EA, Vaeth M, Baker JL, Sorensen T, Olsen J, Rasmussen KM. Combined associations of prepregnancy body mass index and gestational weight gain with the outcome of pregnancy. *Am J Clin Nutr.* 2008; 87:1750–9. [PubMed: 18541565]
24. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. *N Engl J Med.* 2000; 342:1500–7. [PubMed: 10816189]
25. Mestan K, Yu Y, Matoba N, et al. Placental inflammatory response is associated with poor neonatal growth: preterm birth cohort study. *Pediatrics.* 2010; 125:e891–8. [PubMed: 20308216]
26. Fowden AL, Ward JW, Wooding FP, Forhead AJ, Constancia M. Programming placental nutrient transport capacity. *J Physiol.* 2006; 572:5–15. [PubMed: 16439433]
27. Alwasel SH, Abotalib Z, Aljarallah JS, et al. Changes in placental size during Ramadan. *Placenta.* 2010; 31:607–10. [PubMed: 20621763]
28. Jansson T, Powell TL. Role of the placenta in fetal programming: underlying mechanisms and potential interventional approaches. *Clin Sci (Lond).* 2007; 113:1–13. [PubMed: 17536998]
29. Godfrey KM. The role of the placenta in fetal programming-a review. *Placenta.* 2002; 23(Suppl A):S20–7. [PubMed: 11978056]
30. Murphy VE, Smith R, Giles WB, Clifton VL. Endocrine regulation of human fetal growth: the role of the mother, placenta, and fetus. *Endocr Rev.* 2006; 27:141–69. [PubMed: 16434511]
31. Gluckman PD, Hanson MA. Developmental and epigenetic pathways to obesity: an evolutionary-developmental perspective. *Int J Obes (Lond).* 2008; 32(7):S62–71. [PubMed: 19136993]
32. Shields M, Gorber SC, Tremblay MS. Estimates of obesity based on self-report versus direct measures. *Health Rep.* 2008; 19:61–76. [PubMed: 18642520]
33. Rifas-Shiman SL, Rich-Edwards JW, Scanlon KS, Kleinman KP, Gillman MW. Misdiagnosis of overweight and underweight children younger than 2 years of age due to length measurement bias. *MedGenMed.* 2005; 7:56. [PubMed: 16614678]

Figure 1. Smoothing plot of the associations of pre-pregnancy BMI and gestational weight gain with birth weight-for-gestational age z-score stratified by sex- and gestational age-specific tertiles of placental weight, with adjustment for covariates in term and preterm infants. Covariates were sex, maternal age, maternal age², maternal education, maternal race, gestational age, gestational age², parity, smoking during pregnancy, stress during pregnancy.

Figure 2.

Smoothing plot of the associations of pre-pregnancy BMI and gestational weight gain with BMI at birth stratified by sex- and gestational age-specific tertiles of placental weight, with adjustment for covariates in term and preterm infants. Covariates were sex, maternal age, maternal age², maternal education, maternal race, gestational age, gestational age², parity, smoking during pregnancy, and stress during pregnancy.

Table 1
Characteristics of 1035 Mother-Infant Pairs

Characteristics	Term	Preterm	p value
N	611	424	
Maternal factors	Mean $\pm$ SD	Mean $\pm$ SD	
Age (years)	26.3 $\pm$ 4.7	26.5 $\pm$ 4.7	0.398
Weekly GWG (100 grams/week)	3.7 $\pm$ 2.0	3.6 $\pm$ 2.2	0.401
Placental weight (grams)	475 $\pm$ 138	349 $\pm$ 122	<0.001
Infant factors			
Gestational age (weeks)	39.5 $\pm$ 1.4	33.0 $\pm$ 3.6	<0.001
Birth weight (grams)	3168 $\pm$ 655	1972 $\pm$ 722	<0.001
BMI at birth (kg/m ²)	12.8 $\pm$ 1.9	10.6 $\pm$ 2.0	<0.001
Birth weight-for-gestational age z-score	-0.54 $\pm$ 1.26	-0.56 $\pm$ 0.83	0.768
	N (%)		
Infant Sex			0.488
Female	295 (48.3)	214 (50.5)	
Male	316 (51.7)	210 (49.5)	
Maternal factors			
Race			0.064
Black	314 (51.4)	235 (55.4)	
White	74 (12.1)	66 (15.6)	
Hispanic	147 (24.1)	79 (18.6)	
Others	76 (12.4)	44 (10.4)	
Pre-pregnancy BMI (kg/m ²)			0.864
<18.5	30 (4.9)	19 (4.5)	
18.5-24.9	301 (49.3)	208 (49.1)	
25.0-29.9	158 (25.9)	104 (24.5)	
$\geq$ 30	122 (20.0)	93 (21.9)	
GWG per 2009 IOM guidelines			<0.001
Excessive	295 (48.3)	142 (33.5)	
Adequate	191 (31.3)	137 (32.3)	
Inadequate	125 (20.5)	145 (34.2)	
GDM			0.679
No	580 (94.9)	400 (94.3)	
Yes	31 (5.1)	24 (5.7)	
Placental weight			0.960
Low	192 (31.4)	136 (32.1)	
Medium	211 (34.5)	147 (34.7)	
High	208 (34.0)	141 (33.3)	
Parity			0.173
Nulliparous	285 (46.6)	200 (47.2)	
Primiparous	185 (30.3)	109 (25.7)	

Characteristics	Term	Preterm	p value
Multiparous	141 (23.1)	115 (27.1)	
Education			0.063
< High school	183 (30.0)	108 (25.5)	
High school	204 (33.4)	171 (40.3)	
> High school	224 (36.7)	145 (34.2)	
Stress during pregnancy			0.170
None	207 (34.0)	123 (29.0)	
Average	258 (42.4)	184 (43.4)	
Very stressful	144 (23.6)	117 (27.6)	
Smoking during pregnancy			0.013
No	478 (78.2)	303 (71.5)	
Yes	133 (21.8)	121 (28.5)	

BMI: body mass index; GWG: gestational weight gain; GDM: gestational diabetes mellitus; IOM: institute of medicine.

Weekly GWG (100g/week) = 10 * GWG (kg)/gestational age (weeks)

χ^2 test for categorical variables and t-test for continuous variables.

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Table 2
Placental Weight and Measures of Weight Status at Birth According to Maternal and Infant Characteristics

	Term (n=611)			Preterm (n=424)		
	Placental weight (g)	Birthweight (g)	Birthweight-for-gestational agez-score	BMI at birth (kg/m ²)	Placental weight (g)	Birthweight (g)
Mean ± SD						
Infant Sex						
Female	471 ± 143	3036 ± 653	-0.67 ± 1.30	12.6 ± 2.0	340 ± 122	1899 ± 711
Male	478 ± 135	3291 ± 632***	-0.42 ± 1.22*	13.0 ± 1.7*	357 ± 122	2046 ± 727*
Maternal factors						
Race						
Black	473 ± 135	3132 ± 656	-0.62 ± 1.28	12.7 ± 1.9	337 ± 116	1887 ± 728
White	486 ± 134	3224 ± 626	-0.38 ± 1.18	12.9 ± 1.9	411 ± 128	2261 ± 572
Hispanic	468 ± 140	3190 ± 668	-0.48 ± 1.28	12.9 ± 1.8	344 ± 121	1993 ± 729
Others	482 ± 156	3218 ± 653	-0.49 ± 1.26	12.9 ± 1.8	324 ± 116***	1952 ± 785**
Pre-pregnancy BMI						
<18.5	404 ± 86	2758 ± 467	-1.33 ± 0.91	11.9 ± 1.7	355 ± 146	2195 ± 614
18.5-24.9	461 ± 135	3088 ± 637	-0.71 ± 1.20	12.5 ± 1.6	360 ± 126	2041 ± 679
25.0-29.9	493 ± 132	3264 ± 595	-0.36 ± 1.19	13.2 ± 2.1	339 ± 113	1890 ± 767
≥30	502 ± 156***	3339 ± 737***	-0.18 ± 1.44***	13.3 ± 1.9***	333 ± 117	1863 ± 765
GWG per 2009 IOM guidelines						
Excessive	498 ± 138	3333 ± 655	-0.23 ± 1.28	13.2 ± 2.0	371 ± 120	2126 ± 738
Adequate	473 ± 148	3105 ± 633	-0.66 ± 1.21	12.6 ± 1.6	357 ± 123	2002 ± 671
Inadequate	421 ± 107***	2873 ± 564***	-1.10 ± 1.07***	12.1 ± 1.5***	319 ± 118***	1793 ± 718***
GDM						
No	470 ± 135	3146 ± 641	-0.59 ± 1.24	12.7 ± 1.8	346 ± 121	1946 ± 705
Yes	556 ± 180**	3575 ± 773***	0.33 ± 1.50***	14.1 ± 2.1***	396 ± 133*	2412 ± 867**
Parity						
Nulliparous	467 ± 136	3125 ± 666	-0.64 ± 1.28	12.6 ± 1.9	345 ± 129	1937 ± 750
Primiparous	480 ± 148	3173 ± 637	-0.51 ± 1.21	13.0 ± 1.8	345 ± 116	1939 ± 675

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Term (n=611)					Preterm (n=424)				
Placental weight (g)					Birthweight-for-gestational agez-score				
Birthweight (g)					Birthweight (g)				
BMI at birth (kg/m ²)					Birthweight-for-gestational agez-score				
BMI at birth (kg/m ²)					Birthweight (g)				
13.1 ± 1.8*					2064 ± 713				
358 ± 115					-0.46 ± 0.94				
11.0 ± 2.1									
10.7 ± 2.1									
10.7 ± 1.9									
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Table 3

Associations of Prenatal Factors, Placental Weight and Birth Weight-for-Gestational Age Z-score in Term and Preterm births.

Birth Weight-for-Gestational Age Z-score						
	Model 1: Predictor + Sex	Model 2: covariates ¹	Model 3: Model 2 +placental weight	Model 4: Model 2+ pre-pregnancy BMI	Model 5: Model 4 + placental weight	Model 6: All predictors + sex + covariates
Term	Mean ± SD	β (95%CI)				
Pre-pregnancy BMI						
<18.5 (n=30)	-1.33 ± 0.91	-0.60 (-1.06, -0.15)**	-0.34 (-0.77, 0.09)	NA	NA	-0.21 (-0.56, 0.15)
18.5-24.9 (n=301)	-0.71 ± 1.20	Ref.	Ref.			Ref.
25-29.9 (n=158)	-0.36 ± 1.19	0.39 (0.15, 0.62)***	0.39 (0.16, 0.61)***	0.28 (0.09, 0.47)**		0.27 (0.09, 0.46)**
>=30 (n=122)	-0.18 ± 1.44	0.56 (0.30, 0.81)***	0.55 (0.30, 0.80)***	0.44 (0.23, 0.65)***		0.41 (0.19, 0.62)***
GWG per 2009 IOM guidelines						
Excessive (n=295)	-0.23 ± 1.28	0.43 (0.21, 0.65)***	0.43 (0.23, 0.64)***	0.31 (0.13, 0.48)***	0.34 (0.13, 0.55)***	--
Adequate (n=191)	-0.66 ± 1.21	Ref.	Ref.	Ref.	Ref.	--
Inadequate (n=125)	-1.10 ± 1.07	-0.43 (-0.71, -0.16)**	-0.32 (-0.58, -0.06)*	-0.14 (-0.36, 0.08)	-0.31 (-0.57, -0.06)*	--
Weekly GWG (100g/ week) (n=611)	-0.54 ± 1.26	0.13 (0.08, 0.18)***	0.13 (0.09, 0.18)***	0.08 (0.04, 0.12)***	0.14 (0.10, 0.19)***	0.08 (0.05, 0.12)***
GDM						
No (n=580)	-0.59 ± 1.24	Ref.	Ref.	Ref.	Ref.	Ref.
Yes (n=31)	0.33 ± 1.50	0.94 (0.50, 1.39)***	0.87 (0.45, 1.29)***	0.68 (0.33, 1.04)***	0.67 (0.24, 1.10)**	0.48 (0.12, 0.83)**
Placental weight						
Low (n=192)	-1.32 ± 1.06	-0.69 (-0.90, -0.48)***	-0.68 (-0.87, -0.49)***	NA	-0.68 (-0.87, -0.49)***	-0.63 (-0.81, -0.44)***
Medium (n=211)	-0.63 ± 1.05	Ref.	Ref.	Ref.	Ref.	Ref.
High (n=208)	0.27 ± 1.15	0.90 (0.69, 1.11)***	0.90 (0.72, 1.09)***	0.86 (0.67, 1.04)***	0.86 (0.67, 1.04)***	0.82 (0.64, 1.00)***
Preterm						
Pre-pregnancyBMI						
<18.5 (n=19)	-0.52 ± 1.08	0.10 (-0.29, 0.49)	0.13 (-0.24, 0.50)	0.24 (-0.06, 0.53)	NA	0.25 (-0.05, 0.54)
18.5-24.9 (n=208)	-0.62 ± 0.78	Ref.	Ref.	Ref.		0

Birth Weight-for-Gestational Age Z-score						
	Model 1: Predictor + Sex	Model 2: Model 1 + covariates ^I	Model 3: Model 2 +placental weight	Model 4: Model 2+ pre-pregnancy BMI	Model 5: Model 4 + placental weight	Model 6: All predictors + sex + covariates
	Mean ± SD	β (95% CI)				
25-29.9 (n=104)	-0.50 ± 0.87	0.12 (-0.07, 0.32)	0.02 (-0.17, 0.21)	-0.01 (-0.16, 0.14)		-0.03 (-0.18, 0.12)
>=30 (n=93)	-0.51 ± 0.86	0.12 (-0.09, 0.32)	0.05 (-0.15, 0.24)	0.07 (-0.08, 0.23)		0.01 (-0.15, 0.17)
GWG per 2009 IOM guidelines						
Excessive (n=142)	-0.53 ± 0.85	0.02 (-0.18, 0.21)	0.06 (-0.12, 0.24)	0.02 (-0.12, 0.17)	0.003 (-0.15, 0.15)	--
Adequate (n=137)	-0.55 ± 0.81	Ref.	Ref.	Ref.	Ref.	--
Inadequate (n=145)	-0.60 ± 0.84	-0.05 (-0.24, 0.15)	-0.13 (-0.31, 0.05)	-0.02 (-0.17, 0.12)	-0.04 (-0.18, 0.11)	--
Weekly GWG (100g/week) (n=424)	-0.56 ± 0.83	0.02 (-0.02, 0.06)	0.03 (-0.004, 0.06)	0.003 (-0.02, 0.03)	0.001 (-0.03, 0.03)	-0.01 (-0.03, 0.02)
GDM						
No (n=400)	-0.59 ± 0.80	Ref.	Ref.	Ref.	Ref.	Ref.
Yes (n=24)	-0.04 ± 1.15	0.56 (0.22, 0.90)***	0.65 (0.33, 0.96)***	0.42 (0.16, 0.68)***	0.67 (0.34, 1.00)***	0.43 (0.16, 0.70)**
Placental weight						
Low (n=136)	-1.14 ± 0.68	-0.58 (-0.74, -0.41)***	-0.58 (-0.72, -0.43)***	NA	NA	-0.58 (-0.72, -0.43)***
Medium (n=147)	-0.57 ± 0.67	Ref.	Ref.	Ref.	Ref.	Ref.
High (n=141)	0.00 ± 0.73	0.57 (0.41, 0.73)***	0.56 (0.42, 0.71)***	0.57 (0.42, 0.71)***		0.55 (0.41, 0.69)***

GWG: gestational weight gain; Weekly GWG (100g/week) = 10*GWG (kg)/gestational age (weeks); GDM: gestational diabetes mellitus;

^I Covariates included maternal age, maternal age², maternal education, maternal race, gestational age, gestational age², parity, smoking during pregnancy, and stress during pregnancy.

* p-value <0.05;

** p-value <0.01;

*** p-value <0.001

Table 4
Associations of Prenatal Factors, Placental Weight and Body Mass Index at Birth

BMI (kg/m ²)							
	Model 1: Predictor + Sex	Model 2: Model 1 + covariates ¹	Model 3: Model 2+placental weight	Model 4: Model2 + pre-pregnancy BMI	Model 5: Model 4+ placental weight	Model 6: All predictors + sex+ covariates	
	Mean ±SD	β (95%CI)					
Term							
Pre-pregnancyBMI							
<18.5 (n=25)	11.9 ± 1.7	-0.6 (-1.3, 0.1)	-0.3 (-1.0, 0.4)	-0.2 (-0.8, 0.5)	NA	-0.2 (-0.8, 0.4)	
18.5-24.9 (n=251)	12.5 ± 1.6	Ref.	Ref.	Ref.		Ref.	
25-29.9 (n=129)	13.2 ± 2.1	0.7 (0.3, 1.1)***	0.6 (0.3, 1.0)***	0.5 (0.2, 0.8)**		0.5 (0.2, 0.8)**	
>=30 (n=100)	13.3 ± 1.9	0.8 (0.4, 1.3)***	0.7 (0.3, 1.1)***	0.6 (0.2, 1.0)**		0.5 (0.1, 0.9)**	
GWG							
Excessive (n=240)	13.2 ±2.0	0.7 (0.3, 1.0)***	0.7 (0.3, 1.0)***	0.5 (0.2, 0.8)**	0.5 (0.2, 0.9)**	0.4 (0.06, 0.7)*	
Adequate (n=163)	12.6 ±1.6	Ref.	Ref.	Ref.	Ref.	Ref.	
Inadequate (n=102)	12.1 ±1.5	-0.5 (-0.9, -0.02)*	-0.4 (-0.8, 0.1)	-0.1 (-0.5, 0.2)	-0.4 (-0.8, 0.05)	-0.2 (-0.5, 0.2)	
Weekly GWG (100g/week) (n=505)	12.8 ± 1.9	0.1 (0.1, 0.2)***	0.2 (0.1, 0.2)***	0.1 (0.03, 0.2)**	0.2 (0.1, 0.3)***	0.1 (0.04, 0.2)**	
GDM							
No (n=477)	12.7 ±1.8	Ref.	Ref.	Ref.	Ref.	Ref.	
Yes (n=28)	14.1 ±2.1	1.4 (0.7, 2.1)***	1.2 (0.6, 1.9)***	0.9 (0.3, 1.6)**	1.0 (0.3, 1.6)**	0.8 (0.1, 1.4)*	
Placental weight							
Low (n=157)	11.9 ±1.4	-0.9 (-1.2, -0.5)***	-0.8 (-1.2, -0.5)***	NA	-0.8 (-1.1, -0.5)***	NA	
Medium (n=174)	12.7 ±1.9	Ref.	Ref.		Ref.	Ref.	
High (n=174)	13.7 ±1.6	1.0 (0.7, 1.4)***	1.0 (0.7, 1.3)***		0.9 (0.6, 1.3)***	0.9 (0.6, 1.2)***	
Preterm							
Pre-pregnancyBMI							
<18.5 (n=14)	11.4 ± 1.2	0.5 (-0.6, 1.6)	0.1 (-0.8, 0.9)	0.1 (-0.6, 0.9)	NA	NA	
18.5-24.9 (n=140)	10.8 ± 1.9	Ref.	Ref.	Ref.		Ref.	
						0.1 (-0.6, 0.9)	

BMI (kg/m ²)						
	Model 1: Predictor + Sex	Model 2: Model 1 + covariates ^I	Model 3: Model 2+placental weight	Model 4: Model2 + pre-pregnancy BMI	Model 5: Model 4+ placental weight	Model 6: All predictors + sex+ covariates
	β (95%CI)					
Mean $\pm$ SD						
25-29.9 (n=61)	10.3 $\pm$ 2.1	-0.6 (-1.2, 0.9)	-0.3 (-0.7, 0.1)			-0.2 (-0.6, 0.2)
>=30 (n=61)	10.4 $\pm$ 2.2	-0.5 (-1.1, 0.1)	-0.1 (-0.5, 0.3)			-0.1 (-0.5, 0.3)
GWG						
Excessive (n=101)	11.0 $\pm$ 2.1	0.4 (-0.2, 1.0)	0.03 (-0.4, 0.4)	0.1 (-0.3, 0.5)	0.05 (-0.3, 0.5)	--
Adequate (n=89)	10.6 $\pm$ 2.0	Ref.	Ref.	Ref.	Ref.	--
Inadequate (n=86)	10.3 $\pm$ 1.9	-0.3 (-0.9, 0.3)	-0.2 (-0.6, 0.2)	-0.4 (-0.9, 0.01)	-0.2 (-0.6, 0.2)	--
Weekly GWG (100g/week) (n=276)	10.6 $\pm$ 2.0	0.1 (0.01, 0.2)*	0.1 (-0.01, 0.1)	0.1 (0.03, 0.2)**	0.07 (-0.01, 0.1)	0.1 (-0.02, 0.1)
GDM						
No (n=260)	10.6 $\pm$ 2.0	Ref.	Ref.	Ref.	Ref.	Ref.
Yes (n=16)	11.6 $\pm$ 2.6	1.0 (-0.1, 2.0)	0.5 (-0.2, 1.2)	0.9 (0.1, 1.7)*	0.6 (-0.2, 1.3)	0.5 (-0.3, 1.2)
Placental weight						
Low (n=86)	9.7 $\pm$ 2.1	-0.9 (-1.5, -0.4)***	NA	-0.7 (-1.1, -0.3)***	NA	-0.7 (-1.05, -0.3)***
Medium (n=100)	10.7 $\pm$ 1.6	Ref.	Ref.	Ref.	Ref.	Ref.
High (n=90)	11.4 $\pm$ 2.0	0.7 (0.1, 1.2)*	0.9 (0.5, 1.3)***	0.9 (0.5, 1.3)***		0.9 (0.5, 1.3)***

GWG: Gestational weight gain; GDM: Gestational Diabetes.BMI: Body Mass Index.

^I Covariates included maternal age, maternal age², maternal education, maternal race, gestational age, gestational age², parity, smoking during pregnancy,and stress during pregnancy.Final sample size was 781 due to missing lengths at birth.

* p-value <0.05;

** p-value<0.01;

*** p-value<0.001