Sex-specific Associations of Maternal Birthweight with Offspring Birthweight in the Omega Study: The role of pre-pregnancy body mass index

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Abstract

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Background: Birthweight is an indicator of fetal growth and development, important determinants of life course health. Maternal birthweight (BW) is one of the strongest predictors of offspring BW, perpetuating generational cycles of poor health and risk for adverse birth outcomes. However, potential non-linear relationships or modifying or mediating factors of maternal and offspring BW associations have not been fully described. *Objective*: We examined (1) the overall maternal-offspring BW association, (2) offspring sex-specific differences in the association, as well as (3) the role of pre-pregnancy body mass index (BMI) as modifier or mediator of the association. *Methods*: The study was conducted among N = 3745 participants of the Omega pregnancy cohort study in Washington State (1996-2008). The exposure variable was maternal BW, modeled as a continuous variable, a linear spline with knots at 2500 grams and 4000 grams (macrosomia), and a binary variable indicating low birthweight (LBW) status (< 2500 grams vs. ≥ 2500 grams). Outcomes were offspring BW and LBW status. Linear and logistic regression models, adjusted for potential confounders, were used to estimate differences in mean offspring BW and odds of LBW, respectively, and corresponding 95% confidence intervals. Effect modification (by offspring sex or pre-pregnancy BMI) was assessed using stratified analyses and interaction terms. Mediation of associations by pre-pregnancy BMI was examined

using the potential outcomes framework of causal analysis. *Results*: The average offspring BW in the study population was 3450.8 grams. Overall, 4.2% of the offspring had LBW. An increase in maternal BW was positively associated with offspring BW among mothers with normal BW (β =22.05 grams offspring BW per 100 grams maternal BW, 95% CI: 17.32, 26.79) or macrosomia (β =23.86 grams offspring BW per 100 grams maternal BW, 95%CI: 7.26, 40.46). LBW mothers had a two-fold higher risk of having LBW infants (OR = 1.96, 95% CI: 1.24, 3.09). Across the distribution of maternal BW we observed a non-linear slope for males (likelihood ratio test (LRT) p-value for improvement in fit by linear spline vs continuous model < 0.001) and a linear slope for females (LRT p-value = 0.9231). The relationship between maternal and offspring BW, as represented by the linear spline, differed by offspring sex (p-value for interaction = 0.0149). Mothers who were LBW and had male offspring had a statistically insignificant 1.2-fold (95% CI: 0.55, 2.72) higher risk of having a LBW infant while mothers who were LBW and had female offspring had a 2.67-fold (95% CI: 1.51, 4.75) higher risk of having a LBW infant (p-value for interaction = 0.120). In sex-specific analyses, maternal-offspring BW associations were similar among women of normal pre-pregnancy BMI or overweight/obese pre-pregnancy BMI groups. Maternal pre-pregnancy BMI mediated 2.57% (95% CI: 2.16%, 3.21%) of the associations between maternal and offspring BW, overall. However this mediation was not evident in offspring sex-specific models. *Conclusion*: We found that the association between maternal and offspring BW may differ by offspring sex, with a non-linear relationship among males, but not females. Pre-pregnancy BMI did not appear to modify maternal-offspring BW associations and it mediated only a small proportion of the associations. Our findings, if supported by other replication studies in diverse populations, provide a new paradigm to understand factors involved in transgenerational BW transmission and guide future investigations of potential mechanisms accounting for maternal-offspring BW associations.

INTRODUCTION

Birth outcomes have both short and long-term impact on life course health. Birthweight is a marker of early life exposures, fetal growth, and development. Poor birth outcomes such as low birthweight (LBW), less than 2500 grams, are associated with an increase in risk for morbidity and mortality in infancy (1, 2), and, chronic diseases in adulthood (3-5). In addition, there is growing evidence that macrosomia (birthweight > 4000 grams or 4500 grams, depending on criteria used) is associated with increased risk for metabolic syndrome later in life (6, 7). LBW (8) and macrosomia (6) have multifactorial origin. A number of proximal risk factors including risk factors during or immediately prior to the pregnancy (such as maternal age and pre-pregnancy body mass index (BMI)) have been identified (8, 9). However, there are factors more distal to the pregnancy which may have more bearing on the perpetuation of poor birth outcomes among certain groups. Researchers have investigated factors antecedent to the pregnancy, such as transgenerational factors – those in one generation that affect the health of the next – as predictors of poor birth outcomes (10).

In 1968,Ounsted and Ounsted theorized that women who had constrained *in utero* growth, resulting in their LBW, were more likely to have offspring with intrauterine growth retardation (11). Since this seminal paper, a number of studies that examined maternal and offspring birth outcomes have been published (12-14). Maternal birthweight (BW) has been consistently shown to be one of the strongest predictors of offspring BW (15). Each 100 gram increase in maternal BW was associated with, on average, an additional 11-28 gram increase in offspring BW (16-19); mothers that were LBW at their own birth had a two-fold increase in risk of having a LBW infant (20). However, relationships, including potential non-linear relationships, between maternal and offspring BW have not been fully described (21, 22). Further, offspring sex-specific differences in maternal-offspring BW associations (23) are not clear. Despite the association of BW with adult BMI (24, 25) and the importance of pre-pregnancy BMI on the course and outcomes of the pregnancy (26), the role of maternal pre-pregnancy BMI as moderator or mediator of maternal-offspring BW associations has also not been examined. To address these potential limitations, we used a well-characterized pregnancy cohort to investigate associations between maternal and offspring BW. We examined offspring sex specific differences in associations as well as the role of pre-pregnancy BMI as modifier or mediator of the associations.

METHODS

Study setting and study population

The study was conducted among participants of the Omega study. The Omega study is a prospective cohort study (1996-2008) of pregnant women designed to examine risk factors for pregnancy complications and adverse outcomes (27). Women were recruited from prenatal care clinics affiliated with Swedish Medical Center and Tacoma General Hospital in Washington State, and were eligible to enroll if they were at least 18 years of age, able to speak and read English, initiated prenatal care before 16 weeks of gestation, and planned to carry the pregnancy to term and deliver at one of the two study hospitals. Approximately 4600 women were enrolled in the study and 4343 had singleton live-births. We had complete BW data (for the mother and the singleton live-born offspring) for N=3804 Omega study participants. In the current analyses, we included infants with BW at least 300 grams (N=3800). Participants were then excluded from the final analysis if they were missing data on offspring sex (n=3), smoking history (n=4), gestational diabetes (n=48), or preeclampsia (n=1). These were not mutually exclusive. We performed complete case analysis, thus making the assumption that the data are missing completely at random (MCAR), and the final sample for analysis included 3745 mother-offspring dyads. The protocol used in the Omega study was approved by the Institutional Review Boards of Swedish Medical Center and Tacoma General Hospital and all women provided written informed consent.

Data collection

In-person interviews by trained study personnel were conducted using structured questionnaires shortly after enrollment (on average 17 weeks gestation). The interviews were used to collect data on socio-demographic characteristics, medical and family history of participants, including self-reported mothers' BW at their own birth in pounds and ounces, race, education, height, pre-pregnancy weight, age, and prenatal cigarette smoking and alcohol consumption. Pregnant women were followed until delivery. Information on infant BW in grams, clinical estimate of gestational age based on early ultra

sound, and offspring-sex (male/female) were abstracted from the hospital record after delivery, as was information on maternal health during the pregnancy and pregnancy complications.

Exposure, outcome, effect modifiers/mediator, and covariates

The primary exposure of interest was maternal BW, which was converted from pounds and ounces to grams. Maternal BW was modeled as 1) a continuous variable with each 1-unit change corresponding to a 100 gram change, 2) a linear spline with knots at 2500 grams (LBW) and 4000 grams (macrosomia), and 3) a binary variable indicating LBW status (< 2500 grams vs. ≥ 2500 grams). The outcomes were offspring BW (as a continuous variable) and LBW status. Offspring sex was examined as a potential effect modifier, as was maternal pre-pregnancy BMI. The latter was calculated using the standard BMI formula for adults, weight (kg)/[height (m)]^2 and the following categories: underweight (< 18.5 kg/m^2), normal weight (18.5 – 24.99 kg/m^2) and overweight/obese (≥ 25 kg/m^2). Pre-pregnancy BMI was also examined as a mediator. It was included as a nominal categorical variable when testing effect modification, and as a continuous variable when testing mediation. Race (dummy variables: white, black, Asian, other), family history of diabetes (yes/no), smoking history (dummy variables: never, current, former smoker), educational attainment (≤ high school/ > high school), maternal age (linear spline: knots at 25 and 35 years), marital status (married/ unmarried), parity (nulliparous/ multiparous), gestational diabetes (yes/no), preeclampsia (yes/no), and chronic hypertension (yes/no) were included as covariates in the analyses, described below.

Statistical analyses

We used means (standard deviation) and counts (percentage) to summarize continuous variables and categorical variables, respectively, which characterize study participants. First, we examined overall maternal-offspring BW associations by fitting linear regression models to estimate beta coefficients (ß) and 95% confidence intervals (95% CIs) of the association between offspring BW and maternal BW. Maternal BW was modeled as a continuous variable, linear spline (28) and binary variable, as described above. In the first scenario, the slope estimated the average difference in mean offspring BW associated with a 100 gram increase in maternal BW. In the second scenario, the slope estimated the

difference in mean offspring BW associated with a 100 gram increase in maternal BW among LBW mothers (< 2500 grams), normal BW (2500-3999 grams) mothers, and macrosomic (≥ 4000 grams) mothers. The statistical significance of the change in slope between groups defined by maternal BW (i.e. LBW, normal BW, and macrosomia) was determined by the p-value of the coefficients obtained from a marginal linear spline model. We used the likelihood ratio test (LRT) to test the hypothesis that the maternal-offspring BW relationship was linear, against the alternative that it was not linear throughout the entire distribution of maternal BW and is better approximated using the linear spline. In the third scenario, we estimated the difference in mean BW of offspring delivered by LBW mothers compared to non-LBW mothers. We also fit logistic regression models to estimate the odds ratios (ORs) and corresponding 95% CIs of offspring LBW associated with maternal BW modeled as a continuous variable, linear spline, and binary variable, as described above. We fit three Models in these analyses: Model 1 (unadjusted), Model 2 (adjusted for potential confounders and precision variables selected on the basis of our causal framework: maternal race, family history of diabetes, smoking history and educational attainment, maternal age, marital status, parity, and offspring sex), and Model 3 (adjusted for Model 2 variables and potential factors in the causal pathway: gestational diabetes, preeclampsia, chronic hypertension, and pre-pregnancy BMI).

We then examined differences in this association by offspring sex by repeating the analyses and including in the model indicators for maternal BW, offspring sex, and an interaction term between maternal BW and offspring sex. We used the Wald test to determine the statistical significance of the multiplicative interaction (two-sided p-value < 0.05). Similarly, we examined effect modification by pre-pregnancy BMI, among males and females separately, by fitting the previously described models and including indicators for maternal BW, pre-pregnancy BMI, and an interaction term between maternal BW and pre-pregnancy BMI. The second and third scenario analyses for the underweight pre-pregnancy BMI category, and all logistic regression, was omitted here due to small numbers within pre-pregnancy BMI strata.

Finally, we assessed mediation by pre-pregnancy BMI of the sex-specific association between maternal and offspring BW using the potential outcomes approach to mediation analysis (29). This is a simulation approach in which the outcome (offspring BW) is imputed under various counterfactual

states of exposure (maternal BW) and mediator (pre-pregnancy BMI) amalgamations. The average indirect effect is then calculated based on the imputed outcomes as the average difference in the outcome under counterfactual states when the exposure was held constant, but the mediator is allowed to vary. The average direct effect is conversely the average difference in the outcome under counterfactual states when the exposure is allowed to vary but the mediator is held constant.

Statistical significance was determined using a two-sided p-value < 0.05.All analyses were carried out using Stata version 13.1, software (Stata Corporation, College Station, Texas).

RESULTS

Average age of study participants was 32.7 years (SD = 4.4; range 18-48) (**Table 1**). About half of the offspring were male (51.2%) and the majority of mothers were white (86.4%), nulliparous (62.1%), married (91.5%), and with a high school education (96.6%). Overall, an increase in maternal BW was positively associated with offspring BW (adjusted ß = 18.39 grams of offspring BW per 100 grams of maternal BW; 95% CI: 15.14, 21.63) and inversely associated with the risk of LBW (adjusted OR = 0.95 per 100 grams of maternal BW; 95% CI: 0.92, 0.98) (**Table 2**). These associations did not change after additional adjustment for pregnancy complications. The maternal-offspring BW association was positive and statistically significant among mothers with normal BW (adjusted ß = 22.05 grams of offspring BW per 100 grams of maternal BW; 95% CI: 17.32, 26.79) or macrosomia (adjusted ß = 23.86 grams of offspring BW per 100 grams of maternal BW; 95% CI: 7.26, 40.46), but not among LBW mothers (adjusted ß = -8.56; 95% CI: -22.88, 5.75). The change in slope between LBW and normal BW/macrosomic mothers was statistically significant and the linear spline models fit the maternal-offspring BW association better than the continuous model (LRT p-value = 0.0005). Offspring of LBW mothers weighed less, on average, than offspring of non-LBW mothers (adjusted ß = -166.43; 95% CI: -229.17, -103.70) and were almost twice as likely to be LBW themselves (adjusted OR = 1.96; 95% CI: 1.24, 3.09) (**Table 2**).

The overall maternal-offspring BW association was positive among males (adjusted ß = 17.22 grams of offspring BW per 100 grams of maternal BW; 95% CI: 12.74, 21.69) and females (adjusted ß = 19.68 grams of offspring BW per 100 grams of maternal BW; 95% CI: 14.99, 24.37). Maternal BW was

inversely associated with the odds of LBW among male (adjusted OR = 0.95 per 100 grams of maternal BW; 95% CI 0.91, 0.99) and female (adjusted OR = 0.94 per 100 grams of maternal BW; 95% CI: 0.91, 0.98) offspring (**Table 3**). Among females, there was no evidence that the maternal-offspring BW association differed among groups defined by maternal BW (i.e. LBW, normal BW, and macrosomia; see **Figure 1**) (LRT for improvement in fit by linear spline vs continuous model p-value = 0.9231). Females of LBW mothers weighed less, on average, than those of non-LBW mothers (adjusted ß = -224.94; 95% CI: -312.50, -137.37) and were at increased risk of being LBW themselves (adjusted OR = 2.67; 95% CI: 1.51, 4.75) (**Table 3**). However, among males, there was evidence of a difference in the maternal-offspring BW association between groups defined by maternal BW (LRT p-value < 0.001); LBW mothers (adjusted ß = -31.13 grams of offspring BW per 100 grams of maternal BW; 95% CI: -50.97, -11.28), normal BW mothers (adjusted ß = 23.97 grams of offspring BW per 100 grams of maternal BW; 95% CI: 17.41, 30.53), and macrosomic mothers (adjusted ß = 24.30 grams of offspring BW per 100 grams of maternal BW; 95% CI: 3.90, 44.69). Males of LBW mothers weighed less, on average, than those of non-LBW mothers (adjusted ß = -104.56; 95% CI: -194.62, -14.50) but the potential increase in risk of LBW was not statistically significant (adjusted OR = 1.22; 95% CI: 0.55, 2.72) (**Table 3**). The relationship between maternal and offspring BW, as represented by the linear spline, differed by offspring sex (p-value for interaction = 0.0149; see **Figure 1**).

Among mothers that were underweight pre-pregnancy, the overall maternal-offspring BW association was not significant for males (adjusted ß = 6.70; 95% CI: -12.44, 25.84) or females (adjusted ß = 19.60; 95% CI: -7.99, 47.19) (**Table 4**). Among normal and overweight/obese pre-pregnancy BMI mothers, we observed comparable non-linearity in the maternal-offspring BW association for male offspring (**Figure 2**), and comparable linearity in the association among female offspring (**Figure 3**). Male offspring of LBW mothers with normal pre-pregnancy BMI weighed less, on average, than those of non-LBW mothers (adjusted ß = -117.09; 95% CI: -227.69, -6.50), as did female offspring of LBW mothers, compared with their counterparts (adjusted ß = -170.61; 95% CI: -273.57, -67.66) (**Table 4**). Among overweight/obese pre-pregnancy BMI mothers, females of LBW mothers weighed less, on average, than those delivered by non-LBW mothers (adjusted ß = -367.94; 95% CI: -528.28, -207.59);

however, the corresponding association among males of LBW mothers was not statistically significant (adjusted ß = -19.57; 95% CI: -201.90, 162.76) in this BMI category (**Table 4**).

The overall direct effect of maternal BW on offspring BW was 18.177 (95% CI: 14.525, 21.619). The overall indirect effect of maternal BW on offspring BW mediated through pre-pregnancy BMI was 0.480 (95% CI: 0.068, 0.973) (**Table 5**). On average, 2.57% (95% CI: 2.16%, 3.21%; p = 0.038) of the total effect of maternal BW on offspring BW was mediated through pre-pregnancy BMI. The sex-specific indirect effects of maternal BW on offspring BW through pre-pregnancy BMI were not statistically significant for males (0.724; 95% CI: -0.031, 1.635) or females (0.290; 95% CI: -0.102, 0.818).

DISCUSSION

In the current study, maternal BW was positively associated with offspring BW, particularly among normal BW and macrosomic mothers. On average, offspring of LBW mothers weighed 166.4 grams less than those born to non-LBW mothers and were about twice as likely to be LBW themselves. We also found evidence of potential effect modification of the maternal-offspring BW associations by offspring sex. More specifically, we identified a J-shaped relationship among males and a linear relationship among females. The reduction in offspring BW and the higher risk of offspring LBW among LBW mothers, compared with non-LBW mothers, was more pronounced and statistically significant among female offspring. The sex-specific maternal-offspring BW associations were not modified by pre-pregnancy BMI among women with normal and overweight/obese pre-pregnancy BMI. Due to small numbers in the underweight pre-pregnancy BMI group, conclusions could not be made about associations in this strata. Pre-pregnancy BMI mediated a small proportion of the overall maternal-offspring BW associations, but mediation did not appear to be statistically significant in offspring sex-specific analyses.

The findings of this study are consistent with previous reports which have described a positive association between maternal and offspring BW (16-19). For instance, Magnus et al. in 1993 published a cohort study using medical birth registry data in Norway and reported a three-fold risk of LBW among mothers born LBW, with decreasing odds with increasing maternal BW (30). See **Table 6** for a description of studies (and findings) that examined maternal and offspring BW associations. Few studies

have explored offspring sex-specific differences in this association. A study by Carr-Hill et al. (1987) reported correlations between maternal and offspring BW among mother-daughter pairs (Pearson's correlation r = 0.173; 95% CI: 0.053, 0.287) that were stronger than corresponding correlations among mother-son pairs (Pearson's correlation r = 0.140; 95% CI: 0.013, 0.262) (23); and, a study by Voldner et al. (2009) reported results from multivariable regression models for female offspring (β = 184 grams per 1 kg of maternal BW; 95% CI: 87, 280) and male offspring (β = 148 grams per 1 kg of maternal BW; 95% CI: 51, 243) (31). These previous findings are consistent with our findings of stronger associations among female offspring. To our knowledge, our study is the first to report sex-specific transgenerational transmission of LBW risk, having found higher offspring risk of LBW among females born to LBW mothers, than for males.

Findings from epidemiologic (32) and animal studies (33) support the matrilineal transmission of small birth size. The biological mechanisms by which this happens, however, are less clear. The role of offspring sex in associations of maternal characteristics with trajectories and ultimate potentials of fetal growth and development are active areas of investigation, and still remain unclear (34). Most prior research deals with exposures and maternal characteristics during the perinatal period (35, 36). Researchers have argued for mediation of the maternal-offspring BW association through genetic, environmental, or epigenetic mechanisms involving intrauterine growth retardation (11, 37), short gestational length, or a combination of the two (38-45). The role of these factors in offspring sex-specific differences in associations is a potential area of future research.

Although the results of studies by Hackman et al. and Klebanoff et al. from the early 1980s suggested non-linearity in the maternal-offspring BW association (the lowest BW mothers did not have offspring of lowest mean BW) (21, 22), few recent studies have explored this. Stein and Lumey (2000), using the Dutch Famine Cohort, limited their sample to term infants and reported a non-linear relationship between maternal and offspring birthweight (46). Hypoppen et al. (2004) found a positive maternal-offspring BW association only among mothers with maternal BW between -1 SD and +1 SD, while mothers with BW on the tail ends of the distribution had level slopes which did not reach statistical significance (47). These studies adjusted for offspring sex and other covariates, and did not evaluate sex-specific differences.

Previous studies suggest a positive association between maternal BW and maternal adulthood BMI (25), and several others report a positive association between pre-pregnancy BMI and offspring BW in offspring sex-adjusted analyses (26, 48). Hyppopen et al. reported that adjustment for pre-pregnancy BMI in a linear regression model did not affect the maternal-offspring BW association much (47). Similarly, in our mediation analyses, we did not find that maternal pre-pregnancy BMI mediated the offspring sex-specific relationship between maternal and offspring BW in a meaningful way. However, this research should be replicated in a cohort with larger numbers of women that are underweight pre-pregnancy.

The strengths of this study include the prospective cohort study design, the well-characterized study population, large sample size, the modeling of the exposure using different forms (including linear splines), examining sex-specific associations, and exploring potential effect modification or mediation (using the potential outcomes framework for causal analysis) by pre-pregnancy BMI. Our study has several limitations that deserve mention. First, we used self-reported maternal BW and pre-pregnancy height and weight. This may lead to potential misclassification. However, self-reported height and weight has been found to have high sensitivity and specificity among females (49). In addition, the cohort study design will minimize the risk of differential misclassification. Second, racial/ethnic minorities were not well represented in our study population. Researchers have found potential race-specific differences in transgenerational LBW risk (50). Unfortunately, we were not able to assess potential effect modification by race. Third, the potential outcomes approach to mediation analysis requires the assumption of sequential ignorability, i.e. the assumption that the exposure is unconfounded after adjustment for covariates and the mediator is random after adjustment for the exposure and pre-exposure covariates. We were unable to perform sensitivity analysis to investigate the robustness of the mediation analysis results to the violation of the sequential ignorability assumption. Fourth, we performed complete case analysis, excluding from the final analysis participants with any missing data on the variables of interest. Almost 14% of participants with live-births were excluded through list-wise deletion, the majority of whom were missing data on the exposure of interest. Complete case analysis decreases efficiency, and a violation of the untestable MCAR assumption may lead to biased estimates. Finally, the generalizability of our findings may be

limited to other populations that have similar characteristics to the Omega study population. Future studies in other populations are warranted.

In sum, we found that offspring sex is an effect modifier of the well-established association between maternal and offspring BW. Our findings, if supported by other replication studies in diverse populations, provide a new paradigm to understand transgenerational BW transmission that motivates and guides future investigations of potential mechanisms for maternal-offspring BW associations. This is of public health significance as it could help improve identification of populations at risk for poor birth outcomes and institute preventative and/or early diagnostic intervention.

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Table1. Selected Study Participant Characteristics (N=3745)

	Mean (SD)	
Maternal age	32.74 (4.44)	
Maternal birthweight	3,271.78 (529.34)	
Offspring birthweight	3,450.80 (547.79)	
Maternal pre-pregnancy BMI	23.51 (4.73)	
	N	Percentage
Male offspring	1,916	51.16
Maternal race		
White	3,237	86.44
Black	61	1.63
Asian	259	6.92
Other	188	5.02
Smoking		
Never	2,729	72.87
Former smoker	798	21.31
Smoked during pregnancy	218	5.82
Nulliparous	2,325	62.08
≤High school education	127	3.39
Unmarried	320	8.54
Gestational diabetes	186	4.97
Family history of diabetes	539	14.39
Preeclampsia	97	2.59
Chronic hypertension	155	4.14
Maternal pre-pregnancy BMI		
Underweight	163	4.35
Normal weight	2,648	70.71
Overweight/obese	934	24.94
Offspring birthweight		
Low birthweight	158	4.22
Normal birthweight	3,055	81.58
Macrosomia	532	14.21
Maternal birthweight		
Low birthweight	311	8.30
Normal birthweight	3,137	83.77
Macrosomia	297	7.93

Note: BMI = body mass index. underweight (< 18.5 kg/m2), normal weight (18.5 – 24.99 kg/m2) and overweight/obese (≥ 25 kg/m2)

Table 2. Associations of maternal birthweight with offspring birthweight and offspring risk of low birthweight

	Infant Birthweight (grams) – Linear Regression Analyses		
	Model 1 β [a] 95% CI	Model 2 β [b] 95% CI	Model 3 β [c] 95% CI
Maternal BW (grams), continuous [d] (N=3745)	**19.42 ** (16.16, 22.68)**	**18.39 ** (15.14, 21.63)**	**17.75 ** (14.54, 20.95)**
Maternal BW (grams), linear spline [d]			
LBW mothers (N=311)	-6.97 (-21.38, 7.44)	-8.56 (-22.88, 5.75)	-8.40 (-22.53, 5.74)
NBW mother (N=3,137)	**22.97 ** (18.22, 27.73)**	**22.05 ** (17.32, 26.79)**	**21.21 ** (16.53, 25.89)**
Macrosomic mothers (N=297)	**24.86 * (8.18, 41.55)**	**23.86 * (7.26, 40.46)**	**23.74 * (7.34, 40.15)**
Maternal LBW status, categorical [e]	**-182.52 ** (-245.86, -119.18)**	**-166.43 ** (-229.17, -103.70)**	**-160.73 ** (-222.64, -98.83)**

	Infant Low Birthweight Risk – Logistic Regression Analyses		
	Model 1 OR[a] 95% CI	Model 2 OR[b] 95% CI	Model 3 OR[c] 95% CI
Maternal BW (grams), continuous [d](N=3745)	**0.94 ** (0.92, 0.97)**	**0.95 ** (0.92, 0.98)**	**0.95 * (0.92, 0.98)**
Maternal BW (grams), linear spline [d]			
LBW mothers (N=311)	0.95 (0.87, 1.05)	0.96 (0.87, 1.06)	0.96 (0.87, 1.07)
NBW mother (N=3,137)	**0.95 * (0.91, 0.99)**	**0.96 * (0.91, 1.00)**	0.96 (0.91, 1.00)
Macrosomic mothers (N=297)	0.78 (0.55, 1.11)	0.78 (0.54, 1.11)	0.79 (0.56, 1.13)
Maternal LBW status, categorical [e]	**2.06 * (1.31, 3.23)**	**1.96 * (1.24, 3.09)**	**1.83 * (1.14, 2.94)**

Note: BW = birthweight. LBW = low birthweight. * p-value < 0.05; ** p-value < 0.001

[a]Model 1 - Unadjusted: crude change in mean infant BW. [b]Model 2 - adjusted: adjusted for potential confounding variables: maternal race, family history of diabetes, maternal smoking history and educational attainment; precision variables: age, marital status, parity, and offspring-sex. [c]Model 3 –adjusted: adjusted for Model 2 variablesplus gestational diabetes, preeclampsia, chronic hypertension, and pre-pregnancy body mass index. [d] Per 100 grams maternal birthweight. [e]Comparing LBW mothers and non-LBW mothers (reference).

Table 3. Offspring sex-specific associations of maternal birthweight with offspring birthweight and offspring risk of low birthweight

	Infant Birthweight (grams) – Linear Regression Analyses					
	Model 1		Model 2		Model 3	
	β [a] 95% CI		β [b] 95% CI		β [c] 95% CI	
	Male (N=1,916)	Female (N=1,829)	Male (N=1,916)	Female (N=1,829)	Male (N=1,916)	Female (N=1,829)
Maternal BW (grams), continuous [d] (N=3745)	**17.51 ** (13.03, 21.99)**	**21.71 ** (16.02, 25.41)**	**17.22 ** (12.74, 21.69)**	**19.68 ** (14.99, 24.37)**	**16.54 ** (12.12, 20.96)**	**19.07 ** (14.44, 23.71)**
Interaction P-value	0.333		0.455		0.437	
Maternal BW (grams), linear spline [d]						
LBW mothers (N=311)	**-31.16 *** (-51.09, -11.24)	19.23 (-1.35, 39.82)	**-31.13 *** (-50.97, -11.28)	15.78 (-4.89, 36.45)	**-29.80 *** (-49.41, -10.20)	14.62 (-5.80, 35.04)
NBW mother (N=3,137)	**24.23 ** (17.67, 30.79)**	**20.73 ** (13.87, 27.59)**	**23.97 ** (17.41, 30.53)**	**19.97 ** (13.13, 26.82)**	**22.55 ** (16.07, 29.04)**	**19.84 ** (-13.08, 26.60)**
Macrosomic mothers (N=297)	**24.84 *** (4.42, 45.27)	22.55 (-5.88, 50.99)	**24.30 *** (-3.90, 44.69)	22.89 (-5.50, 51.28)	**26.09 *** (5.92, 46.25)	19.35 (-8.68, 47.37)
Interaction P-value	0.0065		0.0149		0.0183	
Maternal LBW status, categorical [e]	**-105.80 *** (-196.16, -15.43)	**-247.23 ** (-334.92, -159.54)**	**-104.56 *** (-194.62, -14.50)	**-224.94 ** (-312.50, -137.37)**	**-97.36 *** (-186.19, -8.52)	**-220.70 ** (-307.11, -134.29)**
Interaction P-value	0.028		0.061		0.051	

	Infant Low Birthweight Risk – Logistic Regression Analyses					
	Model 1		Model 2		Model 3	
	OR[a] 95% CI		OR[b] 95% CI		OR[c] 95% CI	
	Male (N=1,916)	Female (N=1,829)	Male (N=1,916)	Female (N=1,829)	Male (N=1,916)	Female (N=1,829)
Maternal BW (grams), continuous [d] (N=3745)	**0.95 *** (0.91, 0.99)	**0.94 *** (0.90, 0.97)	**0.95 *** (0.91, 0.99)	**0.94 *** (0.91, 0.98)	**0.96 *** (0.91, 1.00)	**0.95 *** (0.91, 0.99)
Interaction P-value	0.535		0.805		0.789	
Maternal BW (grams), linear spline [d]						
LBW mothers (N=311)	1.13 (0.89, 1.45)	**0.88 *** (0.79, 0.98)**	1.12 (0.88, 1.42)	0.90 (0.80, 1.01)	1.12 (0.87, 1.44)	0.90 (0.80, 1.02)
NBW mother (N=3,137)	**0.93 *** (0.87, 1.00)**	0.97 (0.91, 1.03)	**0.94 *** (0.88, 1.00)**	0.97 (0.91, 1.03)	0.94 (0.88, 1.01)	97 (0.91, 1.03)
Macrosomic mothers (N=297)	0.75 (0.43, 1.31)	0.82 (0.52, 1.29)	0.74 (0.42, 1.31)	0.81 (0.51, 1.29)	0.75 (0.43, 1.31)	0.84 (0.53, 1.33)
Interaction P-value	0.3006		0.4151		0.4893	
Maternal LBW status, categorical [e]	1.17 (0.53, 2.59)	**3.01 ** (1.71, 5.28)**	1.22 (0.55, 2.72)	**2.67 * (1.51, 4.75)**	1.11 (0.49, 2.52)	**2.57 * (1.42, 4.66)**
Interaction P-value	0.057		0.120		0.105	

Note: BW = birthweight. . LBW = low birthweight. * p-value < 0.05; ** p-value < 0.001

[a] Model 1 - Unadjusted: crude change in mean infant BW. [b] Model 2 - adjusted: adjusted for potential confounding variables: maternal race, family history of diabetes, maternal smoking history and educational attainment; precision variables: age, marital status, parity, and offspring-sex. [c] Model 3 –adjusted: adjusted for Model 2 variables plus gestational diabetes, preeclampsia, chronic hypertension, and pre-pregnancy body mass index. [d] Per 100 grams maternal birthweight. [e] Comparing LBW mothers and non-LBW mothers (reference).

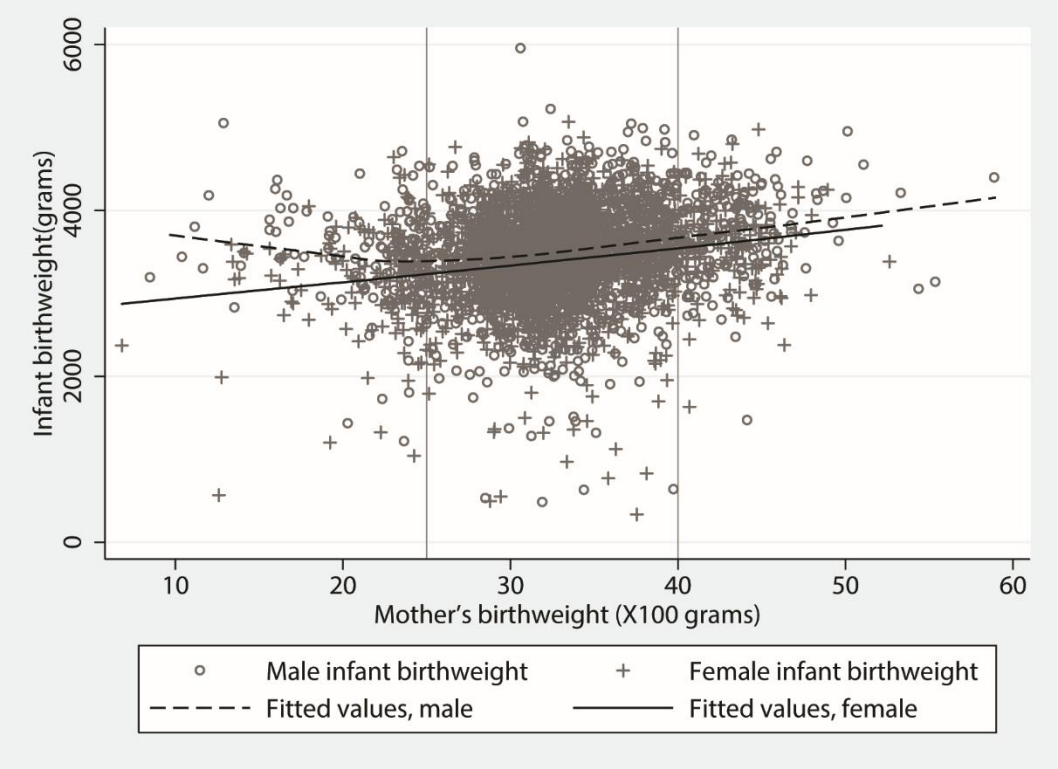

Figure 1. Sex-specific associations of maternal and offspring birthweight. Fitted values.

Table 4. Associations of maternal birthweight with offspring birthweight and offspring risk of low birthweight, by maternal pre-pregnancy body mass index

	Infant Birthweight (grams) – Linear Regression Analyses					
	Model 1 β [a] 95% CI		Model 2 β [b] 95% CI		Model 3 β [c] 95% CI	
	Male (N=1,916)	Female (N=1,829)	Male (N=1,916)	Female (N=1,829)	Male (N=1,916)	Female (N=1,829)
Underweight pre-pregnancy BMI (<18.5kg/m^2)						
Maternal BW (grams), continuous [d]	8.15 (-11.08, 27.37)	22.02 (-5.52, 49.56)	6.70 (-12.44, 25.84)	19.60 (-7.99, 47.19)	5.46 (-13.50, 24.43)	20.05 (-7.40, 47.50)
Normal pre-pregnancy BMI (18.5-25kg/m^2)						
Maternal BW (grams), continuous [d]	**18.92** ** (**13.33, 24.51**)	**18.30** ** (**12.79, 23.80**)	**18.34** ** (**12.76, 23.93**)	**17.74** ** (**12.22, 23.27**)	**18.06** ** (**12.52, 23.59**)	**17.78** ** (**12.29, 23.28**)
Maternal BW (grams), linear spline [d]						
LBW mothers(N=311)	**-32.21** * (**-57.52, -6.91**)	17.67 (-5.40, 40.74)	**-30.58** * (**-55.81, -5.35**)	14.37 (-9.01, 37.76)	**-30.02** * (**-54.99, -5.04**)	14.70 (-8.57, 37.97)
NBW mother (N=3,137)	**26.00** ** (**18.04, 33.96**)	**19.80**** (**11.69, 27.91**)	**24.80** ** (**16.83, 32.78**)	**19.84** ** (**11.72, 27.96**)	**24.38** ** (**16.48, 32.27**)	**19.89** ** (**11.82, 27.97**)
Macrosomic mothers (N=297)	26.79 (-2.00, 55.57)	6.88 (-26.95, 40.73)	28.86 (0.05, 57.66)	5.44 (-28.45, 39.33)	28.56 (0.05, 57.08)	4.97 (-28.75, 38.68)
Maternal LBW status, categorical [e]	**-117.75** * (-228.89, -6.61)	**-187.35** ** (-290.01, -84.69)	**-117.09** * (-227.69, -6.50)	**-170.61** * (-273.57, -67.66)	**-118.65** * (-228.18, -9.13)	**-170.12** * (-272.56, -67.69)
Overweight and obese pre-pregnancy BMI (>25kg/m^2)						
Maternal BW (grams), continuous [d]	**14.01** * (**5.39, 22.63**)	**25.36** ** (**16.80, 33.92**)	**13.56** * (**4.93, 22.19**)	**24.23** ** (**15.66, 32.79**)	**13.76** * (**5.21, 22.31**)	**23.78** ** (**15.24, 32.33**)
Maternal BW (grams), linear spline [d]						
LBW mothers(N=311)	-34.06 (-72.18, 4.06)	26.71 (-16.44, 69.87)	-37.43 (-75.53, 0.68)	23.51 (-19.77, 66.79)	-37.31 (-75.05, 0.43)	14.61 (-28.58, 57.81)
NBW mother (N=3,137)	**18.65** * (**5.14, 32.15**)	**22.18 *** (**9.74, 34.96**)	**19.11** * (**5.62, 32.59**)	**20.74 *** (**7.97, 33.52**)	**17.74** * (**4.37, 31.10**)	**21.40 *** (**8.65, 34.14**)
Macrosomic mothers (N=297)	29.65 (-4.13, 63.42)	46.62 (-2.59, 95.83)	27.32 (-6.52, 61.16)	**49.77 *** (**0.53, 99.01**)	**34.15 *** (**0.50, 67.80**)	**49.97 *** (**0.99, 98.95**)
Maternal LBW status, categorical [e]	-25.59 (-208.11, 156.92)	**-396.13** ** (**-556.26, 236.01**)	-19.57 (-201.90, 162.76)	**-367.94** ** (**-528.28, -207.59**)	-3.62 (-184.30, 177.06)	**-353.55** ** (**-513.61, -193.49**)

Note: BW = birthweight. LBW = low birthweight. BMI = body mass index. * p-value < 0.05; ** p-value < 0.001

[a] Model 1 - Unadjusted: crude change in mean infant BW. [b] Model 2 - adjusted: adjusted for potential confounding variables: maternal race, family history of diabetes, maternal smoking history and educational attainment; precision variables: age, marital status, parity, and offspring-sex. [c] Model 3 –adjusted: adjusted for Model 2 variables plus gestational diabetes, preeclampsia, chronic hypertension, and pre-pregnancy body mass index. [d] Per 100 grams maternal birthweight. [e] Comparing LBW mothers and non-LBW mothers (reference).

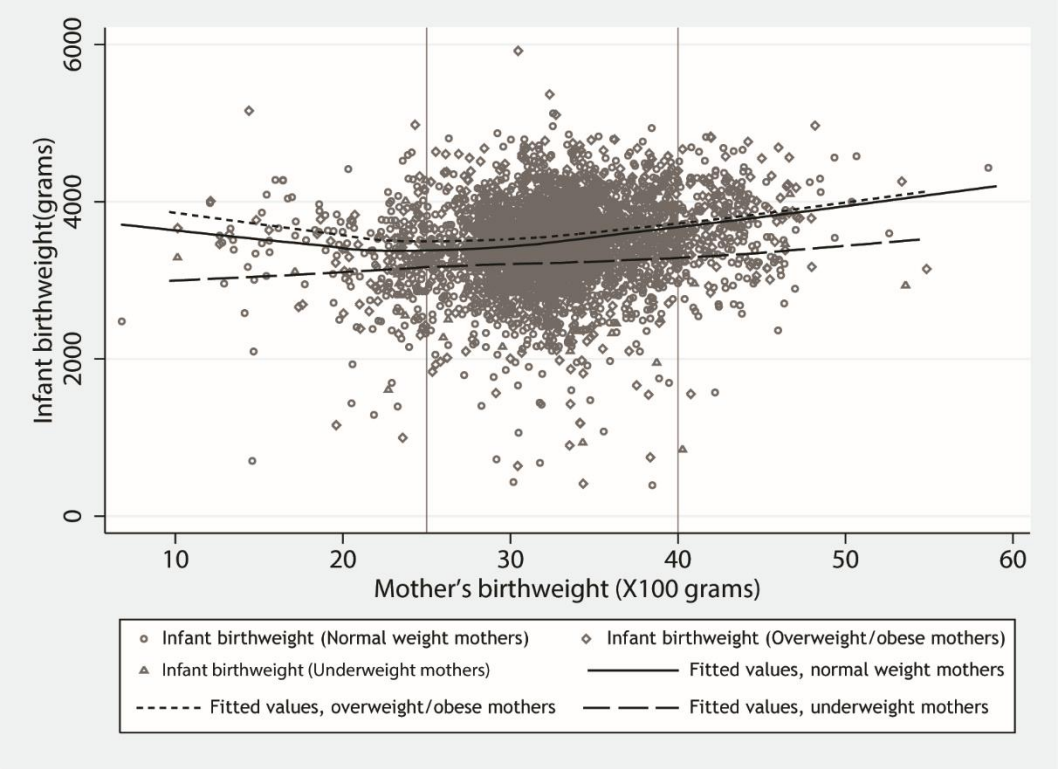

Figure 2. Associations of maternal and male offspring birthweight, by pre-pregnancy body mass index. Fitted values.

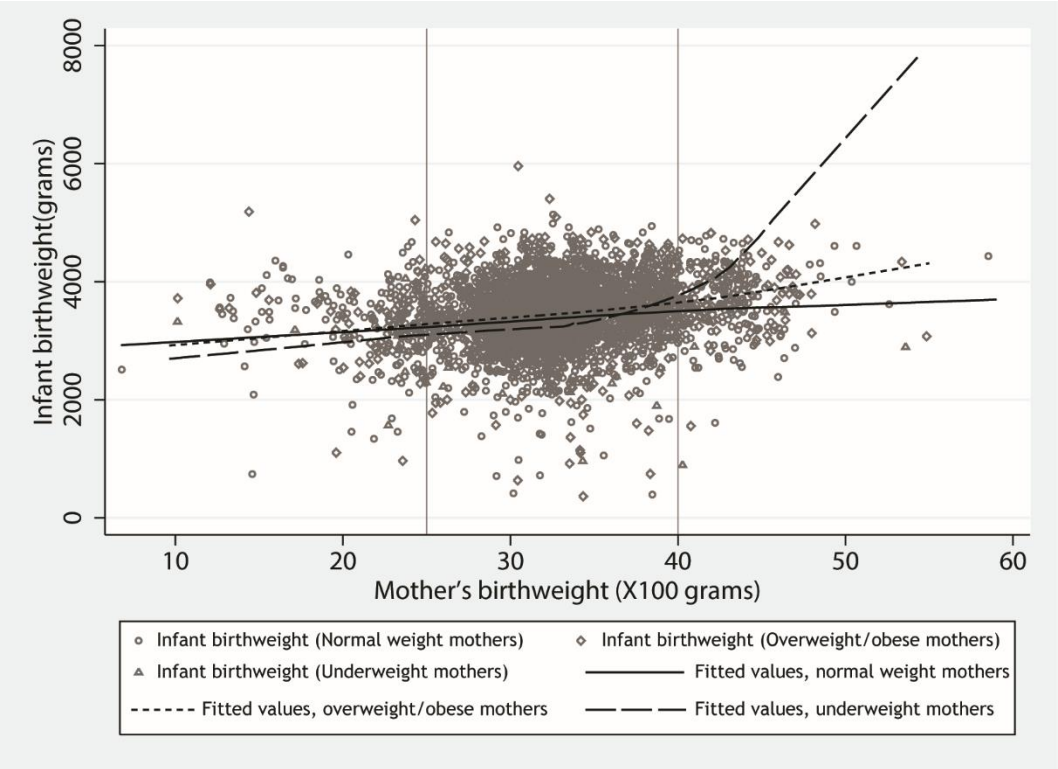

Figure 3. Associations of maternal and female offspring birthweight, by pre-pregnancy body mass index. Fitted values.

Table 5. Infant sex-specific direct/indirect effects of maternal birthweight on infant birthweight – potential mediation (indirect effect) by maternal pre-pregnancy body mass index

	Overall Mean effect (95% CI)	**Males** Mean effect (95% CI)	**Females** Mean effect (95% CI)
Average indirect effect	0.480 (0.068, 0.973)	0.724 (-0.031, 1.635)	0.290 (-0.102, 0.818)
Average direct effect	18.177 (14.525, 21.619)	16.092 (11.132, 20.765)	19.713 (14.520, 24.607)
Average total effect	18.658 (14.959, 22.188)	16.816 (11.754, 21.648)	20.003 (14.766, 24.969)
% Mediated	2.57% (2.16%, 3.21%)		

Note: The relationship between maternal birthweight and pre-pregnancy body mass index (modeled as a continuous variable) was adjusted for: potential confounders of maternal race, family history of diabetes, maternal smoking history, and educational attainment. The relationship between pre-pregnancy body mass index and offspring birthweight, independent of maternal birthweight, was adjusted for: potential confounders of maternal race, family history of diabetes, maternal smoking history, and educational attainment; potential precision variables of maternal age, marital status, and parity; other potential mediators of gestational diabetes, preeclampsia, and chronic hypertension. We used Imai, Keele & Yamamoto's (2010) approach to cause mediation analysis using the potential outcomes framework

Table 6. Summary of the literature on the association between maternal and offspring birthweight

Author (Year)	Sample source	N	Exposure assessed	Outcome assessed	Adjustment variables	Results
Hackman 1983	Hospital-based	748	MBW in grams	Infant BW in grams	Grandfather's occupation Grandmother's gravidity Grandmother's marital status Grandmother's age Maternal height Pre-pregnancy weight Mother's gravidity Maternal smoking Mother's marital status Maternal age Mother's referral status	r = 0.110, p < 0.05
Klebanoff 1984	Hospital-based	1,427	MBW in pounds and ounces. Categorized as <4lbs, 4-5.9lbs, 6-7.9lbs, and ≥8lbs.	Infant BW in grams. Categorized as < 2,500g & > 2,500g.	Maternal height Maternal weight Gestational weight gain Maternal age Socioeconomic index Cigarette smoking Parity Gravidity Maternal education	Compared to ≥8lbs women: <4lbs women had infants with 179g lower BW 4-5.9lbs women had infants with 244g lower BW 6-7.9lbs women had infants with 99g lower BW. None of the <4lbs women had LBW infants 4-5.9lbs women had OR=3.46 (95%CI: 1.51, 7.93) 6-7.9lbs women had OR=1.66 (95%CI: 0.82, 3.39).
Carr-Hill 1987	Population-based	505	MBW in grams. Categorized as < 2,500g & > 2,500g.	Infant BW in grams. Categorized as < 2,500g & > 2,500g.	Maternal height Gestational age Proteinuric pre-eclampsia	r = 0.173 (95%CI: 0.053, 0.287) for mother-daughter pairs r = 0.140 (95%CI: 0.013, 0.262) for mother-son pairs Unadjusted RR=2.38 for infant LBW among LBW women
Klebanoff 1987	Population-based	43,891	MBW in grams. Categorized as <1,000g, 1,000-1,499g, 1,500-1,999g […] & ≥4,000g.	Infant BW in grams. Categorized as < 2,500g & > 2,500g.	None	Unadjusted r = 0.20 for whites and r = 0.18 for non-whites. Among *whites*, compared to women 4000-4,499g: <1,000g women had OR=2.63 (95% CI: 0.60, 11.47) 1,000-1,499g women had OR=2.29 (95% CI: 0.96, 5.45) 1,500-1,999g women had OR=4.75 (95% CI: 3.18, 7.09) 2,000-2,499g women had OR=3.32 (95% CI: 2.50, 4.41) 2,500-2,999g women had OR=2.39 (95% CI: 1.85, 3.08) 3,000-3,499g women had OR=1.78 (95% CI: 1.39, 2.28) 3,500-3,999g women had OR=1.22 (95% CI: 0.94, 1.58) Among *non-whites*, compared to women 4000-4,499g: <1,000g women had OR=1.30 (95% CI: 0.16, 10.74) 1,000-1,499g women had OR=4.24 (95% CI: 2.09, 8.58) 1,500-1,999g women had OR=2.00 (95% CI: 1.15, 3.47) 2,000-2,499g women had OR=2.43 (95% CI: 1.53, 3.86) 2,500-2,999g women had OR=1.91 (95% CI: 1.22, 2.98) 3,000-3,499g women had OR=1.46 (95% CI: 0.93, 2.28) 3,500-3,999g women had OR=0.94 (95% CI: 0.58, 1.51)

Emanuel 1992	Population-based	3,346	MBW in grams.	Infant BW converted from pounds and ounces to grams.	Infant gestational age Parental occupation Pre-pregnancy weight Maternal height Cigarette smoking	Each 100g in MBW associated with 16g for infant BW
Leff 1992	Hospital-based	505	MBW in grams. Categorized as < 2,500g & > 2,500g.	Infant BW in grams. Categorized as < 2,500g & > 2,500g.	Parity Maternal age, Marital status, trimester of 1st prenatal care Type of health insurance Gestational age Gender Congenital anomalies	Among *Hispanics*, compared to women ≥2,500g: <2,500g women has OR=2.24 (95% CI: 1.12-4.47) Among *blacks*, compared to women ≥2,500g: <2,500g women has OR=1.74 (95% CI: 0.64-4.71) Among *whites*, compared to women ≥2,500g: <2,500g women has OR=0.88 (95% CI: 0.24-3.26)
Magnus 1993	Population-based	11,092	MBW in grams. Categorized as <2,500g, 2,500-2,999g, 3,000-3,499g, 3,500-3,999g & >3,999g.	Infant BW in grams. Categorized as < 2,500g & > 2,500g.	Maternal gestational age Maternal birth order	Unadjusted *r* = 0.242. Compared to women >3,999g: <2,500g women had OR=3.03 (95% CI: 1.79, 5.11) 2,500-2,999g women had OR=2.46 (95% CI: 1.69, 3.58) 3,000-3,499g women had OR=1.77 (95% CI: 1.26, 2.49) 3,500-3,999g women had OR=1.04 (95% CI: 0.72, 1.49)
Sanderson 1995	Population-based	8,558	MBW in pounds and ounces. Categorized as <4lb, 4-5lb, 6-7lb, ≥8lb	Infant BW in grams. Categorized as <1,500g, 1,500-2,499g, and ≥2,500g.	Maternal age Maternal education Marital status Gravidity Cigarette smoking Trimester of first prenatal care visit Rate of gestational weight gain Pre-pregnancy weight Maternal height	Among *whites*, compared to women 8+lb: <4lb women had OR=2.8 (95% CI: 1.5, 5.4) for VLBW, and OR=3.0 (95% CI: 1.4, 6.3) for MLBW 4-5lb women had OR=1.6 (95% CI: 1.1, 2.2) for VLBW, and OR=2.4 (95% CI: 1.7, 3.4) for MLBW 6-7lb women had OR=1.0 (95% CI: 0.8, 1.3) for VLBW, and OR=1.4 (95% CI: 1.0, 1.8) for MLBW Among *blacks*, compared to women 8+lb: <4lb women had OR=2.8 (95% CI: 1.5, 3.9) for VLBW, and OR=1.3 (95% CI: 0.7, 2.4) for MLBW 4-5lb women had OR=1.7 (95% CI: 1.2, 2.3) for VLBW, and OR=1.8 (95% CI: 1.3, 2.6) for MLBW 6-7lb women had OR=1.0 (95% CI: 0.7, 1.3) for VLBW, and OR=1.0 (95% CI: 0.7, 1.3) for MLBW
Tavares 1996	Hospital-based	106			Paternal age Paternal height Maternal education Parity Gestational weight gain Month of first prenatal care visit Number pf prenatal care visits Cigarette smoking Gestational age	Unadjusted *r* = 0.29 Each 100g in MBW associated with 11g for infant BW
Coutinho 1997	Population-based	132,995	MBW converted from pounds and ounces to grams.	Infant BW in grams.	Not specified	Each 100g in MBW associated with 24-27g for infant BW. Each 100g in paternal BW associated with 9-14g in infant BW

			Categorized into 250g groups.	Categorized as < 2,500g & > 2,500g.		
Skjærven 1997	Population-based	101,579	MBW in grams	Infant BW in grams	None	Each 100g in MBW associated with 28g for infant BW
Emanuel 1999	Population-based	37,660	MBW in grams. Categorized as <2,500g, 2,500-3,999g, & ≥4,000g	Infant BW in grams. Categorized as < 2,500g & > 2,500g.	Maternal age Parity Marital status Type of health insurance Cigarette smoking Month of first prenatal care visit	Among *whites*, compared to women 2,500-3,999g: <2,500g women had RR=1.98 (95% CI: 1.59, 2.50) for LBW, and RR=2.28 (95% CI: 1.15, 4.53) for VLBW ≥4,000g women had RR=0.68 (95% CI: 0.44, 0.90) for LBW, and RR=0.96 (95% CI: 0.39, 2.38) for VLBW Among *blacks*, compared to women 2,500-3,999g: <2,500g women had RR=1.39 (95% CI: 1.12, 1.73) for LBW, and RR=1.22 (95% CI: 0.63, 2.37) for VLBW ≥4,000g women had RR=0.60 (95% CI: 0.33, 1.07) for LBW, and RR=0.98 (95% CI: 0.32, 3.06) for VLBW Among *Native Americans*, compared to women 2,500-3,999g: <2,500g women had RR=1.73 (95% CI: 1.18, 2.54) for LBW, and RR=0.82 (95% CI: 0.20, 3.40) for VLBW ≥4,000g women had RR=0.47 (95% CI: 0.27, 0.84) for LBW Among *Hispanics*, compared to women 2,500-3,999g: <2,500g women had RR=2.16 (95% CI: 1.49, 3.14) for LBW, and RR=1.22 (95% CI: 0.36, 4.09) for VLBW ≥4,000g women had RR=0.59 (95% CI: 0.32, 1.09) for LBW, and RR=0.50 (95% CI: 0.14, 2.45) for VLBW
Conley 2000	Population-based	4,431	MBW categorized as < 2,500g & > 2,500g.	Infant BW categorized as < 2,500g & > 2,500g.	Offspring sex Birth order Income-needs ratio Maternal age Maternal marital status Maternal education	Among *whites*, compared to ≥2,500g: < 2,500g women had OR=8.83, p<0.01 Among *blacks*, compared to ≥2,500g: <2,500g women had OR=6.61, p<0.01
Stein 2000	Hospital-based	1,111	MBW in grams.	Infant BW in grams.	Birth order (effect modifier) Trimester of famine exposure Maternal weight at 18 Maternal height at 18 Maternal age Cigarette smoking Offspring sex	Among 1st born offspring, each 100g in MBW associated with 23g for infant BW. Among 2nd born offspring, each 100g in MBW associated with 11g for infant BW. Among 3rd born offspring, each 100g in MBW associated with 14g for infant BW.