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Does vaginal delivery mitigate or strengthen the intergenerational association of overweight and obesity? Findings from the Boston Birth Cohort

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Abstract

Background/Objectives—The intergenerational association of obesity may be driven by mother-to-newborn transmission of microbiota at birth. Yet Cesarean delivery circumvents newborn acquisition of vaginal microbiota, and has been associated with greater childhood adiposity. Here we examined the independent and joint associations of maternal pre-pregnancy BMI (kg/m²) and delivery mode with childhood overweight or obesity.

Subjects/Methods—We prospectively followed 1,441 racially and ethnically diverse mother-child dyads in the Boston Birth Cohort until age 5y (range 2.0–8.0y). We used logistic regression to examine the independent and joint associations of delivery mode (Cesarean and vaginal delivery) and pre-pregnancy BMI with childhood overweight or obesity (age-sex specific BMI 85th percentile).

Results—Of 1,441 mothers, 961 delivered vaginally and 480 by Cesarean. Compared to vaginally delivered children, Cesarean delivered children had 1.4 (95% CI 1.1–1.8) times greater odds of becoming overweight or obese in childhood, after adjustment for maternal age at delivery, race/ethnicity, education, air pollution exposure, pre-pregnancy BMI, pregnancy weight gain, and

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Conflicts of interest

The authors have no conflicts of interest to declare.

birth weight. Compared to children born vaginally to normal weight mothers, after multivariable adjustment, odds of childhood overweight or obesity were highest in children born by Cesarean delivery to obese mothers (OR 2.8, 95% CI 1.9–4.1), followed by children born by Cesarean delivery to overweight mothers (OR 2.2, 95% CI 1.5–3.2), then children born vaginally to obese mothers (OR 1.8, 95% CI 1.3–2.6), and finally children born vaginally to overweight mothers (OR 1.7, 95% CI, 1.2–2.3).

Conclusions—In our racially and ethnically diverse cohort, Cesarean delivery and pre-pregnancy overweight and obesity were associated with childhood overweight or obesity. Needed now are prospective studies that integrate measures of the maternal and infant microbiome, and other potentially explanatory covariates, to elucidate the mechanisms driving this association and to explore whether exposure to vaginal microbiota in Cesarean delivered newborns may be an innovative strategy to combat the intergenerational cycle of obesity.

Keywords

Delivery mode; Cesarean delivery; Vaginal Delivery; Obesity; Body Mass Index; Pregnancy

Introduction

An increasing number of women who become pregnant are overweight or obese (OWOB) ^{1–3}. Women carrying excess weight into pregnancy are at higher risk of delivering offspring that will become OWOB^{4–7}. These women are also at higher risk of delivering by Cesarean section (C-section)⁸, and a systematic review found that, compared to women who deliver vaginally, those who deliver by C-section have a 30% higher odds of having OWOB children⁹. To date, no studies have examined the joint contribution of maternal OWOB and C-section delivery on the offspring's risk of developing OWOB.

Human gut microbiota can transfer the obesity phenotype from humans to germ-free mice¹⁰, suggesting a causal effect of gut microbiota on obesity. However, whether the vaginal microbiota of obese mothers is associated with offspring risk of obesity is unknown. We recently observed that maternal OWOB was associated with altered gut microbiota composition in neonates delivered vaginally, yet an association between maternal OWOB and gut microbiota was not observed in neonates delivered by C-section¹¹. Due to differential sharing of microbiota at birth during labor, delivery mode should also modify the intergenerational association between mother and child weight status. In the present study, we prospectively examined the independent and joint association of maternal pre-pregnancy OWOB and mode of delivery with offspring risk of OWOB in childhood.

Subjects and Methods

Participants and Data Collection Procedures

The Boston Birth Cohort (BBC) was initially designed as a molecular epidemiologic study on determinants of low birth weight and preterm birth¹². Participants were recruited at birth at the Boston Medical Center (BMC) from 1998 to 2014. Multiple gestation pregnancies, pregnancies resulting from in-vitro fertilization, deliveries resulting from maternal trauma,

and infants born <23 completed gestation weeks or with major birth defects were not included.

After consent was obtained from all participating mothers, we conducted a face-to-face interview 24 to 72 hours postpartum using a standardized questionnaire. We also abstracted clinical data, including prenatal care data, pregnancy complications, labor and delivery course, and birth outcomes, from maternal and infant electronic medical records (EMR). All enrolled children who continued to seek postnatal care at BMC were then followed.

From the 2,045 mothers and children who had complete information on height and weight, we excluded 535 preterm deliveries (<37 weeks), 58 with pre-pregnancy underweight (BMI < 18.5 kg/m²), because of inadequate power in this category, and 11 missing information on delivery mode (Supplemental Figure 1). These exclusions left us with 1,441 mother-child dyads for the current analysis. This sample size afforded us greater statistical power than our previous publication on delivery mode and childhood obesity¹³. The institutional review board of Johns Hopkins Bloomberg School of Public Health and Boston University Medical Center approved the study.

Exposures

The primary exposures for this study were pre-pregnancy BMI and mode of delivery. Mode of delivery (Cesarean vs. vaginal) recorded from EMR. Pre-pregnancy height and weight, ascertained from the maternal postpartum interview, was used to calculate pre-pregnancy BMI. We categorized pre-pregnancy BMI as normal weight (18.5 ≤ BMI < 25.0 kg/m²); overweight (25.0 ≤ BMI < 30.0 kg/m²); and obese (30.0 kg/m² ≤ BMI).

Outcomes

The primary outcome for this study was childhood OWOB measured at age ~5 years (median=4.8 y; interquartile range 3.2 to 6.3y; range: 2.0 to 8.0y). To derive childhood BMI, height and weight were abstracted from EMRs. We defined OWOB using age and sex specific BMI z scores ≥ 85th percentile, according to Center for Disease Control growth charts.

Covariates

We extracted maternal age at delivery and birth weight directly from EMRs, and maternal race/ethnicity and maternal education level from standardized questions. To further characterize participants socioeconomic status, we estimated maternal exposure to ambient air pollution, in the form of particulate matter (PM_{2.5}), in the 2nd trimester by obtaining data from air monitors near their residence, as described previously¹⁴. We calculated gestational weight gain from EMR weight measurement data or, if EMR was missing, from the standardized questionnaire self-report weight data. When using EMR data, gestational weight gain was defined as the weight difference between earliest weight measurement during first trimester and latest weight measurement before delivery. The end-of-pregnancy weight measurements were restricted to weight measured within 3 weeks of delivery. We considered the EMR weight measurement as missing if it occurred outside this time range. We replaced the missing earliest weight measurement data with the self-reported pre-

pregnancy weight for participants that only had the last pregnancy weight measurement available in EMR.

Data analysis

We described maternal and child characteristics using percentages (%) for categorical variables, means and standard deviation (SD) for normally distributed continuous variables, and median (1st quartile (Q₁), 3rd quartile (Q₃)) for non-normally distributed continuous variables. We used multivariable logistic regression model to examine the associations of delivery mode and pre-pregnancy BMI with our primary outcome, childhood overweight or obesity. We further used generalized linear models to evaluate associations with childhood BMI z-scores.

To assess confounding, we began with an unadjusted model and then added covariates known to be associated with our exposure (either pre-pregnancy BMI or delivery mode) and childhood overweight or obesity, not including covariates that were on the causal pathway between our exposure and outcome. For pre-pregnancy BMI analyses, we included maternal age at delivery (quintiles), maternal race (black, not black or unknown), and maternal education (middle school and below; high school; college and above). For delivery mode analyses, we included maternal age at delivery (quintiles), maternal race/ethnicity (black, not black or unknown), maternal education (middle school and below; high school; college and above), 2nd trimester exposure to air pollution in the form of ambient PM_{2.5} (PM_{2.5} ≥ 12 μg/m³ or not), maternal pre-pregnancy BMI (normal weight, overweight, obese), gestational weight gain (inadequate, normal, excess weight gain) and birth weight (quartiles). We further considered but did not include in the final model maternal smoking status during pregnancy (never smoked; quit before pregnancy; continued to smoke in pregnancy), diabetes (no; gestational diabetes; pre-pregnancy diabetes) maternal marriage status (married; other; unknown), prenatal and intra-partum antibiotics (use antibiotics during pregnancy; not; unknown), and household income (household income ≥ \$50000 per year; less than \$50000; unknown); none of these variables significantly changed the relationship of maternal pre-pregnancy BMI or delivery mode with childhood OWOB. We also conducted sensitivity analyses after excluding women who developed pre-eclampsia or gestational diabetes.

We evaluated effect modification on the multiplicative scale by including cross-product terms for mode of delivery and pre-pregnancy BMI in multivariable models. We considered a two-sided alpha of < 0.05 as evidence of statistical significance. Data management and analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). Code is available upon request. Figures were generated by Sigmaplot for Windows Version 12.5 (Build 12.5.0.38, Systat Software, Inc).

Results

Baseline characteristics for mother-child dyads according to delivery mode and maternal pre-pregnancy BMI are provided in Table 1 (characteristics according to mode of delivery alone are provided in Supplemental Table 1). Of the 1,441 mothers in our sample, 480

(33.3%) delivered by Cesarean section, and 396 (27.4%) were overweight and 362 (25.1%) obese. Mothers with greater pre-pregnancy BMI had lower gestational weight gain, higher prevalence of gestational diabetes, and were more likely to deliver children with greater birth weight to deliver by C-section. Compared to children delivered vaginally, those delivered by C-section were more likely to be girls and have greater birth weight. Mothers who delivered by C-section were more likely to be older, and have greater pre-pregnancy BMI, gestational weight gain and prevalence of gestational diabetes.

Of the children in our sample, 601 (47.2%) were overweight or obese at follow up. In Table 2 we show unadjusted and multivariable adjusted associations of delivery mode with childhood overweight or obesity. Before adjustment for potential confounders, C-section delivery compared to vaginal delivery was associated with 1.5 (95% CI: 1.2, 1.8) times greater odds of childhood overweight or obesity. This association was slightly attenuated but remained statistically significant (OR 1.4; 95% CI: 1.1, 1.8) after adjustment for potential confounders. Overall, compared to children born to normal weight mothers, those born to overweight and obese mothers had, respectively, 1.7 (95% CI: 1.3, 2.2) and 2.1 (95% CI: 1.6, 2.7) times greater odds of becoming overweight or obese, after multivariable adjustment.

In Table 3 we present the joint effects of maternal pre-pregnancy BMI status and mode of delivery on childhood OWOB, before and after multivariable adjustment. Compared to vaginally-delivered children from normal weight mothers (reference), vaginally-delivered children from overweight and obese mothers had, respectively, 1.7 (95% CI: 1.2, 2.3) and 1.8 (95% CI: 1.3, 2.6) times greater odds of OWOB, and C-section delivered children from overweight and obese mothers had, respectively, 1.9 (95% CI: 1.2, 3.1) and 2.5 (95% CI: 1.5, 3.9) times greater odds of OWOB, after adjustment for confounders. These associations are depicted in Figure 1.

In Supplemental Tables 2–4 we present associations with continuous BMI *z* score as the outcome and our findings are consistent with our primary outcome of childhood OWOB. Finally, in Supplemental Tables 5–6 we present results for sensitivity analyses in which we examined the individual and joint effects on maternal pre-pregnancy BMI and delivery mode with the odds of childhood OWOB after excluding women who developed pre-eclampsia or gestational diabetes. These findings were also consistent with the findings from our primary analyses.

Discussion

In this multiethnic urban birth cohort study, compared to vaginally-delivered children, C-section delivered children had higher odds of developing OWOB, after adjusting for key confounders. Furthermore, compared to children born to normal weight mothers, children born to overweight or obese mothers had higher odds of developing OWOB, but this intergenerational association of OWOB was attenuated if the children were delivered vaginally.

Our findings on the association of delivery mode with childhood OWOB are consistent with a growing body of literature^{9,13,15}. A meta-analysis that found Cesarean delivery increases odds of childhood overweight or obesity by approximately 30%⁹—a magnitude of association comparable to our study. Our study had the added strength of adjustment for a number of confounders, including maternal pre-pregnancy BMI and gestational weight gain, and our findings were robust to exclusion of women who developed gestational diabetes or pre-eclampsia.

Similar to previous reports, in our study maternal pre-pregnancy BMI was strongly positively associated with childhood OWOB. A meta-analysis found that pre-pregnancy overweight or obesity was associated with 2.0 (95% CI: 1.8, 2.1) and 3.1 (2.7, 3.5) times greater odds of childhood overweight and obesity⁷. To the best of our knowledge, we are the first study to rigorously examine whether this association is modified by delivery mode. The association between maternal and child OWOB tended to be slightly stronger among C-section delivered children than among vaginally delivered children, although the test for statistical interaction on the multiplicative scale was not significant ($p=0.57$).

The observation that among overweight or obese women, vaginally delivered children tended to have lower odds of developing overweight or obesity than C-section delivered children suggests that among other possibilities the vertical transmission of microbiota during vaginal delivery may reduce the transmission of obesity risk to the next generation. Previously, we found that maternal overweight and obesity was associated with the neonatal gut microbiome in vaginally delivered neonates, but not C-section delivered neonates¹¹. Taken collectively, these findings suggest that the mother-to-newborn transmission of vaginal and intestinal microbiota during vaginal delivery may serve to improve extra-uterine metabolic homeostasis of the newborn delivered to an overweight or obese mother. Due to their mothers' weight status, these children may already be genetically programmed for obesity. The differential acquisition of microbiota by the newborn may (a) directly modify caloric extraction from the infants diet or (b) provide a hormetic stimulation that has a 'priming' effect on early development and immune responses^{16,17}. C-section delivered newborns may miss this potentially protective microbial exposure. While it is intriguing to think that priming newborns to obese microbiota may contribute to long-term risks of metabolic disease, this hypothesis needs to be tested in a longitudinal birth cohort study that has collected offspring stool and measures of body composition from birth into childhood or in a clinical trial that tests whether exposure to vaginal microbiota prevents OWOB in children delivered by C-section.

There are limitations of the current study that merit mention. First, we did not have data on indication for Cesarean delivery. When we excluded women who developed gestational diabetes or pre-eclampsia, two common indications for Cesarean delivery, our effect estimates were similar. Further, the most common reasons for medically necessary Cesarean delivery, fetal intolerance of labor or failure to progress, are not known risk factors for obesity and thus unlikely to confound the association between Cesarean delivery and offspring obesity. Nevertheless, future research is needed to delineate whether the obesity risk associated with Cesarean delivery depends on whether women went into labor or whether membranes were ruptured. Another limitation to our study is that we relied on self-

report of maternal pre-pregnancy height and weight when maternal height and weight from EMR was not available. However, misclassification was unlikely because in the BBC there was high correlation (Pearson $r=0.91$) between maternal self-report and EMR recorded BMI in a subset of 738 mothers who had height and weight during preconception or within 6 wks of gestation in their EMR¹⁸. Finally, as this is an observational study, we cannot rule out the possibility for residual or unmeasured confounding.

The major strengths of the current study lay in the prospective collection of data in a multi-ethnic, urban sample of mother-child dyads. Furthermore, the comprehensive set of covariates, collected through questionnaire and EMRs from birth through childhood, allowed us to control for many potential confounding factors for which other studies have not been able to adjust.

Conclusion

We found that the exposures of Cesarean (versus vaginal) delivery and maternal pre-pregnancy overweight and obesity (versus normal weight) are each, independent of each other, associated with higher odds of offspring obesity in this multiethnic study of mother-child dyads from Boston. Our findings suggest that, even among overweight and obese mothers, Cesarean delivery may predispose offspring to greater risk of obesity in childhood. Future studies, which directly measure the maternal and infant microbiomes and other potential explanatory factors, are needed to understand the drivers of this association, and to explore the possibility that exposure to vaginal microbiota in Cesarean delivered newborns may provide an innovative opportunity to combat the vicious cycle of intergenerational obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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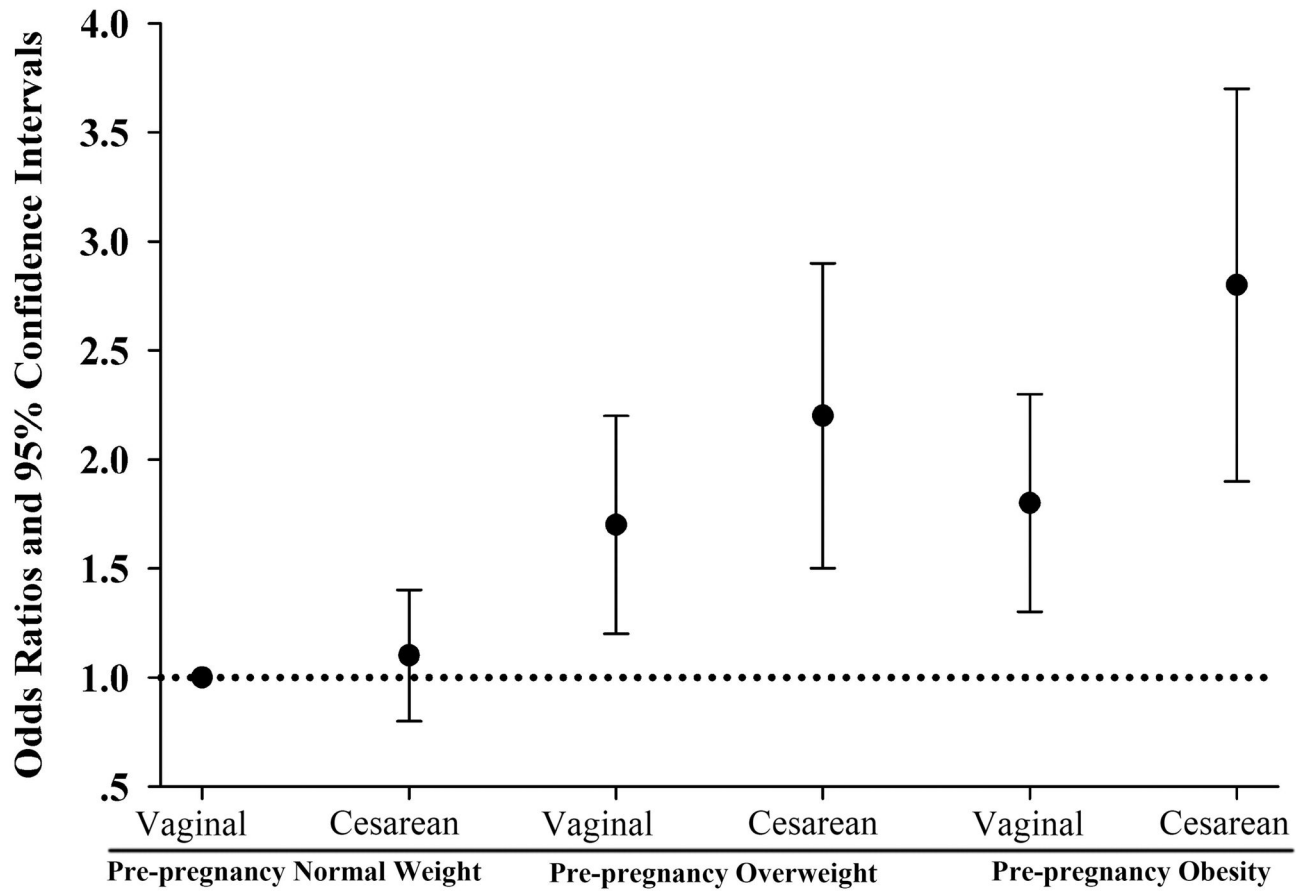


Figure 1. Odds ratios and 95% confidence intervals of childhood overweight or obesity according to joint categories of maternal pre-pregnancy body weight status and delivery mode.

Table 1

Characteristics of mother-child pairs (n=1441) from the Boston Birth Cohort by delivery mode and pre-pregnancy BMI category.

<i>Characteristics</i>	<i>Vaginal Delivery</i>			<i>Cesarean Delivery</i>		
	Normal weight (n=506)	Overweight (n=251)	Obese (n=204)	Normal weight (n=177)	Overweight (n=145)	Obese (n=158)
<i>Child</i>						
Male, %	52.0	51.8	56.9	49.2	39.3	52.5
Hispanic, %	20.5	13.7	14.4	20.0	16.8	13.9
Gestational age, weeks, median (Q1, Q3)	39.4 (38.4, 40.3)	39.6 (38.6, 40.4)	39.7 (38.7, 40.6)	39.3 (38.4, 40.1)	39.4 (38.4, 40.4)	39.0 (38.6, 40.0)
Birth weight, g, mean±SD	3146.4±493.9	3286.7±482.6	3334.7±573.8	3217.1±567.2	3357.7±559.4	3436.9±626.6
Ever breastfed in the 1 st year, %	61.9	68.9	63.2	64.4	68.3	63.3
<i>Mother</i>						
Age at birth, y, median (Q1, Q3)	25.5 (21.6, 30.3)	29.5 (24.5, 35.0)	27.9 (23.2, 32.1)	29.1 (25.3, 33.2)	31.4 (25.1, 35.3)	30.5 (25.3, 34.9)
* Low education achievement, %	36.1	35.7	35.3	43.9	35.4	41.1
Household income ≤\$50,000, %	47.8	52.2	50.0	50.8	40.0	43.7
Pre-pregnancy BMI, kg/m ² , median (Q1, Q3)	22.2 (20.6, 23.4)	27.4 (25.8, 28.3)	33.6 (31.4, 38.0)	22.8 (21.3, 24.0)	27.4 (26.1, 28.4)	34.0 (32.0, 38.9)
Gestational weight gain, lbs, median (Q1, Q3)	30.0 (23.0, 38.0)	25.0 (15.4, 37.0)	22.0 (15.0, 30.0)	33.5 (26.0, 40.0)	31.0 (23.0, 43.0)	30.0 (18.0, 45.0)
Gestational diabetes, %	0.6	3.2	4.9	1.7	9.7	11.5
Maternal smoking, %	8.5	7.2	9.3	8.5	8.3	12.7
Ambient PM _{2.5} in the 2 nd trimester, median (Q1, Q3)	10.8 (9.3, 12.4)	11.1 (9.2, 12.6)	10.8 (8.8, 12.8)	10.4 (8.5, 12.3)	10.8 (9.3, 12.2)	10.5 (8.8, 12.3)

* Participants whose education level included illiteracy, primary school or middle school. Normally distributed continuous data are described as mean (standard deviation) and non-normally distributed continuous data are described as median (1st quartile [Q1], 3rd quartile [Q3])

Odds ratios (OR) and 95% confidence intervals (95% CI) for childhood overweight or obesity according to pre-pregnancy BMI and delivery mode before and after adjustment for potential confounders.

Table 2

	Maternal pre-pregnancy BMI	n	Cases (%)	Crude		Adjusted ^a	
				OR (95%CI)	p	OR (95%CI)	p
Normal (18.5 – 25 kg/m ²)		683	224 (32.8)	1.0 (Ref.)	Ref.	1.0 (Ref.)	Ref.
Overweight (25.0–30 kg/m ²)		396	188 (47.5)	1.9 (1.4–2.4)	<0.001	1.7 (1.3–2.3)	<0.001
Obesity (> 30 kg/m ²)		362	189 (52.2)	2.2 (1.7–2.9)	<0.001	2.1 (1.6–2.8)	<0.001
Delivery mode		n	Cases (%)	Crude		Adjusted ^b	
				OR (95%CI)	p	OR (95%CI)	p
Vaginal Delivery		961	370 (38.5)	1.0 (Ref.)	Ref.	1.0 (Ref.)	Ref.
Cesarean Delivery		480	231 (48.1)	1.5 (1.2–1.8)	<0.001	1.4 (1.1–1.8)	0.005

^a Adjusted for maternal age at delivery, maternal race/ethnicity, and maternal education.

^b Adjusted for maternal age at delivery, maternal race/ethnicity, maternal education, maternal exposure to ambient PM2.5 exposure in the 2nd trimester, maternal pre-pregnancy BMI, maternal pregnancy weight gain, and birth weight

Table 3

Odds ratios (OR) and 95% confidence intervals (95% CI) for childhood overweight or obesity according to maternal pre-pregnancy BMI status and delivery mode, modeled independently and jointly.

Pre-pregnancy BMI	Cesarean section	n	Cases (%)	Crude		Adjusted ^a	
				OR (95%CI)	p	OR (95%CI)	p
Normal (18.5–25 kg/m ²)	No	506	161 (31.8)	1.0 (Ref.)	Ref.	1.0 (Ref.)	Ref.
Normal (18.5–25 kg/m ²)	Yes	177	63 (35.6)	1.2 (0.8–1.7)	0.357	1.1 (0.8–1.7)	0.459
Overweight (25.0–30 kg/m ²)	No	251	113 (45.0)	1.8 (1.3–2.4)	<0.001	1.7 (1.2–2.3)	0.001
Overweight (25.0–30 kg/m ²)	Yes	145	75 (51.7)	2.3 (1.6–3.3)	<0.001	2.2 (1.5–3.2)	<0.001
Obesity (> 30 kg/m ²)	No	204	96 (47.1)	1.9 (1.4–2.7)	<0.001	1.8 (1.3–2.6)	<0.001
Obesity (> 30 kg/m ²)	Yes	158	93 (58.9)	3.1 (2.1–4.4)	<0.001	2.8 (1.9–4.1)	<0.001
Interaction					0.549		0.569

^a Adjusted for maternal age at delivery, maternal race/ethnicity, and maternal education.