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Association between Caesarean Delivery Types and Obesity in Pre-Adolescence

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Abstract

Background/Objectives: The association between mode of delivery and childhood obesity remains inconclusive. Because few studies have separated C-section types (planned or unplanned C-section), our objective was to assess how these subtypes relate to pre-adolescent obesity.

Subjects/Methods: The study consisted of 570 maternal-child pairs drawn from the WHEALS birth cohort based in Detroit, Michigan. Children were followed-up at 10 years of age where a variety of anthropometric measurements were collected. Obesity was defined based on BMI percentile (≥95th percentile), as well as through gaussian finite mixture modeling on the anthropometric measurements. Risk ratios (RRs) and 95% confidence intervals (CIs) for obesity comparing planned and unplanned C-sections to vaginal deliveries were computed, which utilized inverse probability weights to account for loss to follow-up and multiple imputation for covariate missingness. Mediation models were fit to examine the mediation role of breastfeeding.

Results: After adjusting for marital status, maternal race, prenatal tobacco smoke exposure, maternal age, maternal BMI, any hypertensive disorders during pregnancy, gestational diabetes, prenatal antibiotic use, child sex, parity, and birthweight z-score, children born via planned C-section had 1.77 times higher risk of obesity (≥95th percentile), relative to those delivered

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vaginally ((95% CI)=(1.16,2.72); p=0.009). No association was found comparing unplanned C-section to vaginal delivery (RR (95% CI)=0.75 (0.45, 1.23); p=0.25). Results were similar but slightly stronger when obesity was defined by anthropometric class (RR (95% CI)=2.78 (1.47, 5.26); p=0.002). Breastfeeding did not mediate the association between mode of delivery and obesity.

Conclusions: These findings indicate that children delivered via planned C-section—but not unplanned C-section—have a higher risk of pre-adolescent obesity, suggesting that partial labor or membrane rupture (typically experienced during unplanned C-section delivery) may offer protection. Additional research is needed to understand the biological mechanisms behind this effect, including whether microbiological differences fully or partially account for the association.

Introduction

The prevalence of childhood and adult obesity has increased in the past several decades, in both developed and developing countries.[1] In 2010, overweight and obesity were estimated to have caused 3.4 million deaths and 3.9% of years of life lost.[1] Not only have changes in diet and physical activity been implicated in this trend, prenatal and early life exposures such as maternal obesity, excessive weight gain during pregnancy, and early life feeding practices are also thought to shape the development of obesity.[2] Concurrently, rates of caesarean section (C-section) delivery have increased globally[3] and have also been shown to increase the risk of childhood obesity.[4–6] The biological mechanism(s) of this effect are not yet fully understood, but several have been proposed. Most prominently, we and others have demonstrated alterations of the infant gut microbiome in C-section delivered children (primarily a depletion of *Bacteroides* taxa),[7–10] which may relate to obesity later in life.[11] Delivery via C-section may also cause immune dysregulation,[12] altered metabolism,[13] or epigenetic alterations in the offspring,[14] independent of (or dependent on) gut microbiota.

Despite mounting evidence results remain inconclusive, with some meta-analyses suggesting strong publication bias, lack of confounder adjustment, and small effect sizes.[15] Additionally, most studies compare all C-section to vaginal deliveries rather than separating C-section types (unplanned/emergency versus planned/elective), which may mask important differences caused by partial labor or amniotic membrane rupture. Some mechanistic studies support this concept. For example, microbial differences have been found between elective and emergency C-section deliveries,[16] and adiponectin—which regulates glucose levels—has been shown to be lower in cord blood following elective C-section.[17] Our objective was to examine the association between mode of delivery and anthropometric outcomes at 10 years of age. We hypothesized that children born via both planned and unplanned C-section are at an increased risk of obesity, but that the effects are stronger in children delivered via planned C-section, due to not experiencing the beneficial effects of partial labor.

Methods

Study population

Data from the Wayne County Health Environment Allergy and Asthma Longitudinal Study (WHEALS)—a birth cohort study of 1,258 maternal-child pairs—were analyzed. Cohort details have been previously published.[18–20] Briefly, pregnant women ages 21 to 49 years receiving care at Henry Ford Health System (HFHS) obstetrics clinics in metropolitan Detroit were recruited from 2003 to 2007. Women either resided in the city of Detroit or surrounding suburban areas, resulting in a racially and socioeconomically diverse population. Maternal-child pairs have been followed longitudinally with assessments including a prenatal questionnaire, 1-month, 6-month, and 1-year questionnaires and home visits, a 2-year clinic visit, a 4-year phone questionnaire, and a 10-year clinic visit. All participants provided written, informed consent (pre-adolescents provided written, informed assent); the study was approved by the institutional review board at HFHS. For the current analysis, participants were included if they had information on both mode of delivery and child anthropometric measurements at 10-years of age.

Covariates

During the prenatal interview, mothers self-reported: race, insurance coverage, household income, education, marital status, previous pregnancies, smoking during pregnancy, household environmental tobacco smoke (ETS), prenatal alcohol use, indoor pets, history of asthma and allergies, and home address, which was used to define urban or suburban residence. Prenatal and delivery records were abstracted to obtain mode of delivery and specific c-section type (planned vs. unplanned due to dysfunctional labor, fetal malposition, fetal distress, or maternal distress), body mass index (BMI) at the first prenatal visit (obesity defined as ≥30 kg/m^2), prenatal antibiotic and antifungal use, any hypertensive disorders during pregnancy, gestational diabetes, gestational age at delivery, and birth weight. Sex- and gestational-age adjusted birth weight z-scores were calculated using the US population in 1999-2000 as a reference.[21] Breastfeeding was maternal-reported during a study visit at 1-month of age, defined as never breastfed (formula only), mixed feeding, or breastfed without the use of formula.

Anthropometric measurements

At a 10-year clinic visit (mean=10.3, SD=0.9, min=8.1, max=13.6), several anthropometric measurements were collected: height, weight, body fat percentage, circumference measurements (neck, chest, and waist), and skinfold thickness measurements (tricep, subscapular, and suprailiac). Protocols were adapted from the PhenX Toolkit.[22] Weight was measured in light clothing using an electronic balance; raw BMI was calculated as kg/m^2. Skinfold thickness was performed using calipers to obtain measures of regional fat. Percent body fat was measured using bioimpedance with a Tanita SC-240 body composition analyzer. In order to adjust for sex and age, BMI, height, and weight z-scores were calculated using the 2000 CDC growth charts.[23] BMI categories were defined as underweight (<5th percentile), normal (5-<85th percentile), overweight (85-<95th percentile), and obese (≥95th percentile), per CDC guidelines.[24, 25] For all other measurements, sex-adjusted z-scores were manually computed by subtracting the mean and dividing by the standard deviation, separately for males and females.

Statistical analysis

Two-sided testing and a significance level of 0.05 was pre-specified for all analyses. Given that this is a secondary study using pre-existing birth cohort data, the sample size is fixed

(N=570). However, a power calculation was performed to determine what effect size could be detected with this sample size. Based on a two group t-test (comparing mean difference in BMI z-score at age 10 in c-section and vaginally delivered children), an effect size of 0.24 (defined as the difference in means divided by the standard deviation) can be detected with 80% power, which is a relatively small effect size according to Cohen.[26]

ANOVA and chi-square tests were used for basic descriptive purposes. Because loss to follow-up and non-response can affect the internal validity of estimates, inverse probability weighting (IPW) was used to correct for this bias.[27, 28] Analytic sample inclusion was used as the outcome in a logistic regression model and predicted using covariates hypothesized to affect loss to follow-up (see Table S1 for complete list). The predicted probability of inclusion (p) for each subject was extracted from this model; weights (w) were calculated as $w = 1/p$ for included children, and $w = 1/(1-p)$ for excluded children. Covariate balance was assessed using standardized differences before and after weighting, with imbalance defined as absolute value>0.20.

In addition to examining anthropomorphic measurements individually, we also conceptualized body size as an unmeasured construct which can be characterized by these measurements. Gaussian finite mixture modeling was used to determine 10-year anthropometric class—based on the z-scores described previously—using the mclust package in R.[29] Briefly, gaussian finite mixture models are probabilistic models that assume all the data points are generated from a mixture of multivariate normal densities; these can be used to classify data with previously unknown structure into meaningful groups.[29] Bayesian Information Criteria (BIC) values were used to aid in model selection; class size, variability, and interpretability were also considered in the determination of the most appropriate number of classes (range: 1–5). Z-scores were compared by anthropometric class using the Kruskal-Wallis test; pairwise comparisons were Bonferroni-corrected.

Three main 10-year outcomes were evaluated for association with mode of delivery: BMI category, anthropometric class, and BMI z-score. To evaluate the association between mode of delivery and BMI category/anthropometric class, risk ratios were obtained from Poisson regression models using a robust error variance.[30] Linear regression was used to model BMI z-scores. For each outcome, three exposure comparisons were modeled: C-section vs. vaginal, planned C-section vs. vaginal, and unplanned C-section versus vaginal. Inverse probability weighting was used in all models. Models were evaluated both before and after adjusting for a set of pre-specified potentially confounding covariates (variables thought to be associated with exposure and outcome that are not in the causal pathway): marital status, maternal race, prenatal ETS exposure, maternal age at birth, maternal BMI, any hypertensive disorders during pregnancy, gestational diabetes, prenatal antibiotic use, child sex, parity, and birthweight z-score. A priori we did not consider 10-year diet or physical activity as a confounder in the relationship between mode of delivery and pre-adolescent body size; indeed, in this sample mode of delivery was not associated with average daily intake of food groups (fruits, vegetables, potatoes, whole grains, legumes, meat/fish/poultry and dairy; all $p \geq 0.12$) measured using the Block Kids Food Screener (BKFS)[31] nor with estimated daily energy expenditure, measured using the Block Kids Physical Activity Screener ($p=0.28$).[32] Effect modification by maternal race and child sex was pre-specified and tested using interaction terms. E-values[33] were used to quantify how strong an unmeasured confounder would have to be in order to negate the observed results.

Because there was some missingness in the confounding covariates and specific delivery type, multiple imputation (assuming missing at random) was performed in addition to complete-case analysis. Using a rule of thumb recommended by White et al.,[34] a total of 28 imputed datasets were calculated, as 28% of children in the analysis subset had incomplete data. Multiply imputed datasets were created using the following variables: marital status, household income, maternal education, location of residence, maternal race, prenatal ETS exposure, maternal age, maternal BMI, any hypertensive disorders during pregnancy, gestational diabetes, prenatal antibiotic use, child sex, parity, birthweight z-score, breastfeeding status at 1-month, the IPW for loss to follow-up, specific delivery type, and 10-year outcomes (anthropometric class, BMI category, BMI z-score). The SAS procedure *mi* with the fully conditional specification (FCS) algorithm[35] was used to generate imputed datasets, while the *mianalyze* procedure was used to pool estimates.

Additionally, we tested for a mediating effect of breastfeeding at 1-month, as women who deliver via C-section have been shown to be less likely to initiate and sustain breastfeeding,[36] which has been implicated in childhood obesity.[37] Mediation models were fit using the R *mediation* package,[38] using inverse probability weights and adjusting for the previously-described potential confounders.

Results

Basic descriptives

Of the 1258 maternal-child pairs in the WHEALS cohort, 1250 were successfully classified as vaginal vs. C-section delivery via chart abstraction. Of these 1250, 570 children had at least one anthropometric measurement collected at the 10-year clinic visit, and were therefore included in the analytic dataset. Among these children, a total of 212 (37.2%) were born via C-section; among C-section deliveries, 97 (54.2%) were unplanned while 82 (45.8%) were planned (specific C-section type was unable to be abstracted on 33 of the C-section deliveries). The observed mean BMI z-score was 0.41 and the standard deviation was 1.3. A total of 33 (5.8%) children were underweight, while 339 (59.5%) were normal weight, 82 (14.4%) were overweight, and 116 (20.3%) were obese. Mothers of children included in the analysis had higher household incomes, were more educated, were more likely to be married, were more likely to have insurance coverage, were older, and were more likely to have dogs (Table S1; all $p<0.05$). Additionally, they were less likely to live in an urban residence, to smoke, or to be exposed to ETS prenatally in the household. Babies included in the analysis were also on average heavier at birth. A large imbalance between groups was reflected by the standardized differences prior to IPW, which were as large as 0.66 (insurance coverage). However, after IPW, these imbalances were effectively removed (absolute value of all standardized differences<0.20).

When delivery mode was compared across a wide range of maternal and early life characteristics, marital status, maternal race, maternal age, ETS exposure, maternal BMI/ obesity, any hypertensive disorders during pregnancy, child sex, parity, gestational age at delivery, birthweight z-score, and breastfeeding status at 1-month were all significantly associated with delivery mode (Table 1; all $p<0.05$). Specifically, mothers who delivered via planned C-section were more likely to be married, were older, had babies with higher birthweight z-scores, were less likely to be exposed to prenatal ETS, and on average delivered at earlier gestational ages. Mothers who delivered via unplanned C-section were more likely to be African American, and to have given birth to their first child. Mothers who delivered vaginally had lower prenatal BMIs and obesity rates, were more likely to have given birth to a female child, were less likely to have a hypertensive disorder during pregnancy, and were more likely to breastfeed without the use of formula at 1-month of age.

Anthropometric classes

Four anthropometric classes were found to be the best fit to the data according to BIC, closely followed by the 3-class solution. However, upon further inspection of the 4-class solution, one of the classes had a very small sample size (N=19) and extremely high variability relative to the other three classes. Additionally, the interpretation of this class was not clear, as it had the largest circumference measurements, but intermediate BMI, body fat percentage, and skinfold measurements (Figure S1). For these reasons combined, the 3-class solution was selected as the most appropriate fit to the data.

The model had high entropy (0.95), meaning that individuals were precisely assigned to classes. Class 2 was the most common class (N=280, 49%), followed by class 1 (N=246, 43%) and class 3 (N=44, 8%). All measurements were significantly associated with anthropometric class (Figure 1; all $p<0.001$). Pairwise comparisons revealed a significant difference for each pair (Bonferroni-corrected p-value<0.05), except for class 2 vs. 3 on height for age (Bonferroni p=1). Each of the body size measurements increased from class 1 to 3 and generally suggested labels of “normal”, “overweight” and “obese”, respectively. When compared with traditional BMI categories based on percentiles, class 1 was primarily normal weight (87%), followed by underweight (13%); class 2 was primarily normal weight (44%), followed by obese (29%) and overweight (27%); class 3 was primarily obese (77%), followed by overweight (9%) and normal weight (9%).

Association between delivery mode and anthropometric outcomes

In models evaluating the association between mode of delivery and 10-year BMI category (Table 2), children born via C-section had 1.79 times higher risk of obesity (Model 1; (95% CI)=(1.23,2.60); p=0.002), but this association did not persist after covariate adjustment (Model 2; RR (95% CI)=1.22 (0.77, 1.93); p=0.41). Results were similar when multiple imputation was used rather than complete-case analysis (Model 3; RR (95% CI)=1.27 (0.89, 1.81); p=0.19). However, when C-section was separated by specific type, children born via planned C-section had 1.77 times higher risk of obesity, relative to those delivered vaginally (Model 3; (95% CI)=(1.16,2.72); p=0.009). This association was not observed comparing unplanned C-section to vaginal delivery (Model 3; RR (95% CI)=0.75 (0.45, 1.23); p=0.25). Additionally, the effect of planned C-section on obesity significantly differed by maternal race (Table S2; interaction p=0.009), with the effect being stronger in white versus black women (RR (95% CI)=3.02 (1.13,8.05); 1.49 (0.85,2.62), respectively). Effect modification by child sex was not found (Table S2; interaction p=0.80). In multivariable models, mode of delivery was not associated with the risk of being overweight, normal weight, or underweight.

Results examining 10-year anthropometric classes were very similar (Table 3). Specifically, no differences in the risk of being in class 2 ("overweight") were observed, comparing C-section to vaginally delivered children (Model 3; RR (95% CI)=0.88 (0.72, 1.08); p=0.28). However, children delivered via C-section had 2.5 times higher risk (Model 1; (95% CI)=(1.33, 4.70); p=0.004) of being in class 3 ("obese"); this association was diminished, but remained statistically significant in the imputed multivariable model (Model 3; RR (95% CI)=1.79 (1.05, 3.04); p=0.032). This effect was driven by planned C-section deliveries, as these children had 2.78 times higher risk of being in class 3 ("obese") compared to vaginally delivered children (Model 3; (95% CI)=(1.47, 5.26); p=0.002), whereas no difference was found comparing unplanned C-section deliveries to vaginal deliveries (Model 3; RR (95% CI)=0.92 (0.40, 2.10); p=0.84). Sample size in class 3 was inadequate to evaluate effect modification by maternal race or child sex. There was no difference in the risk of being in class 2 ("overweight") or class 1 ("normal") by mode of delivery.

Prior to potential confounder adjustment, the association between mode of delivery and 10-year BMI z-score suggested a significant association (Table 4), where the BMI z-scores of children delivered via C-section were on average 0.39 standard deviations higher than children delivered vaginally (Model 1; (95% CI)=(0.18, 0.61); p<0.001), but this association was no longer present after potential confounder adjustment and multiple imputation (Model 3; β (95% CI)=0.06 (−0.18, 0.30); p=0.61). Prior to potential confounder adjustment, the BMI z-scores of children delivered via planned C-section were on average 0.51 standard deviations higher than vaginally delivered children (Model 1; (95% CI)=(0.21, 0.81); p=0.001); however, this effect size was also attenuated and no longer significant following potential confounder adjustment and multiple imputation (Model 3; β (95% CI)=0.29 (−0.03, 0.61); p=0.071).

When mediation models were fit to examine the mediating effect of breastfeeding status at 1-month in the association between planned C-section (versus vaginal delivery) and 10-year anthropometric outcomes (Figure 2), the total effects for both obesity and anthropometric class were statistically significant (p=0.002, p<0.001, respectively), indicating an overall effect of planned C-section on these outcomes. Additionally, the average direct effects (ADEs, the effect of planned C-section when breastfeeding is held constant) were both significant (p<0.001) and very close to the total effect estimates, while the average causal mediation effects (ACMEs, the effect that arrives as a result of breastfeeding rather than "directly" from planned C-section) were both very small and non-significant (p=0.090, p=0.26, respectively). For example, for 10-year obesity, the ADE was 0.17 (p<0.001), meaning there is a 17% increase in the probability of having obesity due to planned C-section delivery, when breastfeeding status is held constant. On the other hand, breastfeeding alone decreased the risk of obesity by 1% after covariate adjustment, and this did not reach statistical significance (ACME=−0.01, p=0.090). Together, these results suggest that the effect of planned C-section on obesity is not explained by breastfeeding status. Additionally, for the outcome of 10-year BMI z-score, the total effect was not significant (p=0.16), indicating that planned C-section is not significantly associated with this outcome, through breastfeeding or otherwise.

The association between unplanned C-section and obesity was also assessed for robustness to unmeasured confounding using E-values. For obesity defined by anthropometric class, the observed risk ratio of 2.78 could be explained away by an unmeasured confounder that was associated with both planned C-section and obesity by a risk ratio of 5.0-fold each, above and beyond the measured confounders, but weaker confounding could not do so; the confidence interval could be moved to include the null by an unmeasured confounder that was associated with both planned C-section and obesity by a risk ratio of 2.3-fold each (beyond the measured confounders). Similarly, for obesity defined by BMI percentile, the observed risk ratio of 1.77 has corresponding E-values of 2.94 and 1.59 for the point estimate and the confidence interval, respectively.

Discussion

Consistent with our hypothesis, children who were born via planned C-section had a significantly higher risk of 10-year obesity, relative to children who were delivered vaginally. This association remained after adjusting for marital status, maternal race, prenatal ETS exposure, maternal age, maternal BMI, any hypertensive disorders during pregnancy, gestational diabetes, prenatal antibiotic use, child sex, parity, and birthweight z-score. Further, the association was not mediated by breastfeeding status at 1-month of age. Results were consistent using two distinct definitions of obesity (defined by BMI percentile as well as based on similarity in several anthropometric measurements). Though planned C-section was associated with a higher risk of obesity, it was not associated with a higher risk of being overweight or having greater BMI z-scores. These findings suggest that associations may be non-linear and emphasizes the importance of examining obesity as a distinct outcome. Though we hypothesized that children born via unplanned C-section would also have a higher risk of obesity relative to vaginal delivery—albeit, with smaller effect sizes due to benefits of partial labor—significant differences were not observed. Additionally, though the overall effect of any C-section on obesity initially appeared to be significant, the association was largely diminished—and at times no longer significant—after covariate adjustment, emphasizing the importance of capturing a wide range of confounders on an adequate sample size to adjust for them.

A prominent theory on the biological mechanism behind this association is microbiological differences due to mode of delivery. Children delivered via planned C-section are not exposed to their mother's vaginal microbiota, which is likely the case for those delivered via unplanned C-section (through labor or membrane rupture). The developmental origins of health and disease (DOHaD) hypothesis postulates that exposures during critical periods of early development may have consequences on long-term health.[39] Consistent with this hypothesis, a lack of exposure to these microbes in infancy may increase the risk of obesity later in life, as microbial dysbiosis or depletion may hinder normal energy harvest and alter metabolic programming. Indeed, a recent study examining the association between early life gut microbiota and BMI at age 12 found that gut microbiota composition at 10 days and 2 years of age explained over 50% of the variability in BMI at age 12.[40] However, the causes of obesity are complex and multifactorial. Other biological mechanisms may also play a role, such as epigenetic or immunological differences, which could act independently or synergistically.

A key point of rigor for this study was the use of precise exposure and outcome definitions. The fact that an effect was only found comparing planned C-section to vaginal deliveries could explain why some studies combining all C-sections fail to find significant associations.[41, 42] Additionally, our use of gaussian mixture models to identify anthropometric classes based on a wide range of measurements may reduce heterogeneity in the classification of obesity relative to BMI percentiles only, and could potentially explain why larger effect sizes were seen for planned C-section delivery (RR=2.78 versus 1.77, respectively). Indeed, though BMI is easy to collect and is the most commonly used anthropometric measurement to assess adiposity, there are limitations to its use alone. Namely, it does not distinguish between lean and fat mass, and has poor sensitivity in diagnosing excess body fat, especially in some populations.[43] The Obesity Society itself explicitly states that they define obesity as excess body fat rather than BMI≥30 kg/m^2.[44] The identified anthropometric classes may also capture a more "extreme" obesity phenotype, as obesity rates were lower using this definition. For these reasons, future studies should consider the use of a wider range of anthropometric measurements (beyond BMI) coupled with data reduction techniques, which may lead to definitions of obesity with reduced measurement error.

Our results are consistent with recently published findings on this association. Cai et al. demonstrated in a Singaporean birth cohort study that elective C-section was significantly associated with overweight at 12 months of age.[45] Similarly, a recent small retrospective study of US children found that children born via elective C-section had greater adiposity in preadolescence (7-10 years of age), relative to vaginal and emergency C-section born children.[46] Nonetheless, some inconsistencies still remain. A study using a population-based survey in Canada did not find an association between specific C-section types and childhood obesity at age 10-11, though their obesity rate was low (9.8%).[47] Another found that while C-section delivery conferred a higher risk of obesity at age 7, the association did not differ between those born via elective or non-elective C-section.[48] Given the discrepancies in these findings and the relatively few studies that have examined specific C-section type, additional studies are still needed.

Our study is not without limitations. As Mitchell and Chavarro called attention to,[49] the classification of specific C-section types is not always obvious, which may introduce misclassification bias and a lack of consistency in across-study exposure definitions. As not all unplanned deliveries were explicitly required to have at least some labor, classification based on "with or without labor", "length of labor", or "membrane rupture" (which were not collected in this cohort) may provide even more precise exposure definitions for this specific hypothesis. However, the potential misclassification of C-section type in our study would be non-differential with respect to 10-year anthropometric outcomes, likely biasing results toward the null. Additionally, inherent to all observational research studies, unmeasured or residual confounding is possible. For example, the definition of breastfeeding at 1-month used may not fully capture the effect of breastfeeding due to differences in duration or amount (residual confounding), and gestational weight gain was not adjusted for in analyses due to limited data (unmeasured confounding). The E-values for the confidence intervals were 1.59 and 2.30 for obesity defined by BMI percentile and anthropometric class, respectively, meaning that an unmeasured confounder associated with both planned C-section and obesity by these risk ratios could move the confidence interval to include the null value. Unmeasured confounding of this magnitude is certainly not implausible. However, E-values are interpreted as “above and beyond the measured confounders”, and given that our analysis has captured an extensive range of confounders that likely account for much of the confounding effects, the evidence for causality is moderately strong.

In addition to unmeasured confounding, other biases may be present in our analysis. Selection bias due to loss to follow-up and/or non-response is common in longitudinal cohort studies and can affect the internal validity of estimates[27]. We attempted to correct for this bias by using inverse probability weighting to account for systematic differences in loss to follow-up; however, this method may not fully account for inherent differences. Given that missing data were present in the analysis subset, bias and loss of power are possible using complete-case analysis.[50] However, because data are likely missing at random, multiple imputation was used to overcome this challenge. Further, though the generalizability of our results is limited given that WHEALS is a primarily African-American cohort (~60%), examining the consistency of these findings in a wide range of populations is important, and African-Americans are often underrepresented in relevant literature. Indeed, we found that the effect of planned C-section on 10-year obesity was stronger in white women compared to black women. Given that our previous results suggested that C-section delivery is associated with a higher odds of obesity at age 2 in children born to African-American women only,[51] further investigation into biological, social, and behavioral mechanisms throughout childhood by race is warranted.

In conclusion, compared to vaginally delivered children, children born via planned C-section have a higher risk of 10-year obesity, which was not explained by a wide range of confounding covariates and was not mediated by breastfeeding. The same association was not observed for unplanned C-section, potentially indicating beneficial effects of partial labor. Future studies should consider examining planned and unplanned c-section separately, or perhaps more precisely, spontaneous versus induced c-section, length of labor, and rupture or membranes. Additional work is still needed to understand the biological mechanisms behind this effect, including whether microbiological differences underlie the association.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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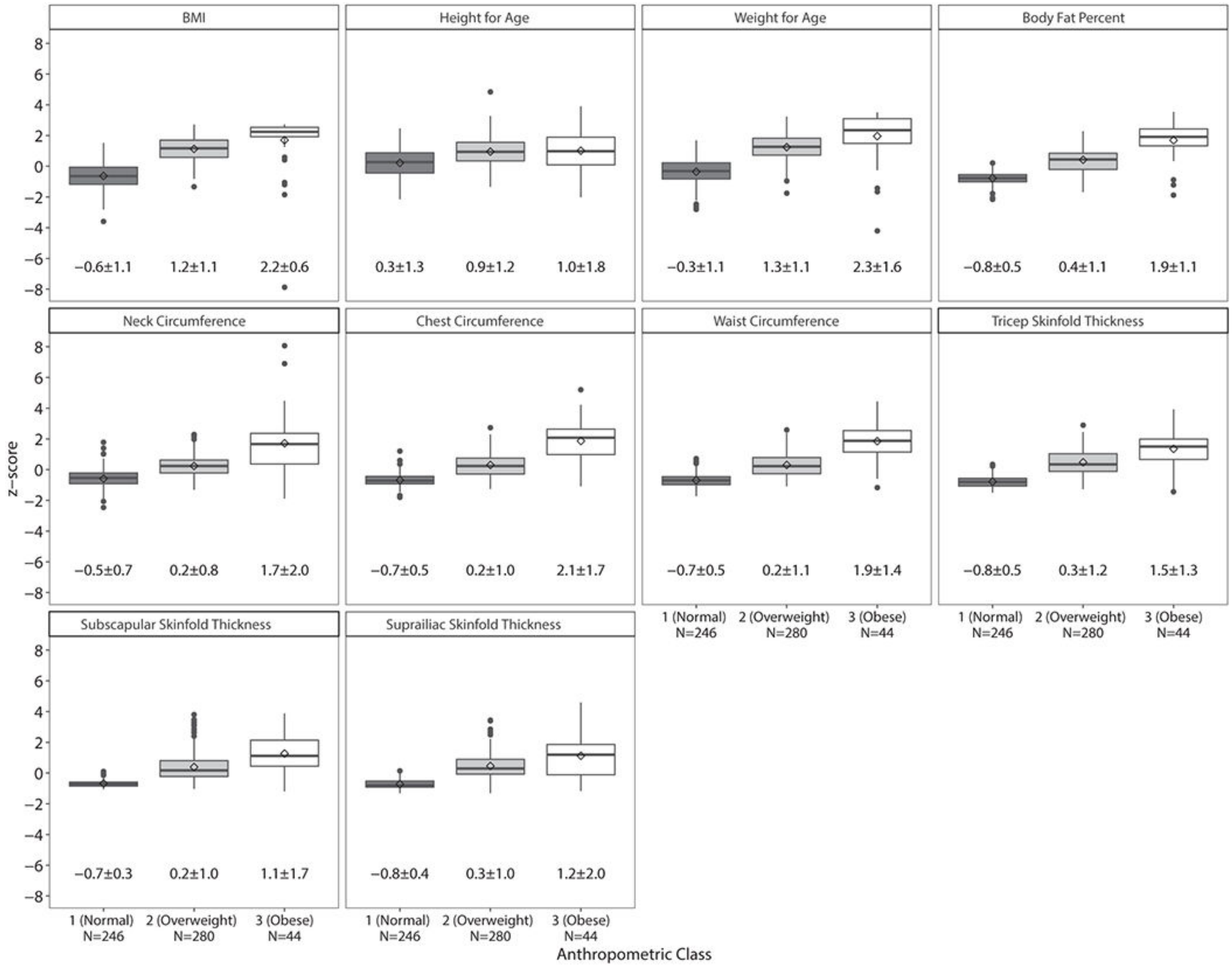

Figure 1:

Description of anthropometric classes at age 10. Z-scores were calculated using CDC growth curves, or were manually calculated to adjust for child sex. All Kruskal-Wallis p<0.001. Values shown are Median±IQR (means also displayed by hollow point).

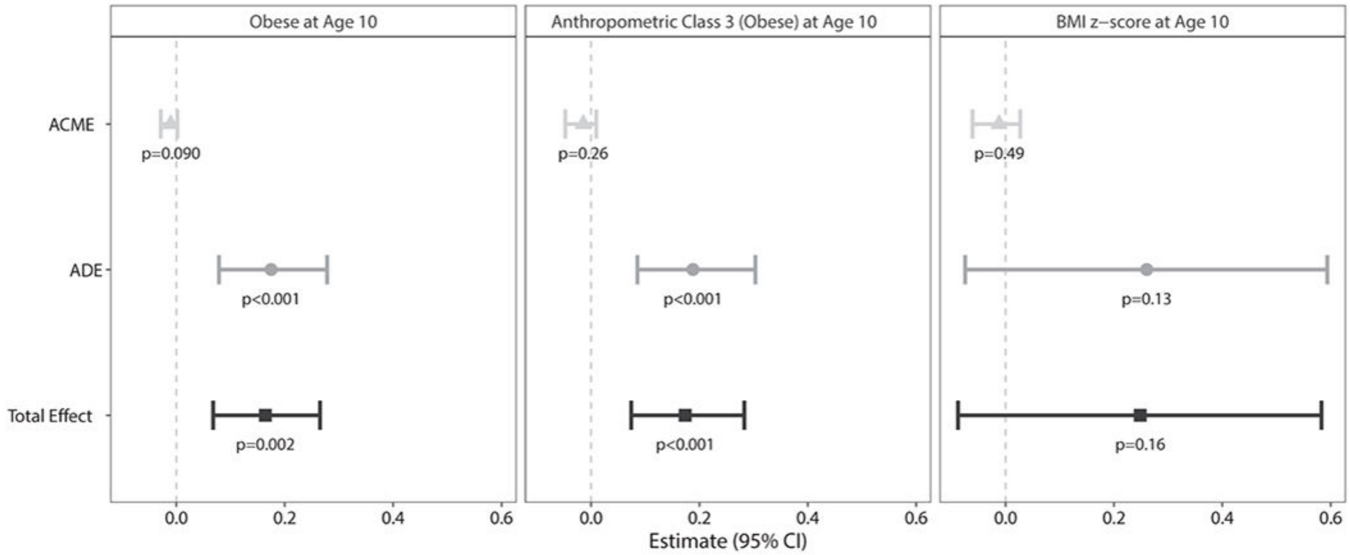

Figure 2:

The mediating effect of breastfeeding in the association between planned C-section vs. vaginal delivery and 10-year anthropometric outcomes. Estimates represent the increase in probability that a child has obesity (column 1), the increase in probability that a child is in anthropometric class 3 (column 2), and the mean difference in BMI z-score (column 3). All models use inverse probability weights and are adjusted for potential confounders (marital status, maternal race, prenatal ETS exposure, maternal age, maternal BMI, any hypertensive disorders during pregnancy, gestational diabetes, prenatal antibiotic use, child sex, parity, and birthweight z-score). ACME=average causal mediation effect, ADE=average direct effect.

Table 1:

Association between mode of delivery and maternal/early life characteristics

Covariate	Level	Mode of Delivery: Vaginal N=358	Planned C-Section N=82	Unplanned C-Section N=97	p-value[a]
		N (Column %) or N, Mean±SD			
Maternal education	<HS diploma	10 (2.8%)	3 (3.7%)	3 (3.1%)	0.67
	HS diploma	58 (16.2%)	8 (9.8%)	12 (12.4%)	
	Some college	162 (45.3%)	36 (43.9%)	49 (50.5%)	
	≥Bachelor's Degree	128 (35.8%)	35 (42.7%)	33 (34%)	
Mother married	No	123 (34.4%)	17 (20.7%)	40 (41.2%)	**0.013**
	Yes	235 (65.6%)	65 (79.3%)	57 (58.8%)	
Household income	<$20K	36 (10.1%)	11 (13.4%)	9 (9.3%)	0.99
	$20K-<$40K	79 (22.1%)	17 (20.7%)	23 (23.7%)	
	$40K-<$80K	99 (27.7%)	22 (26.8%)	23 (23.7%)	
	$80K-<$100K	53 (14.8%)	13 (15.9%)	16 (16.5%)	
	≥$100K	52 (14.5%)	11 (13.4%)	14 (14.4%)	
	Refused to Answer	39 (10.9%)	8 (9.8%)	12 (12.4%)	
Maternal race	White	91 (25.4%)	23 (28%)	15 (15.5%)	**0.036**
	African American	218 (60.9%)	41 (50%)	69 (71.1%)	
	Other/Mixed	49 (13.7%)	18 (22%)	13 (13.4%)	
Location of residence	Suburban	168 (46.9%)	44 (53.7%)	45 (46.4%)	0.52
	Urban	190 (53.1%)	38 (46.3%)	52 (53.6%)	
Maternal age at birth (years)		358, 27±5	82, 33±5	97, 30±6	**<0.001**
Mom smoked during pregnancy	No	326 (91.1%)	75 (91.5%)	89 (91.8%)	0.98
	Yes	32 (8.9%)	7 (8.5%)	8 (8.2%)	
Prenatal ETS exposure	No	261 (72.9%)	70 (85.4%)	76 (78.4%)	**0.048**
	Yes	97 (27.1%)	12 (14.6%)	21 (21.6%)	
Prenatal indoor pets	Neither	217 (60.6%)	55 (67.1%)	62 (63.9%)	0.35
	Dog(s) only	75 (20.9%)	16 (19.5%)	21 (21.6%)	
	Cat(s) only	46 (12.8%)	5 (6.1%)	6 (6.2%)	
	Both	20 (5.6%)	6 (7.3%)	8 (8.2%)	
Maternal BMI at first prenatal care visit (kg/m^2)		339, 29.2±7.5	81, 32.3±7.6	97, 33.8±8.4	**<0.001**
Maternal obesity at first prenatal care visit	No	203 (59.9%)	34 (42%)	38 (39.2%)	**<0.001**
	Yes	136 (40.1%)	47 (58%)	59 (60.8%)	
Any hypertensive disorders during pregnancy	No	276 (92.3%)	61 (78.2%)	71 (77.2%)	**<0.001**
	Yes	23 (7.7%)	17 (21.8%)	21 (22.8%)	
Gestational diabetes	No	282 (93.4%)	66 (86.8%)	82 (88.2%)	0.096
	Yes	20 (6.6%)	10 (13.2%)	11 (11.8%)	
Prenatal antibiotic use	No	138 (43.7%)	44 (55%)	45 (47.9%)	0.18
	Yes	178 (56.3%)	36 (45%)	49 (52.1%)	

Covariate	Level	Mode of Delivery			p-value[a]
		Vaginal N=358	Planned C-Section N=82	Unplanned C-Section N=97	
		N (Column %) or N, Mean±SD			
Prenatal antifungal use	No	259 (82%)	63 (78.8%)	78 (83%)	0.75
	Yes	57 (18%)	17 (21.3%)	16 (17%)	
Child sex	Male	165 (46.1%)	47 (57.3%)	57 (58.8%)	**0.031**
	Female	193 (53.9%)	35 (42.7%)	40 (41.2%)	
Parity	≥1	234 (65.4%)	64 (78%)	34 (35.1%)	**<0.001**
	0	124 (34.6%)	18 (22%)	63 (64.9%)	
Gestational age at delivery (weeks)		352, 38.9±1.6	82, 38.3±1.7	97, 39.0±1.8	**0.007**
Birth Weight (grams)		341, 3337±529	79, 3446±758	92, 3352±579	0.32
Birthweight z-score		337, −0.10±1.0	79, 0.3±1.2	92, −0.10±1.0	**0.007**
Breastfeeding status at 1-month	Never breastfed	61 (17.3%)	23 (29.1%)	17 (18.3%)	**0.013**
	Mixed Feeding	230 (65.3%)	49 (62%)	69 (74.2%)	
	Breastfeeding Only	61 (17.3%)	7 (8.9%)	7 (7.5%)	

[a]calculated by ANOVA for numerical covariates and chi-square test for categorical covariates.

Table 2:

Association between mode of delivery and BMI category at age 10

		Model 1[a]		Model 2[b]		Model 3[c]	
Obese							
Mode of Delivery	**N (%)**	**RR (95% CI)[d]**	**p-value**	**RR (95% CI)[d]**	**p-value**	**RR (95% CI)[d]**	**p-value**
Vaginal	56 (15.6%)	1 [*Reference*]		1 [*Reference*]		1 [*Reference*]	
C-section	60 (28.3%)	1.79 (1.23, 2.60)	0.002	1.22 (0.77, 1.93)	0.41	1.27 (0.89, 1.81)	0.19
Planned C-section	28 (34.2%)	2.12 (1.38, 3.26)	<0.001	1.67 (0.95, 2.92)	0.073	1.77 (1.16, 2.72)	0.009
Unplanned C-section	22 (22.7%)	1.21 (0.74, 1.97)	0.45	0.74 (0.40, 1.38)	0.35	0.75 (0.45, 1.23)	0.25
Overweight							
Vaginal	44 (12.3%)	1 [*Reference*]		1 [*Reference*]		1 [*Reference*]	
C-section	38 (17.9%)	1.34 (0.85, 2.12)	0.20	0.94 (0.55, 1.61)	0.83	0.99 (0.65, 1.51)	0.98
Planned C-section	13 (15.9%)	1.43 (0.76, 2.67)	0.26	0.92 (0.46, 1.84)	0.81	1.01 (0.60, 1.69)	0.98
Unplanned C-section	16 (16.5%)	1.25 (0.70, 2.23)	0.46	1.14 (0.59, 2.19)	0.70	1.02 (0.60, 1.72)	0.94
Normal							
Vaginal	234 (65.4%)	1 [*Reference*]		1 [*Reference*]		1 [*Reference*]	
C-section	105 (49.5%)	0.78 (0.66, 0.94)	0.008	0.97 (0.80, 1.16)	0.73	0.93 (0.77, 1.12)	0.42
Planned C-section	39 (47.6%)	0.70 (0.53, 0.92)	0.012	0.86 (0.66, 1.12)	0.27	0.78 (0.60, 1.02)	0.071
Unplanned C-section	53 (54.6%)	0.93 (0.76, 1.13)	0.44	1.05 (0.85, 1.29)	0.68	1.04 (0.83, 1.31)	0.70
Underweight							
Vaginal	24 (6.7%)	1 [*Reference*]		1 [*Reference*]		1 [*Reference*]	
C-section	9 (4.3%)	0.51 (0.23, 1.12)	0.092	0.67 (0.26, 1.70)	0.40	0.83 (0.43, 1.59)	0.58
Planned C-section	2 (2.4%)	0.35 (0.08, 1.50)	0.16	0.22 (0.03, 1.81)	0.16	0.44 (0.15, 1.29)	0.14
Unplanned C-section	6 (6.2%)	0.75 (0.30, 1.88)	0.54	1.34 (0.47, 3.84)	0.58	1.39 (0.63, 3.04)	0.42

[a] Inverse probability weighted+unadjusted.

[b] Inverse probability weighted+adjusted for marital status, maternal race, prenatal ETS exposure, maternal age, maternal BMI, any hypertensive disorders during pregnancy, gestational diabetes, prenatal antibiotic use, child sex, parity, and birthweight z-score. Complete-case estimates.

[c] Inverse probability weighted+adjusted for marital status, maternal race, prenatal ETS exposure, maternal age, maternal BMI, any hypertensive disorders during pregnancy, gestational diabetes, prenatal antibiotic use, child sex, parity, and birthweight z-score. Multiple imputation estimates.

[d] risk ratios (RRs) represent the probability of the specified BMI category at age 10, comparing the specified mode of delivery to vaginal delivery.

Table 3:

Association between mode of delivery and anthropometric class at age 10

		Model 1[a]		Model 2[b]		Model 3[c]	
Class 3 (“Obese”)							
Mode of Delivery	**N (%)**	**RR (95% CI)[d]**	**p-value**	**RR (95% CI)[d]**	**p-value**	**RR (95% CI)[d]**	**p-value**
Vaginal	18 (5.0%)	1 [*Reference*]		1 [*Reference*]		1 [*Reference*]	
C-section	26 (12.3%)	2.50 (1.33, 4.70)	0.004	1.96 (0.89, 4.30)	0.095	1.79 (1.05, 3.04)	0.032
Planned C-section	11 (13.4%)	3.08 (1.40, 6.81)	0.005	3.00 (1.33, 6.77)	0.008	2.78 (1.47, 5.26)	0.002
Unplanned C-section	8 (8.3%)	1.36 (0.59, 3.14)	0.47	0.97 (0.32, 3.00)	0.96	0.92 (0.40, 2.10)	0.84
Class 2 (“Overweight”)							
Vaginal	176 (49.2%)	1 [*Reference*]		1 [*Reference*]		1 [*Reference*]	
C-section	104 (49.1%)	0.95 (0.79, 1.16)	0.64	0.84 (0.66, 1.07)	0.17	0.88 (0.72, 1.08)	0.28
Planned C-section	42 (51.2%)	1.00 (0.77, 1.29)	0.98	0.86 (0.64, 1.17)	0.34	0.88 (0.67, 1.14)	0.33
Unplanned C-section	46 (47.4%)	0.91 (0.71, 1.18)	0.50	0.84 (0.61, 1.17)	0.30	0.90 (0.69, 1.16)	0.42
Class 1 (“Normal”)							
Vaginal	164 (45.8%)	1 [*Reference*]		1 [*Reference*]		1 [*Reference*]	
C-section	82 (38.7%)	0.89 (0.70, 1.13)	0.34	1.05 (0.83, 1.33)	0.66	1.04 (0.83, 1.30)	0.73
Planned C-section	29 (35.4%)	0.78 (0.55, 1.11)	0.17	0.85 (0.61, 1.20)	0.37	0.89 (0.64, 1.22)	0.47
Unplanned C-section	43 (44.3%)	1.06 (0.81, 1.40)	0.66	1.18 (0.91, 1.55)	0.22	1.14 (0.87, 1.49)	0.34

[a] Inverse probability weighted+unadjusted.

[b] Inverse probability weighted+adjusted for marital status, maternal race, prenatal ETS exposure, maternal age, maternal BMI, any hypertensive disorders during pregnancy, gestational diabetes, prenatal antibiotic use, child sex, parity, and birthweight z-score. Complete-case estimates.

[c] Inverse probability weighted+adjusted for marital status, maternal race, prenatal ETS exposure, maternal age, maternal BMI, any hypertensive disorders during pregnancy, gestational diabetes, prenatal antibiotic use, child sex, parity, and birthweight z-score. Multiple imputation estimates.

[d] risk ratios (RRs) represent the probability of the specified anthropometric class at age 10, comparing the specified mode of delivery to vaginal delivery.

Table 4:

Association between mode of delivery and BMI z-score at age 10

			Model 1[a]		Model 2[b]		Model 3[c]	
Mode of Delivery	**N**	**Mean±SD**	**β (95% CI)[d]**	**p-value**	**β (95% CI)[d]**	**p-value**	**β (95% CI)[d]**	**p-value**
Vaginal	358	0.27±1.24	0 [*Reference*]		0 [*Reference*]		0 [*Reference*]	
C-section	212	0.65±1.36	0.39 (0.18, 0.61)	<0.001	0.02 (−0.24, 0.28)	0.89	0.06 (−0.18, 0.30)	0.61
Planned C-section	82	0.76±1.27	0.51 (0.21, 0.81)	0.001	0.27 (−0.06, 0.61)	0.11	0.29 (−0.03, 0.61)	0.071
Unplanned C-section	97	0.49±1.46	0.17 (−0.12, 0.46)	0.26	−0.23 (−0.56, 0.11)	0.18	−0.17 (−0.47, 0.13)	0.27

[a]Inverse probability weighted+unadjusted.

[b]Inverse probability weighted+adjusted for marital status, maternal race, prenatal ETS exposure, maternal age, maternal BMI, any hypertensive disorders during pregnancy, gestational diabetes, prenatal antibiotic use, child sex, parity, and birthweight z-score. Complete-case estimates.

[c]Inverse probability weighted+adjusted for marital status, maternal race, prenatal ETS exposure, maternal age, maternal BMI, any hypertensive disorders during pregnancy, gestational diabetes, prenatal antibiotic use, child sex, parity, and birthweight z-score. Multiple imputation estimates.

[d]β *values represent the mean difference in BMI z-score at age 10, comparing the specified mode of delivery to vaginal delivery.*