Race-specific Association of Caesarean-Section Delivery with Body Size at Age 2 Years

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Objectives: African American children are at higher risk of obesity than White children and African American women are more likely to undergo caesarean-section (CS) delivery than White women. CS is associated with childhood obesity; however, little is known whether this relationship varies by race. We examined if the association of CS with obesity at age 2 years varied by race.

Design: Longitudinal birth cohort.

Setting: Birth cohort conducted in a health care system in metropolitan Detroit, Michigan with follow-up at age 2 years.

Participants: 639 birth cohort participants; 367 children (57.4%) were born to African American mothers and 230 (36.0%) children were born via CS.

Main Outcome Measure: Obesity defined as body mass index ≥95th percentile at age 2 years.

Results: Slightly more children of African American (n=37; 10.1%) than non-African American mothers (n=18; 6.6%) were obese (P=.12). There was evidence of effect modification between race and delivery mode with obesity at age 2 years (interaction P=.020). In children of African American mothers, CS compared to vaginal birth was associated with a significantly higher odds of obesity (aOR=2.35 (95% CI: 1.16, 4.77), P=.017). In contrast, delivery mode was not associated with obesity at age 2 years in children of non-African American mothers (aOR=.47 (95% CI: .13, 1.71), P=.25).

Conclusions: There is evidence for a race-specific effect of CS on obesity at age 2 years; potential underlying mechanisms may be racial differences in the developing gut microbiome or in epigenetic programming. Future research is needed to determine if this racial difference persists into later childhood. *Ethn Dis.* 2016;26(1):61-68; doi:10.18865/ed.26.1.61

Keywords: Birth Cohort, Childhood Obesity, Delivery Mode, Race, Disparities

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Introduction

Considerable racial disparities exist in the prevalence of pediatric overweight and obesity in the United States.[1] Among children aged 2-5 years, rates of obesity (body mass index [BMI] ≥95th percentile) are 3.5% for non-Hispanic White and 11.3% for non-Hispanic Black children.[2] Childhood BMI tracks to adulthood[3] where the relationship between childhood obesity and adult obesity is stronger in Blacks compared with Whites.[4]

Mode of delivery is a potential risk factor for childhood obesity.[5-8] Several studies demonstrate that cesarean section (CS) may increase risk of childhood obesity/overweight;[5-9] however, results have been inconsistent across different study groups.[10-13] In a recent meta-analysis a moderate-sized association was found between CS and childhood overweight/obesity (at aged 3-8 years) with an overall pooled odds ratio (OR) of 1.32 (95% CI OR 1.15, 1.51).[14] As the United States CS rates are higher in African American than White women,[15,16] mode of delivery may be a potential factor contributing to racial differences in childhood obesity.

Potential mechanisms explaining the association of mode of delivery with offspring obesity risk include differences in establishment of the gut microbiome or epigenetic programming.[5,6,14,17,18] Work in animal models and in humans has demonstrated that the gut microbiome influences body size.[19-22] In

adults, racial differences exist in the gut microbiome.[23] Such racial differences in gut microbiome structure and function are also observed in early life,[24] and may be in part due to the microbiome inherited at birth, particularly since evidence indicates that the vaginal microbiome of White and Black women differ.[25] Mode of delivery is associated with differences in infant gut microbiome composition; infants born vaginally have an oral, gut and skin microbiome that resembles the mother's vaginal microbiome while infants born via CS possess microbial communities that more closely resemble the mother's skin microbiome.[26] Epigenetic modifications may be another mechanism by which early-life exposures, including mode of delivery, predispose offspring to future obesity.[27] There are racial differences in epigenetic patterns (ie, DNA methylation) present at birth,[28] including racial differences in methylation at regions known to impact growth and obesity risk.[29] Epigenetic changes in cord blood DNA are associated with body size in childhood.[30] There is growing evidence that mode of delivery is associated with epigenetic changes in the both the placenta and the infant.[17,18,31]

To our knowledge, no study has examined if there are race-specific associations between CS and risk of obesity. We therefore examined if the association of CS delivery with childhood body size at age 2 years varied by race in the racially and socioeconomically diverse Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS) birth cohort.[32-34]

We examined if the association of CS delivery with childhood body size at age 2 years varied by race in the racially and socioeconomically diverse participants of the WHEALS birth cohort.

Methods

Study Population

The Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS) recruited pregnant women with due dates from September 2003 through December 2007 and who were seeing a Henry Ford Health System (HFHS) obstetrics practitioner at one of five clinics to establish an unselected birth cohort.[32-34] All women were in their second trimester or later, were aged 21-49 years, and were living in a predefined geographic area in western Wayne County that included the western portion of the city of Detroit as well as the suburban areas west of the city. Post-partum interviewer-administered questionnaires were completed at child aged 1, 6, 12, and 24 months. Children and their parent/guardian were invited to return for a clinic visit at child aged 2 years for a health assessment. All participants provided written, informed consent and study protocols were approved by the Institutional Review Board at HFHS.

The WHEALS cohort included 1,258 babies; 706 children (56.1%) completed a 2-year follow-up visit in the clinic. We excluded 10 sets of twins (n=20 children). Seventeen children missing delivery mode and 30 children missing height and weight information at the 2-year visit were also excluded. Our final sample size consisted of 639 children.

Covariate Measurement

Maternal race was self-reported. For primary analysis, race was defined using maternal self-report as either African American or non-African American. Maternal rather than child race was used as the racial difference in CS rate is attributed to maternal race.

Delivery records for WHEALS women were abstracted to obtain delivery mode. Delivery mode was categorized as vaginal or CS. Additionally, type of CS (planned/scheduled vs. unplanned/emergent), birth weight and gestational age at delivery were also abstracted from the delivery record. Sex- and gestational-age adjusted birth weight Z-scores were calculated using the US population as a reference.[35] Maternal prenatal care records were abstracted to obtain BMI at first prenatal care visit (mean gestational age at measure 8.4 ± 4.3 weeks); maternal obesity was defined as BMI≥30 kg/m^2.

Maternal smoking during pregnancy was self-reported and is defined as report of at least one tobacco product (cigarette, cigarillo, pipe, cigar) per day. Maternal education was self-reported and classified as high-school or less vs greater than a high-school education. Mothers also self-reported

marital status (defined as married vs all other categories), total household income (defined as <$40,000 compared to ≥$40,000), and number of children (child in study defined as first born vs other). At all postpartum visits, whether the child was breastfed was self-reported and was defined as ever vs never breastfed.

Body Size Measurement

At the 2-year clinic visit, trained field staff measured child height in stocking feet with a wall stadiometer; child weight was measured with the child in light clothing using a balance beam physician scale. BMI was calculated as weight (in kg) divided by the square of height (m^2). BMI Z-scores and percentiles were calculated according to the 2000 Centers for Disease Control and Prevention age- and sex-specific growth charts. Obesity was defined as BMI≥95th percentile.[36]

Statistical Analysis

For descriptive purposes, maternal, newborn and child characteristics were compared by maternal race using a likelihood ratio chi-square test for discrete characteristics and a Student's t-test for continuous characteristics. SAS version 9.4 (SAS Institute, Cary, NC) was used for all analysis.

Our two outcome variables were obesity (defined as BMI≥95th percentile) and BMI-Z-score (a continuous measure). Logistic regression was used to examine the association between CS and obesity and linear regression was used to examine the association of CS with BMI Z-score. To examine if there were race-specific effects of the association of CS with childhood obesity, race-by-delivery mode interaction terms were fit. Interaction models were fit unadjusted and then adjusted for maternal age, maternal education, maternal smoking during pregnancy, maternal obesity, ever breastfed, firstborn status, child sex, birth weight Z-score, and child age. Models were then fit stratified by race. In fitting race-specific models, within each race, we first fit an unadjusted model (only including delivery mode). Potential confounding factors were identified as any factor (maternal age, education, smoking during pregnancy, obesity, marital status, and household income, firstborn status, child sex, birth weight Z-score, and gestational age at birth) that when added to the model resulted in a ≥10% change in the parameter estimate for delivery mode on body size measure within each race.[37] In models of children born to African American mothers, maternal obesity met the criteria for confounding, whereas in models of children born to non-African American mothers, birth weight Z-score met the criteria for confounding.

We conducted several sensitivity analyses. Some mothers in the non-African American category reported their race as other than White. Models were re-run excluding 82 mothers self-reporting "other" race. We *a priori* analyzed data according to maternal race; however, we also examined the findings using child's race.

As described elsewhere,[38] not all children completed a 2-year clinic visit; most attrition occurred early in the study (n=185 dropped out at 1 month, 29 at six months and 41 at 1 year). Because the greatest loss-to-follow-up occurred early in the study, we compared prenatal/ maternal characteristics between those who were and were not in the analytic sample. Although rates of CS delivery did not differ between those who were in the analytic sample (36.0%) vs those who were not included (38.9%), there were differences in maternal race (57.4% of those with complete follow-up were African American compared with 67.2% of those without complete follow-up) and mean maternal age at delivery was slightly higher in those with complete follow-up (30.1±5.2 years) compared with those with incomplete follow-up (29.0±5.2 years).[38] To account for the effect of incomplete follow-up and missing data on our effect estimates, we calculated inverse probability weights (IPW)[39-41] for complete follow-up. Inverse probability weights were calculated by fitting a logistic regression model for complete follow-up at aged 2 years with the following baseline maternal factors: age, race, insurance type, income (including whether or not the question was answered), education, smoking status, alcohol use, urban residence, marital status, history of asthma/allergies, and mode of delivery and obtaining the predicted probability of successful follow-up.[42] The data were then re-analyzed using the IPW as weights in the logistic model as a way to adjust for bias due to incomplete follow-up.

Results

Table 1 presents maternal, birth and child characteristics by maternal race. African American women were younger, had larger BMI and were

Table 1. Maternal, birth and child characteristics, by maternal self-reported race, among 639 WHEALS participants. Data are mean ± standard deviation or n (%)

	African American N=367 (57.4%)	Non-African American N=272 (42.6%)	P
Maternal characteristics			
Age at delivery, years	29.5 ± 5.5	30.8 ± 4.8	.002[f]
BMI at first prenatal care visit, kg/m^2[a]	31.1 ± 8.1	28.5 ± 7.8	<.001[f]
Maternal obesity[a]	174 (48.5%)	87 (32.7%)	<.001[g]
>High school education	277 (75.5%)	236 (86.8%)	<.001[g]
Married	191 (52.0%)	237 (87.1%)	<.001[g]
Smoking during pregnancy	32 (8.7%)	29 (10.7%)	.4[g]
Total household income <$40,000[b]	150 (48.9%)	59 (23.5%)	<.001[g]
Child birth characteristics			
CS delivery	139 (37.9%)	91 (33.5%)	.25[g]
Female	176 (48.0%)	135 (49.6%)	.68[g]
Gestational age at birth, weeks[c]	38.7 ± 1.7	39.1 ± 1.5	.002[f]
Birthweight, g[d]	3277.3 ± 577.2	3511.0 ± 529.6	<.001[f]
Birthweight Z-score[e]	-0.18 ± 0.96	0.21 ± 0.96	<.001[f]
First Born	132 (36.0%)	109 (40.1%)	.29[g]
Child characteristics at age 2 clinic visit			
Age at clinic visit, months	27.0 ± 3.1	26.3 ± 2.7	.003[f]
Ever breastfed	280 (76.3%)	229 (84.2%)	.014[2]
Height, cm	90.0 ± 4.7	89.4 ± 4.2	.083[f]
BMI, kg/m^2	16.7 ± 1.8	16.7 ± 1.5	.83[f]
BMI Z-score	0.11 ± 1.17	0.09 ± 1.05	.88[f]
BMI percentile	53.2 ± 29.9	53.2 ± 28.7	.99[f]
BMI category			.15[g]
Underweight (BMI<5th percentile)	26 (7.1%)	16 (5.9%)	
Normal weight (BMI≥5th and <85th percentile)	277 (75.5%)	207 (76.1%)	
Overweight (BMI≥85th and <95th percentile	27 (7.3%)	31 (11.4%)	
Obese (BMI≥95th percentile)	37 (10.1%)	18 (6.6%)	

WHEALS, Wayne County Health, Environment, Allergy and Asthma Longitudinal Study; BMI, body mass index; CS, cesarean section.
a. n=14 with missing data.
b. n=81 with missing or refused income information.
c. n=15 with missing data.
d. n=32 with missing data.
e. n=40 with missing data.
f. Student's t-test was used for continuous covariates.
g. Likelihood ratio chi-square test for discrete covariates.

more likely to be obese during pregnancy, tended to have less education, were less likely to be married, and had lower household income than non-African American women (all P<.05). Infants born to African American compared with non-African American mothers had a lower gestational age at delivery, lower birth weight and were less likely to be ever breastfed (all P<.05). Children of African American mothers were slightly older at the 2-year clinic visit (P=.003).

We found a slightly, but not statistically significant, greater rate of CS among African American (37.9%) compared with non-African American women (33.5%) (P=.25). Of the 230 born via CS, type of CS (ie, planned/scheduled vs unplanned/emergent) was available on 229 deliveries. There was a borderline statistically significant difference in planned vs unplanned CS rates by race (P=.08). In African Americans mothers, 58 (42.0%) were planned and 80 (58.0%) were unplanned CS; in non-African American mothers, 49 (53.8%) were planned and 42 (46.2%) were unplanned CS.

At the time of the 2-year visit, there were no significant associations between maternal race and child body size measures (Table 1). Slightly more children of African American mothers were obese (10.1% vs. 6.6%, respectively; P=.12). Mean BMI Z-score at the 2-year visit did not differ significantly by maternal race (P=.88).

Maternal race modified the association between mode of delivery and childhood obesity at age 2 years. There was a statistically significant race-by-delivery mode interaction for childhood obesity (P=.008); this interaction remained statistically significant even after adjustment for maternal age, maternal education, maternal smoking during pregnancy, maternal obesity, ever breastfed, firstborn status, child gender, birth weight Z-score, and child age (P=.020). In contrast, there was not a statistically significant race-by-delivery mode interaction for BMI Z-score (P=.49).

Among children of African American mothers, CS was associated with a statistically significant unadjusted OR=2.64 (1.32, 5.27) for obesity (P=.006). CS remained statistically significantly associated with obesity after covariate adjustment (P=.017); CS was associated

Table 2. Race-specific adjusted association of caesarean-section (CS) delivery compared with vaginal delivery (referent) with obesity (BMI≥95th percentile) and BMI Z-score, measured at age 2 years in WHEALS. Covariates included in each race-specific model are those that changed the delivery mode parameter estimates by ≥10%

	Obesity		BMI Z-score	
Covariate	aOR (95% CI)	P	β (se)	P
African American mothers				
CS	2.35 (1.16, 4.77)	.017	.22 (.13)	.092
Maternal obesity	2.12 (1.02, 4.42)	.045	.24 (.13)	.052
Model R^2	.067[a]		.022	
Non-African American mothers				
CS	.47 (.13, 1.71)	.25	.19 (.14)	.17
Birth weight Z-score	1.22 (.70, 2.15)	.48	.21 (.07)	.002
Model R^2	.021[a]		.045	

aOR, adjusted odds ratio; CI, confidence interval; se, standard error.
a. R^2 for the logistic model is Nagelkerke's R^2.

with aOR=2.35 (1.16, 4.77) for obesity at aged 2 years in children of African American mothers (Table 2). Among children of African American mothers, CS was also associated with BMI Z-score; children born via C-section had a mean 0.26±0.13 unit higher BMI Z-score compared with children born via vaginal delivery *(P*=.037). After covariate adjustment, this was slightly attenuated (Table 2; β=0.22±0.13; *P*=.092). Either before or after covariate adjustment, in children of non-African American mothers, CS was not associated with obesity or BMI Z-score (Table 2).

Stratified by race, among those born via CS, comparing those with planned vs unplanned CS, there was not a difference in obesity in the children of African American *(P*=.20) or non-African American mothers *(P*=.55) (data not shown).

Sensitivity Analysis

We reran models excluding 82 children of race other than White or African American and all model inferences remained the same. Maternal-child race was highly concordant (91.6% of children had the same race designation as their mother). We repeated the analysis using child rather than maternal race, and all model inferences remained the same.

After including the IPW for complete follow-up, there remained a statistically significant race-by-delivery mode interaction for childhood obesity both before *(P*=.010) and after *(P*=0.029) covariate adjustment. After stratifying by race, CS remained associated with obesity among children born to African Americans mothers (aOR=2.23 [1.13, 4.40]; *P*=.020).

Discussion

In our current study, we found new evidence suggesting that race modified the association of CS with obesity measured at aged 2 years, with CS being associated with obesity at aged 2 years in children of African American mothers. In the US, CS rates are higher in African American than White women,[15,16] even after accounting for pre-pregnancy risk and medical indications.[43] Disparities in rates of CS could be contributing to disparities in childhood obesity rates. Roth et al suggest that racial disparities in CS may be accounted for by lack of maternal education necessary to advocate for oneself to avoid a medically unnecessary CS.[43] Interventions early in pregnancy, particularly in a first pregnancy where risk of CS may be the greatest, to educate women on labor and delivery options may help reduce disparities in rates of CS and subsequently improve offspring health.

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Overall, African American children are at higher risk for obesity than White children.[1,2,44] Although we did not detect statistically significant racial differences in the prevalence of obesity in our sample at aged 2 years, our race-specific estimates of obesity (10.1% in children born to

African American mothers; 6.6% in children born to non-African American mothers) are similar to the 11.3% for non-Hispanic Black and 3.5% for non-Hispanic White children aged 3-5 years reported in the United States.[2] Body size in childhood tracks to adulthood, with children with the largest childhood weight having the greatest risk of obesity as adults.[3] The relationship between childhood and adult obesity also varies by race; obesity in childhood is associated with a greater risk of adult obesity in Blacks compared with Whites.[4] Identification of risk factors associated with racial differences in childhood obesity,[4] such as CS, may be important in primary prevention of childhood, and subsequently, adult obesity.

There are several potential mechanisms by which there may be racial differences in the delivery mode and offspring obesity relationship. Children who are delivered via CS have gut microbiomes that more closely resemble the maternal skin.[26] Data from the Human Microbiome Project have shown that racial differences in the skin microbiome exist;[45] if there are similar racial differences in the maternal skin microbiome, neonates may be differentially exposed to microbial species that contribute to the initial development of their microbiome. Alternatively, epigenetic mechanisms may explain the racial differences in the delivery mode and offspring obesity association. There are racial differences in the epigenetic profiles of newborns,[28] including in regions associated with growth and obesity.[29] Recent studies suggest that mode of delivery is associated with different methylation patterns in infants.[17,18] If epigenetic changes that are associated with delivery mode vary by race in a way that influences weight and/or growth, this could also explain the race-specific association of CS on risk of obesity.

In contrast to other studies, we did not find an association between CS and obesity in our non-African American participants at mean age of 26.3 ± 2.7 months. Relative to Whites, African Americans have a lower age at adiposity rebound and a faster velocity of BMI change over time in early childhood (between approximately ages 1-5 years).[46] Our single point-in-time measure of BMI from the 2-year clinic visit at ages 2-3 years may have been insufficient to examine the association of CS with obesity, particularly in our non-African American children. This is consistent with recent findings from the Avon Longitudinal Study of Parents and Children, a predominantly White cohort, which did not find a statistically significant association between CS and predicted BMI Z-score at age 20 months or overweight/obesity at age 38 months.[47] Future studies that examine the race-specific association of CS on BMI trajectory over childhood are needed.

There are several limitations to our current study. Approximately 44% of the cohort did not complete a study visit at age 2 years potentially increasing risk of selection bias; however, our primary factor of interest, delivery mode, did not differ between these groups. Loss-to-follow up for the 2-year visit was greater for African Americans, reinforcing the need for optimizing retention strategies for racial and ethnic minority participants.[48] However, results were similar after inclusion of IPW for follow-up, which suggests that the impact of this attrition may have been small. Although we found no difference in child obesity by CS type (ie, scheduled vs emergent), the latter of which may be associated with rupture of membranes and exposure of the infant to some vaginal microbes,[49] there still may be residual confounding due to CS indication which we were unable to account for in this analysis.

Strengths of our current study include that data on delivery mode, maternal weight in pregnancy and birth weight were obtained directly from the medical record and child body size was measured at a research clinic visit, eliminating potential recall bias. Our sample included a large number of African American maternal-child pairs, allowing us to estimate the race-specific association of delivery mode and obesity in a high-risk group.[1,44]

Conclusion

In summary, this study provides evidence for a race-specific association of CS with childhood obesity measured at age 2 years, with the association being detectable in African American participants. Potential mechanisms underlying this race-specific association include racial differences in the gut microbiome or in epigenetic changes in the neonate that may be determined in part by mode of delivery; these require future study.

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Conflict of Interest

No conflicts of interest to report.

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Author Contributions

Research concept and design: Cassidy-Bushrow, Wegienka, Levin, Ownby, Woodcroft, Zoratti, Johnson. Acquisition of data: Wegienka, Havstad, Ownby, Woodcroft, Zoratti, Johnson. Data analysis and interpretation: Cassidy-Bushrow, Wegienka, Havstad, Levin, Lynch, Ownby, Rundle, Johnson. Manuscript draft: Cassidy-Bushrow, Wegienka, Havstad, Levin, Lynch, Rundle, Woodcroft, Zoratti. Statistical expertise: Havstad, Levin, Lynch, Rundle. Administrative: Wegienka, Zoratti. Supervision: Cassidy-Bushrow, Wegienka, Levin, Lynch, Ownby, Woodcroft, Zoratti, Johnson

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