Letters

RESEARCH LETTER

Association of Cesarean Delivery With Body Mass Index *z* Score at Age 5 Years

Cesarean delivery rates remain high and variable across hospitals, regions, and countries.[1,2] Cesarean delivery may be a risk factor for childhood obesity,[1,2] possibly because delivery route can influence the intestinal microbiomes,[3] which may influence energy regulation.

Author Audio Interview

Two meta-analyses, summarizing data from 24 studies, have reported an increased risk of obesity for individuals with cesarean birth (pooled odds ratio [OR], 1.22 [95% CI, 1.05-1.42] and 1.33 [1.19-1.48]).[1,2] Limitations of earlier studies include small sample size in several studies and lack of adjustment for maternal body mass index (BMI [calculated as weight in kilograms divided by height in meters squared]) and sociocultural factors. Even after adjusting for these measured maternal characteristics, residual confounding is likely. Within-family analysis is one way of controlling for such confounding. Because siblings grow up in similar social, economic, and cultural environments and share the same genetic predisposition to obesity, sibling studies minimize the variation in several of the noncausal factors that could explain why cesarean delivery could appear to be associated with a higher risk of obesity. The main objective of this study was to examine within-family and additional between-family associations of delivery route with BMI *z* score at 5 years of age in a large cohort of sibling pairs to separate most putative confounding effects from the effects of cesarean delivery.

Methods | We used data from the Linked CENTURY (Collecting Electronic Nutrition Trajectory Data Using Records of Youth) study, a longitudinal clinical database of well-child visits linked to each child's birth certificate.[4] The Linked CENTURY study includes singleton-birth children younger than 18 years who were seen for a well-child visit at Atrius Harvard Vanguard Medical Associates in eastern Massachusetts from 1980 through 2008 and whose data were linked to their Massachusetts birth certificate. We included 16 140 siblings born between 1987 and 2003 and their 8070 mothers. We obtained delivery route, which was the main exposure, from birth certificates. We extracted height and weight data for children at least 5 and less than 6 years of age from electronic health records and calculated BMI as weight in kilograms divided by height in meters squared. This study was approved and informed consent was waived by the Harvard Pilgrim Health Care Institutional Review Board.

Our main outcome was age-specific and sex-specific BMI *z* score at 5 years of age based on Centers for Disease Control and Prevention reference data.[5] We used a single linear mixed model, adjusted for mother's age, parity, and race/ethnicity and for child's age, sex, and birth year, to decompose the total association of cesarean delivery with BMI *z* score into a within-family component and an additional between-family component.[6] The model equation for this is

$$Y_{ij} = \alpha + \beta_w X_{ij} + \beta_d \overline{X}_i + v_i + e_{ij},$$

where Y_{ij} = BMI *z* score for the *i*th individual from the *j*th family, X_{ij} = individual's cesarean delivery status (0 = no and 1 = yes), $\overline{X}_i$ = family average cesarean deliveries (0 = both siblings vaginal delivery, 0.5 = one sibling vaginal delivery and one sibling cesarean, and 1 = both siblings cesarean), v_i = family random effect, and e_{ij} = random error; v_i and e_{ij} are assumed to be uncorrelated and normally distributed, each with a mean value of 0. The estimated within-family component β_w is mostly unconfounded by other factors. We also fit a model that did not decompose the effect of cesarean delivery; this model approximates the possibly confounded results we would have observed without accounting for sibling status. We fit all models using PROC GLIMMIX, SAS, version 9.4 (SAS Institute, Inc).

Results | A total of 3804 of the 16 140 children (23.6%) had nonwhite mothers. A total of 7943 of the 16 140 children (49.2%) were female, 3204 children (19.9%) had cesarean delivery, and the mean (SD) BMI *z* score at 5 years of age was 0.48 (1.00). Mean BMI *z* score was 0.45 among siblings who both had vaginal delivery, 0.51 among siblings with 1 cesarean and 1 vaginal delivery, and 0.63 among siblings who both had cesarean delivery (**Table 1**).

In the covariate-adjusted model, the within-family association of cesarean vs vaginal delivery was 0.04 higher BMI *z* score at 5 years of age (95% CI, −0.04 to 0.11) and the additional between-family association was 0.13 (95% CI, 0.04 to 0.22) (**Table 2**). In a model adjusted for the same covariates, but without decomposing the within-family and between-family effects, children with cesarean delivery had 0.13 higher BMI *z* score (95% CI, 0.08 to 0.17).

Discussion | We found that, within families, cesarean delivery was not associated with higher BMI *z* score at 5 years of age. This null finding suggests that confounding by unmeasured variables, such as maternal BMI and sociocultural factors, accounts for observed associations between cesarean delivery and BMI *z* score in some earlier studies. Such confounding is also reflected in the difference between our within-family estimate (0.04) and our additional between-family estimate (0.13).

This study had several limitations. All patients had health insurance; our results may not be generalizable to individuals without insurance. We did not have data on whether the cesarean delivery was an emergency procedure or data on maternal prepregnancy BMI. Maternal BMI, however, differs more between

Table 1. Participant Characteristics Overall and According to Family Cesarean Delivery Status[a]

Variable	Overall	Both Siblings Vaginal Delivery	One Sibling Vaginal and One Sibling Cesarean Delivery	Both Siblings Cesarean Delivery
No. (%) of siblings	16 140 (100)	11 910 (73.8)	2052 (12.7)	2178 (13.5)
Mother				
Age, mean (SD), y	31.1 (4.8)	30.8 (4.8)	31.4 (4.9)	31.9 (4.6)
Race/ethnicity, No. (%)				
White	12 306 (76.4)	9113 (76.6)	1516 (74.1)	1677 (77.1)
Asian	959 (6.0)	742 (6.2)	102 (5.0)	115 (5.3)
Black	1891 (11.7)	1331 (11.2)	305 (14.9)	255 (11.7)
Hispanic	745 (4.6)	549 (4.6)	96 (4.7)	100 (4.6)
Other	209 (1.3)	155 (1.3)	27 (1.3)	27 (1.2)
Child (N = 16 140)				
Age at outcome, mean (SD), y	5.3 (0.3)	5.3 (0.3)	5.3 (0.3)	5.3 (0.3)
BMI *z* score at 5 y, mean (SD)	0.48 (1.00)	0.45 (0.99)	0.51 (1.04)	0.63 (0.99)
Sex, No. (%)				
Male	8197 (50.8)	5957 (50.0)	1091 (53.2)	1149 (52.8)
Female	7943 (49.2)	5953 (50.0)	961 (46.8)	1029 (47.2)

Abbreviation: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared.

[a] Data for 16 140 siblings and their 8070 mothers from the Linked CENTURY study.[4]

Table 2. Within-Family and Additional Between-Family Associations of Cesarean Delivery With BMI *z* Score at 5 Years[a,b]

Association	Difference in BMI *z* score (95% CI): Unadjusted	Difference in BMI *z* score (95% CI): Adjusted[c]
Cesarean delivery yes vs no β_w = within family	0.02 (−0.05 to 0.09)	0.04 (−0.04 to 0.11)
Family average cesarean delivery β_d = additional between family	0.15 (0.06 to 0.24)	0.13 (0.04 to 0.22)

Abbreviation: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared.

[a] Data from 16 140 siblings and their 8070 mothers from the Linked CENTURY study.[4]

[b] Models were corrected for family clustering. Estimates were determined using the following equation: $Y_{ij} = \alpha + \beta_w X_{ij} + \beta_d \bar{X}_i + v_i + e_{ij}$, where Y_{ij} = BMI *z* score for the *i*th individual from the *j*th family, X_{ij} = individual's cesarean delivery status (0 = no and 1 = yes), $\bar{X}_i$ = family average cesarean delivery (0 = both siblings vaginal delivery, 0.5 = 1 sibling vaginal delivery and 1 sibling cesarean delivery, and 1 = both siblings cesarean delivery), v_i = family random effect, and e_{ij} = random error.

[c] Adjusted for mother's age, parity, and race/ethnicity and child's age, sex, and birth year.

families than across pregnancies, which is another reason to use a sibling-pairs design. Strengths of this study include the large number of sibling pairs and our ability to link clinical data with birth certificates.

We did not observe a within-family effect of cesarean delivery. This finding suggests that reported associations between cesarean delivery and childhood obesity may be confounded by unmeasured variables.

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