JAMA Pediatrics | Original Investigation

Association Between Cesarean Birth and Risk of Obesity in Offspring in Childhood, Adolescence, and Early Adulthood

Changzheng Yuan, ScD; Audrey J. Gaskins, ScD; Arianna I. Blaine, ScM; Cuilin Zhang, MD, PhD; Matthew W. Gillman, MD, SM; Stacey A. Missmer, ScD; Alison E. Field, ScD; Jorge E. Chavarro, MD, ScD

Supplemental content

IMPORTANCE Cesarean birth has been associated with higher risk of obesity in offspring, but previous studies have focused primarily on childhood obesity and have been hampered by limited control for confounders.

OBJECTIVE To investigate the association between cesarean birth and risk of obesity in offspring.

DESIGN, SETTING, AND PARTICIPANTS A prospective cohort study was conducted from September 1, 1996, to December 31, 2012, among participants of the Growing Up Today Study, including 22 068 offspring born to 15 271 women, followed up via questionnaire from ages 9 to 14 through ages 20 to 28 years. Data analysis was conducted from October 10, 2015, to June 14, 2016.

EXPOSURE Birth by cesarean delivery.

MAIN OUTCOMES AND MEASURES Risk of obesity based on International Obesity Task Force or World Health Organization body mass index cutoffs, depending on age. Secondary outcomes included risks of obesity associated with changes in mode of delivery and differences in risk between siblings whose modes of birth were discordant.

RESULTS Of the 22 068 offspring (20 950 white; 9359 male and 12 709 female), 4921 individuals (22.3%) were born by cesarean delivery. The cumulative risk of obesity through the end of follow-up was 13% among all participants. The adjusted risk ratio for obesity among offspring delivered via cesarean birth vs those delivered via vaginal birth was 1.15 (95% CI, 1.06-1.26; P = .002). This association was stronger among women without known indications for cesarean delivery (adjusted risk ratio, 1.30; 95% CI, 1.09-1.54; P = .004). Offspring delivered via vaginal birth among women who had undergone a previous cesarean delivery had a 31% (95% CI, 17%-47%) lower risk of obesity compared with those born to women with repeated cesarean deliveries. In within-family analysis, individuals born by cesarean delivery had 64% (8%-148%) higher odds of obesity than did their siblings born via vaginal delivery.

CONCLUSIONS AND RELEVANCE Cesarean birth was associated with offspring obesity after accounting for major confounding factors. Although additional research is needed to clarify the mechanisms underlying this association, clinicians and patients should weigh this risk when considering cesarean delivery in the absence of a clear indication.

JAMA Pediatr. doi:10.1001/jamapediatrics.2016.2385
Published online September 6, 2016.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Jorge E. Chavarro, MD, ScD, Department of Nutrition, Harvard T. H. Chan School of Public Health, Bldg II 3rd Floor, 655 Huntington Ave, Boston, MA 02115 (jchavarr@hsph.harvard.edu).

Nearly 1.3 million cesarean deliveries are performed yearly in the United States, making it the most common surgical procedure[1] and accounting for one-third of deliveries nationwide.[2] When indicated, cesarean deliveries reduce the risk of morbidity to mother and fetus and, in many cases, are a life-saving intervention.[3] Nevertheless, cesarean deliveries have risks. Women undergoing planned cesarean delivery without known indications for the procedure have a 3-fold greater risk of major morbidity—including a 5-fold greater risk of cardiac arrest, a 3-fold greater risk of hysterectomy and puerperal infection, and a 2-fold greater risk of thromboembolism—compared with women who undergo low-risk planned vaginal deliveries.[4] Cesarean delivery is also associated with an increased risk of maternal mortality.[5] The most significant immediate risk to children delivered via cesarean delivery is a higher frequency of respiratory complications.[6,7] In addition, increasing evidence suggests that children born by cesarean delivery experience higher rates of adverse health outcomes later in life.[8-10] With these concerns in mind, leading professional organizations have advocated for the prevention of primary cesarean delivery as a strategy to reduce the overall frequency of cesarean delivery.[11]

A growing amount of literature suggests that cesarean birth is associated with a higher risk of overweight and obesity in offspring. Two meta-analyses have reported pooled odds ratios (ORs) of 1.22 (95% CI, 1.05-1.42) for offspring obesity associated with cesarean birth.[12,13] However, inference from most existing studies has been hampered by limited sample size,[14] suboptimal control for shared risk factors (eg, prepregnancy body mass index [BMI, calculated as weight in kilograms divided by height in meters squared] and common pregnancy complications),[12,13,15] or both.[16] Therefore, it remains unclear whether the association between mode of birth (cesarean vs vaginal) and obesity in offspring is real or indicative of residual confounding. To overcome these limitations, we investigated the association between cesarean birth and risk of obesity in offspring among participants of the Growing Up Today Study (GUTS),[17] a large prospective cohort of individuals followed up from childhood through early adulthood.

Key Points

Question Is cesarean delivery associated with obesity in offspring from childhood through young adulthood?

Findings In this cohort study, individuals born by cesarean delivery were 15% more likely to become obese during follow-up than those born by vaginal delivery; those born via cesarean delivery had 64% higher odds of obesity compared with their siblings born via vaginal delivery. Vaginal birth after cesarean birth was associated with a 31% lower risk of offspring obesity compared with those born via repeat cesarean delivery.

Meaning These findings support the hypothesis that the association between cesarean delivery and offspring obesity is a true effect whose underlying mechanisms still need to be determined.

Methods

GUTS is an ongoing prospective cohort study of young adults followed up since September 1, 1996. A total of 16 882 children aged 9 to 14 years responded to the baseline questionnaire, and an additional 10 923 children aged 9 to 14 years enrolled in 2004. Participants have been followed up with yearly self-administered follow-up questionnaires between 1997 and 2001 and with biennial questionnaires thereafter.[17,18] Study details have been described previously.[19,20] From the 23 655 GUTS participants for whom complete data on their mothers' pregnancies were available, we excluded those for whom height and weight information was missing (n = 221) and those who were not born of a singleton pregnancy (n = 1366). The final study included 22 068 individuals born to 15 271 women, with follow-up through December 31, 2012. The study was approved by the Human Subjects Committees of the Harvard T. H. Chan School of Public Health and Brigham and Women's Hospital. Return of the questionnaire was considered to be written informed consent.

In each follow-up questionnaire, participants reported their height and weight, which are validly reported by preadolescents,[21] adolescents,[22-24] and adults,[25,26] although there is potential misclassification of obesity based on self-reported anthropometry. Body mass index was calculated from these data as weight in kilograms divided by height in meters squared. For individuals younger than 18 years, we defined obesity according to age- and sex-specific cutoffs proposed by the International Obesity Task Force, which provides continuity in BMI cutoffs used to define overweight and obesity in children and in adults.[27] For individuals older than 18 years, we defined obesity (BMI ≥30) using World Health Organization cutoffs.[28,29] Once an individual was classified as obese, he or she was considered obese for the remainder of follow-up.

Mode of delivery (cesarean vs vaginal) was reported by the participants' mothers in 2009 using a questionnaire aimed at collecting lifetime pregnancy information.[30] A validation study conducted among 154 women enrolled in the Nurses' Health Study and the Collaborative Perinatal Project found perfect maternal recall of cesarean delivery at a mean of 32 years after delivery.[31] The same validation study also showed that long-term maternal recall of many events associated with pregnancy, including diagnosis of major complications (hypertensive disorders of pregnancy, gestational diabetes, placental abruption, and placenta previa), offspring birth weight, gestational age at delivery, and pregnancy multiplicity, were highly reproducible and specific.

Information on covariates of interest in GUTS was prospectively collected from the mothers of GUTS participants as part of their participation in the Nurses' Health Study–II[32,33] (maternal prepregnancy BMI, prepregnancy smoking, race/ethnicity, and region of residence at delivery) and in the GUTS baseline and follow-up questionnaires (participant birth date, sex, and duration of breastfeeding). Maternal age at delivery was calculated as the difference (in years) between participants' date of birth and the mothers' date of birth.

Age-standardized prepregnancy and pregnancy characteristics were calculated for all participants and according to mode of delivery. To evaluate the association between cesarean birth and offspring obesity, we calculated relative risks (RRs) and their 95% CIs using log-binomial regression models with generalized estimating equations to adjust for potential confounders while accounting for correlations in outcomes between siblings. We obtained crude and multivariable-adjusted estimates of this association. The multivariable-adjusted models included terms for maternal age at delivery (continuous variable), race (white or other), region (Northeast, Midwest, West, or South), year of birth (≤1984, 1985-1989, or >1989), prepregnancy BMI (<18.5, 18.5-24.99, 25-29.99, or ≥30), maternal height (continuous variable), gestational diabetes (yes or no), preeclampsia (yes or no), pregnancy-induced hypertension (yes or no), gestational age at delivery (<37, 37-39, 40-42, or ≥43 weeks), birth weight (<2.30, 2.30-3.19, 3.20-3.89, 3.90-4.49, or >4.50 kg), prepregnancy smoking (never, past, or current), previous cesarean delivery (yes or no), offspring sex (boy or girl), and birth order (continuous variable). Missing categories were created for variables with missing values. We also fitted marginal structural models where the probability of undergoing a cesarean delivery was predicted for each woman based on these same factors and subsequently used to weight each observation using stabilized weights.[34,35] In addition, we fitted sex-stratified and age-stratified models and assessed the significance of heterogeneity by adding cross-product terms between mode of delivery and age at BMI report or sex to the main multivariable model. We also performed additional analyses treating BMI at each follow-up period as a continuous or binary (obesity: yes or no) outcome to avoid problems associated with change in classification over time while still capturing changes within individuals over time. Although some lifestyle and behavioral factors during childhood are risk factors for obesity, we did not consider them as confounders because none precede both exposure and outcome and therefore cannot, by definition, confound the association between cesarean birth and obesity in offspring. In fact, it has been shown that inclusion of this type of covariate does not improve precision when the outcome is binary and may instead introduce bias.[36,37]

To address the possibility of residual confounding, we conducted a series of alternative analyses. We first restricted the analysis to participants without known risk factors for cesarean delivery (maternal prepregnancy BMI<25, no gestational diabetes, no hypertensive disorders of pregnancy, never smoker, maternal age <30 years, gestational age at delivery between 37 and 42 weeks, and birth weight between 2.30 and 4.49 kg). We also evaluated adjusting for maternal BMI as a continuous variable, allowing for nonlinear associations. We then estimated the effect of change in mode of delivery on obesity in offspring using data from successive pregnancies of the same woman. Specifically, we estimated the effect on obesity in offspring of vaginal birth among women who had undergone a previous cesarean delivery relative to women with repeated cesarean deliveries, as well as the effect of cesarean delivery among women with a previous vaginal delivery relative to repeated vaginal deliveries. Last, to minimize the effect of postnatal environment and time-invariant maternal factors, we performed a within-family analysis comparing the risk of obesity for siblings whose modes of delivery were discordant.[36-39] Specifically, we used conditional logistic regression adjusted for the same covariates and in which each group of siblings was considered a matched set, to estimate the OR and 95% CI comparing participants born via cesarean delivery with their siblings born via vaginal delivery. In addition, we evaluated the potential for residual confounding by weight gain during pregnancy in the subset of participants for whom this information was available (n = 11 067). All analyses were conducted from October 10, 2015, to June 14, 2016, using SAS, version 9.2 (SAS Institute Inc).

Results

Of the 22 068 individuals in the study (20 950 white; 9359 male and 12 709 female), 4921 (22.3%) were born by cesarean delivery. The cumulative risk of obesity through the end of follow-up was 13% among all participants. Age-standardized characteristics of mothers and offspring, overall and by mode of delivery, are presented in **Table 1**. Women who underwent cesarean delivery had a higher prepregnancy BMI and were more likely to have experienced gestational diabetes, preeclampsia, and pregnancy-induced hypertension. They were also more likely to have had a previous cesarean delivery. Cesarean deliveries were also more frequent in preterm and postterm births and for offspring who had either low birth weight or macrosomia. The rate of cesarean delivery was highest between 1985 and 1989 and decreased thereafter.

Cesarean birth was associated with a higher risk of obesity in crude analyses (RR, 1.30; 95% CI, 1.21-1.41; $P < .001$). After adjustment for potential confounders, the association was attenuated but remained statistically significant (**Table 2**). The multivariable adjusted RR for developing obesity in offspring born via cesarean delivery vs those born via vaginal delivery was 1.15 (95% CI, 1.06-1.26; $P = .002$). Most attenuation resulted from adjustment for maternal prepregnancy BMI. Of the 2766 individuals who were classified as obese at some point during follow-up, 1206 were classified in a later follow-up period as nonobese. When these individuals were excluded from the analyses, the corresponding adjusted RR was 1.16 (95% CI, 1.03-1.30). When using repeated measures of BMI over time, the mean difference in the multivariable analyses in BMI during the follow-up period between individuals born via cesarean and vaginal deliveries was 0.29 (95% CI, 0.18-0.40). The association between cesarean birth and offspring obesity was similar across strata of age. The multivariable adjusted RRs for obesity were 1.23 (95% CI, 1.03-1.46) at ages 9 to 12 years, 1.16 (95% CI, 1.03-1.31) at ages 13 to 18 years, and 1.10 (95% CI, 0.98-1.24) at ages 19 to 28 years ($P = .13$ for heterogeneity) (**Figure** and eTable 1 in the Supplement). Associations were also similar for females (RR, 1.12; 95% CI, 0.99-1.27) and males (RR, 1.18; 95% CI, 1.04-1.34) ($P = .62$ for heterogeneity).

The association between cesarean delivery and offspring obesity remained in analyses aimed at addressing the possibility of residual confounding. Similar results were found when confounders were accounted for using propensity score–based methods, when maternal prepregnancy BMI was modeled as a continuous variable, when repeated obesity status at each follow-up period was considered, and when analyses were restricted to individuals whose mothers had no known risk factors for cesarean delivery or to siblings (Table 2 and eTable 2 in the Supple-

Table 1. Age-Standardized Maternal and Offspring Characteristics According to Mode of Delivery

Variable	Overall[a] (N = 15 271)	Mode of Delivery[a]: Vaginal (n = 11 727)	Mode of Delivery[a]: Cesarean (n = 3544)
Maternal Characteristics			
Age at delivery, mean (SD), y[b]	30.2 (3.9)	30.1 (3.9)	30.7 (3.9)
White race/ethnicity	14 462 (94.7)	11 117 (94.8)	3342 (94.3)
Geographic region			
Northeast	5421 (35.5)	4187 (35.7)	1230 (34.7)
Midwest	5375 (35.2)	4140 (35.3)	1233 (34.8)
West	2291 (15.0)	1747 (14.9)	542 (15.3)
South	2153 (14.1)	1618 (13.8)	528 (14.9)
Missing	46 (0.3)	35 (0.3)	14 (0.4)
Gestational diabetes	580 (3.8)	375 (3.2)	198 (5.6)
Preeclampsia	809 (5.3)	481 (4.1)	344 (9.7)
Pregnancy-induced hypertension	809 (5.3)	493 (4.2)	315 (8.9)
Previous cesarean delivery	1206 (7.9)	293 (2.5)	890 (25.1)
Prepregnancy BMI			
<18.50	1939 (12.7)	1583 (13.5)	365 (10.3)
18.50-24.99	11 804 (77.3)	9112 (77.7)	2690 (75.9)
25.00-29.99	1084 (7.1)	762 (6.5)	330 (9.3)
≥30.00	321 (2.1)	176 (1.5)	135 (3.8)
Missing	122 (0.8)	94 (0.8)	25 (0.7)
Prepregnancy smoking			
Never smokers	10 751 (70.4)	8303 (70.8)	2456 (69.3)
Past smokers	2764 (18.1)	2123 (18.1)	641 (18.1)
Current smokers	458 (3.0)	340 (2.9)	120 (3.4)
Missing	1283 (8.4)	962 (8.2)	326 (9.2)
Offspring Characteristics			
Year of birth			
≤1984	6063 (39.7)	4761 (40.6)	1301 (36.7)
1985-1989	6093 (39.9)	4609 (39.3)	1492 (42.1)
≥1990	3115 (20.4)	2357 (20.1)	751 (21.2)
Sex			
Female	8827 (57.8)	6825 (58.2)	2002 (56.5)
Male	6444 (42.2)	4901 (41.8)	1542 (43.5)
Gestational age at delivery, wk			
<37	932 (6.1)	622 (5.3)	308 (8.7)
37-39	3405 (22.3)	2556 (21.8)	836 (23.6)
40-42	9819 (64.3)	7763 (66.2)	2066 (58.3)
≥43	1069 (7.0)	739 (6.3)	333 (9.4)
Missing	61 (0.4)	47 (0.4)	4 (0.1)
Birth weight group, kg			
<2.30	260 (1.7)	129 (1.1)	131 (3.7)
2.30-3.19	3146 (20.6)	2439 (20.8)	698 (19.7)
3.20-3.89	7712 (50.5)	6086 (51.9)	1620 (45.7)
3.90-4.49	3711 (24.3)	2768 (23.6)	957 (27)
≥4.50	351 (2.3)	211 (1.8)	131 (3.7)
Missing	92 (0.6)	82 (0.7)	7 (0.2)
Breastfeeding duration, mo			
Never	1497 (9.8)	1067 (9.1)	425 (12.0)
≤6	5910 (38.7)	4480 (38.2)	1428 (40.3)
>6	6814 (44.8)	5406 (46.1)	1435 (40.5)
Missing	1023 (6.7)	774 (6.6)	252 (7.1)

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

[a] Data are presented as number (percentage) of patients unless otherwise indicated and are standardized to the age distribution of the study population.

[b] Value is not age adjusted.

Table 2. Crude and Multivariable-Adjusted Risk Ratios for Obesity in Offspring Associated With Cesarean vs Vaginal Delivery

Variable	Obese Offspring/Total Offspring, No./No. (%)	Risk Ratio (95% CI) for Obesity in Offspring	*P* Value
Main analyses	2766/22 068 (12.5)		
Vaginal delivery	2012/17 147 (11.7)	1 [Reference]	
Cesarean delivery, crude	754/4921 (15.3)	1.30 (1.21-1.41)	<.001
Cesarean delivery, model 1[a]	754/4921 (15.3)	1.15 (1.06-1.26)	.002
Sensitivity analyses			
Propensity score–based estimate[b]	754/4921 (15.3)	1.17 (1.08-1.27)	<.001
Treating maternal BMI as continuous variable[c]	754/4921 (15.3)	1.13 (1.03-1.23)	<.001
Repeated measures estimate[d]	754/4921 (15.3)	1.23 (1.11-1.37)	<.001
Restricted to no known risk factors for cesarean delivery[e] (n = 8566)	200/1503 (13.3)	1.30 (1.09-1.54)	.004
Restricted to siblings (n = 12 903)	417/2748 (15.2)	1.24 (1.10-1.41)	<.001

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

[a] See the Methods section for the items adjusted for in the multivariable model.

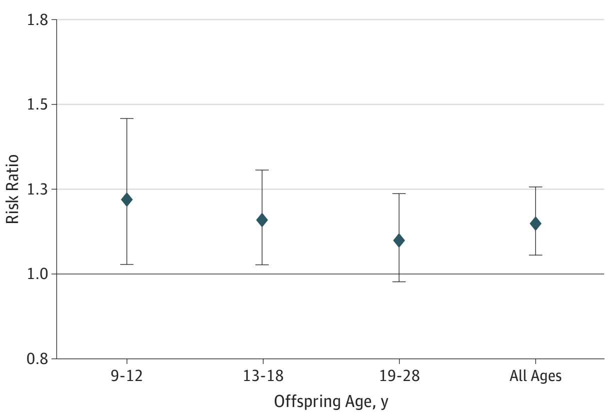
[b] Propensity score–based estimate using a marginal structural model in which the probability of undergoing a cesarean delivery was predicted for each woman based on these same factors and subsequently used to weight each observation using stabilized weights.

[c] This model adjusted for the same covariates in model 1 but modeling prepregnancy BMI as a continuous variable with a linear term and a quadratic term instead of categorical.

[d] Generalized estimating equations estimate using repeated obesity status during each follow-up cycle.

[e] Subgroup of participants without known risk factors for cesarean delivery (maternal prepregnancy BMI <25, no gestational diabetes, no hypertensive disorders of pregnancy, never smoker, maternal age <30 y, gestational age at delivery between 37 and 42 weeks, and birth weight between 2.30 and 4.49 kg).

Figure. Adjusted Risk Ratios for Cesarean Birth and Obesity in Offspring



See the Methods section for the items adjusted for in the multivariable model. Diamond indicates the risk ratio, vertical lines indicate the 95% CIs, and the bold horizontal line indicates the risk ratio reference of 1.0. *P* = .13 for heterogeneity. Data are from the Growing Up Today Study, 1996-2011.

ment). Further adjustment for duration of breastfeeding (RR, 1.15; 95% CI, 1.05-1.26) and gestational weight gain (n = 11 067; RR, 1.10; 95% CI, 0.98-1.24) did not change the conclusions.

We then estimated the effect of change in mode of delivery on obesity in offspring. Among women who had undergone a previous cesarean delivery (n = 2815), the risk of obesity in their offspring was 31% (95% CI, 17%-47%) (RR, 0.69; 95% CI, 0.53-0.83; *P* = .005) lower after a vaginal birth after cesarean delivery compared with a repeat cesarean delivery. Among women who had undergone a previous vaginal delivery (n = 12 815), the estimated increased risk in obesity among offspring (RR, 1.13; 95% CI, 0.98-1.30; *P* = .09) (**Table 3**) was comparable with the equivalent estimate in the entire population (RR, 1.15; 95% CI, 1.06-1.26), although it failed to reach statistical significance.

Last, we used data from successive pregnancies and siblings to perform a within-family analysis of discordant modes of delivery among the 12 903 individuals with 1 or more siblings in GUTS to minimize potential confounding by shared postnatal environment and time-invariant maternal factors. In this analysis, the odds of obesity were 64% (95% CI, 8%-148%) higher among individuals born via cesarean delivery than their siblings born via vaginal delivery. The association was similar for those aged 9 to 18 years and for those aged 19 to 28 years (**Table 4**).

Discussion

In this large cohort of US individuals followed up from childhood, through adolescence, and into young adulthood, cesarean birth was associated with a 15% increase in the risk of obesity in offspring after adjusting for major confounding factors. The association was similar across strata of age and remained consistent in a large number of sensitivity analyses. This association was stronger (30% increased risk) among individuals without known risk factors for cesarean delivery. Analyses of change in mode of delivery across multiple pregnancies revealed that individuals born through vaginal birth after cesarean delivery were 31% less likely to become obese than those born through a repeat cesarean delivery. Moreover, within-family analysis showed that individuals born through cesarean delivery were 64% more likely to be obese than their siblings born through vaginal delivery. The consistency of these findings across multiple strategies to account for potential confounding factors, in particular the analyses restricted to individuals without known risk factors for cesarean delivery and

Table 3. Risk Ratios for Obesity in Offspring Stratified by Mode of Delivery in the Previous Pregnancy

Mode of Delivery	Obese Offspring/Total Offspring, No./No. (%)	Risk Ratio (95% CI)	*P* Value
Previous cesarean birth (n = 2815)			
Repeat cesarean birth	313/2032 (15.4)	1 [Reference]	
Vaginal birth after cesarean birth, model 1[a]	66/783 (8.4)	0.69 (0.53-0.83)	.005
Vaginal birth after cesarean birth, model 2[b]	66/783 (8.4)	0.71 (0.55-0.91)	.008
Vaginal birth after cesarean birth, model 3[c]	66/783 (8.4)	0.73 (0.58-0.91)	.005
Previous vaginal delivery (n = 12 815)			
Successive vaginal delivery	1322/11 537 (11.5)	1 [Reference]	
Cesarean delivery, model 1[a]	184/1278 (14.4)	1.13 (0.98-1.30)	.09
Cesarean delivery, model 2[b]	184/1278 (14.4)	1.12 (0.98-1.28)	.10
Cesarean delivery, model 3[c]	184/1278 (14.4)	1.17 (1.01-1.35)	.04

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

[a] See the Methods section for the items adjusted for in the multivariable model.

[b] Adjusted for the same covariates in model 1 but modeling prepregnancy BMI as a continuous variable with a linear term and a quadratic term instead of categorical.

[c] Propensity score–based estimate using a marginal structural model in which the probability of undergoing a cesarean delivery was predicted for each woman based on these same factors and subsequently used to weight each observation using stabilized weights.

Table 4. Within-Family Odds Ratios for Obesity in Offspring Associated With Cesarean vs Vaginal Delivery

Variable	Obese Offspring/Total Offspring, No./No. (%)	Odds Ratio (95% CI)	*P* Value
Overall			
Vaginal delivery	1091/10 155 (10.7)	1 [Reference]	
Cesarean delivery, model 1[a]	417/2748 (15.2)	1.64 (1.08-2.48)	.02
9-18 y			
Vaginal delivery	719/10 113 (7.1)	1 [Reference]	
Cesarean delivery, model 1[a]	301/2739 (11.0)	1.67 (1.01-2.76)	.04
19-28 y			
Vaginal delivery	677/6714 (10.1)	1 [Reference]	
Cesarean delivery, model 1[a]	233/1772 (13.1)	1.72 (0.89-3.32)	.11

[a] See the Methods section for the items adjusted for in the conditional logistic regression model.

those conducted within families, suggest that this association may not be owing to confounding factors but may instead represent a true biological effect.

Although evidence is still building, the observed higher risk of obesity in offspring associated with cesarean birth may be a consequence of differences in gastrointestinal microbiota established at birth.[40,41] Infants delivered vaginally have greater exposure to their mother's vaginal and gastrointestinal microbiota compared with infants born by cesarean delivery, who are exposed mainly to their mother's skin microbiota and to external environmental bacterial communities at birth.[42-44] This early-life difference in mode of delivery leads to an altered gut microbiota pattern in offspring.[41] Compared with infants born vaginally, those born by cesarean delivery harbor more staphylococci, fewer bifidobacteria, and less diverse bacteria species in microbiota colonization, a pattern that has been linked with increased capacity for energy harvest and risk of overweight and obesity in later life.[41,45,46] Studies documenting differences in microbiota according to mode of delivery have mainly been limited to the first year of life.[41-44] Whether differences in microbiota in offspring are sustained long term remains to be evaluated.

Our findings extend and refine evidence in this area. Despite inconsistent findings from individual studies,[46-53] two recent meta-analyses reported a 22% increased odds of adult obesity[12,13] associated with cesarean delivery. However, many of the studies included in these meta-analyses—particularly in the meta-analyses for adult obesity—failed to account for important potential confounders, most importantly for maternal prepregnancy BMI.[12,13] Several additional studies have reported on the association of cesarean delivery with childhood obesity since the publication of these meta-analyses. A study of 2988 Canadian children found a non-statistically significant higher risk of obesity among children born through cesarean delivery after adjusting for maternal prepregnancy BMI (multivariable OR, 1.20; 95% CI, 0.87-1.65).[15] Similarly, a study of German children found that cesarean birth was associated with a higher risk of obesity in offspring at 2 years (n = 1734; OR, 1.68; 95% CI, 1.10-2.58) but not at 6 (n = 1244; OR, 1.49; 95% CI, 0.55-4.05) or 10 years (n = 1170; OR, 1.16; 95% CI, 0.59-2.29) after adjusting for maternal prepregnancy BMI.[54] Despite the lack of statistical significance of the findings of these 2 studies, which could be explained by their limited sample size, the magnitude of the associations reported is similar to our estimates.

The most important limitation of our study is that we lack data on intrapartum indications for cesarean delivery. However, the most common intrapartum indications of cesarean delivery, namely, fetal intolerance of labor and arrest of labor,[55] are not known risk factors for childhood obesity and are therefore unlikely to be important confounders of the association between cesarean birth and obesity in offspring. Similarly, we do not have detailed data on other potentially important information about labor and delivery, such as whether women underwent labor or whether membranes were ruptured, nor do we have detailed information on antibiotic use during pregnancy or labor and delivery. An additional limitation is the underrepresentation of minorities in our cohort. However, there are no a priori reasons to believe this association would differ across race or ethnicity. In addition, all mothers in our studies were nurses participating in a long-term health study. Although this factor facilitated their long-term follow-up, that of their offspring, and the prospective collection of high-quality detailed data, it may hamper the generalizability of the findings to the larger population. For example, prepregnancy BMI was lower than that of women of reproductive age in the United States around the same time.[56] An additional limitation is that estimates of the prevalence of obesity using self-reported information may be lower than estimates based on direct anthropometry. Nevertheless, it is unlikely that misclassification of obesity status was associated with mode of birth. Hence, the most likely effect of this error is to attenuate the association toward the null. Finally, we lacked information on offspring microbiota or other potential biological mediators to further explore the underlying mechanisms.

Our study also has multiple strengths and was able to address the most salient limitations of previous studies. The prospective study design, large sample size, and long-term follow-up allowed us to examine the association between cesarean birth and risk of obesity in offspring from childhood through early adulthood and to provide precise estimates of the association. The availability of key prepregnancy and pregnancy information allowed for multiple sensitivity analyses aimed at addressing residual confounding. In addition, information on multiple pregnancies from the same woman and extensive family data enabled us to estimate, for the first time in this literature, to our knowledge, the effects of changes in mode of delivery and to minimize the effect of confounding owing to environmental factors and time-invariant maternal characteristics by conducting within-family analyses.

Conclusions

We observed an association between cesarean delivery and increased risk of obesity in offspring that persisted through early adult life. We also report for the first time, to our knowledge, a protective effect of vaginal birth after cesarean delivery on obesity in offspring and a significant difference in risk of obesity between siblings whose modes of birth were discordant. The association between cesarean birth and obesity in offspring was stronger in analyses restricted to individuals without known risk factors for cesarean delivery and in within-family analyses. These findings suggest that this association may be a true adverse outcome of cesarean delivery that clinicians and patients should weigh when considering cesarean birth in the absence of a clear medical or obstetric indication. Since large randomized trials of cesarean vs vaginal birth may not be ethically feasible, additional research from large, prospective studies with high-quality data on prepregnancy, pregnancy, and delivery is needed to address whether these findings are generalizable to minorities and to investigate whether increased rates of obesity translate to increased risk of adverse cardiometabolic outcomes among individuals born by cesarean delivery.

ARTICLE INFORMATION

Accepted for Publication: July 5, 2016.

Published Online: September 6, 2016. doi:10.1001/jamapediatrics.2016.2385.

Author Affiliations: Department of Nutrition, Harvard T. H. Chan School of Public Health, Boston, Massachusetts (Yuan, Gaskins, Gillman, Chavarro); Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, Massachusetts (Yuan, Gaskins, Missmer, Chavarro); The Dartmouth Institute for Health Policy and Clinical Practice, Dartmouth College, Lebanon, New Hampshire (Blaine); Epidemiology Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, Maryland (Zhang); Department of Population Medicine, Harvard Medical School/Harvard Pilgrim Health Care Institute, Boston, Massachusetts (Gillman); Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Missmer, Chavarro); Department of Obstetrics, Gynecology, and Reproductive Biology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Missmer); Division of Adolescent/Young Adult Medicine, Department of Medicine, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts (Missmer); Department of Epidemiology, Brown University School of Public Health, Providence, Rhode Island (Field).

Author Contributions: Drs Yuan and Chavarro had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Blaine, Missmer, Chavarro.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Yuan, Blaine, Missmer, Chavarro.
Critical revision of the manuscript for important intellectual content: Yuan, Gaskins, Zhang, Gillman, Missmer, Field, Chavarro.
Statistical analysis: Yuan, Gaskins, Blaine, Chavarro.
Obtaining funding: Gillman, Chavarro.
Administrative, technical, or material support: Zhang, Field, Chavarro.
Study supervision: Missmer, Chavarro.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by grants UM1-CA176726, P30-DK046200, U54-CA155626, T32-DK007703-16, HD066963, HL096905, DK084001, and MH087786 from the National Institutes of Health. Dr Zhang is supported by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank the thousands of participants in the Growing Up Today Study as well as their mothers.

REFERENCE

1. Pfuntner A, Wier LM, Stocks C. Most frequent procedures performed in US hospitals, 2011. Rockville, MD: Agency for Healthcare Research and Quality. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb165.pdf. Healthcare Cost and Utilization Project statistical brief #165. Published October 2013. Accessed March 1, 2016.

2. Martin JA, Hamilton BE, Osterman MJ, Curtin SC, Matthews TJ. Births: final data for 2013. *Natl Vital Stat Rep*. 2015;64(1):1-65.

3. Gregory KD, Jackson S, Korst L, Fridman M. Cesarean versus vaginal delivery: whose risks? whose benefits? *Am J Perinatol*. 2012;29(1):7-18.

4. Liu S, Liston RM, Joseph KS, Heaman M, Sauve R, Kramer MS; Maternal Health Study Group of the Canadian Perinatal Surveillance System. Maternal mortality and severe morbidity associated with low-risk planned cesarean delivery versus planned vaginal delivery at term. *CMAJ*. 2007;176(4):455-460.

5. Clark SL, Belfort MA, Dildy GA, Herbst MA, Meyers JA, Hankins GD. Maternal death in the 21st century: causes, prevention, and relationship to cesarean delivery. *Am J Obstet Gynecol*. 2008;199(1):36.e1-36.e5.

6. Hansen AK, Wisborg K, Uldbjerg N, Henriksen TB. Risk of respiratory morbidity in term infants delivered by elective caesarean section: cohort study. *BMJ*. 2008;336(7635):85-87.

7. Loebel G, Zelop CM, Egan JF, Wax J. Maternal and neonatal morbidity after elective repeat cesarean delivery versus a trial of labor after previous cesarean delivery in a community teaching hospital. *J Matern Fetal Neonatal Med*. 2004;15(4):243-246.

8. Nielsen NM, Bager P, Stenager E, et al. Cesarean section and offspring's risk of multiple sclerosis: a Danish nationwide cohort study. *Mult Scler*. 2013;19(11):1473-1477.

9. Cho CE, Norman M. Cesarean section and development of the immune system in the offspring. Am J Obstet Gynecol. 2013;208(4):249-254.

10. Blustein J, Liu J. Time to consider the risks of caesarean delivery for long term child health. BMJ. 2015;350:h2410.

11. American College of Obstetricians and Gynecologists; Society for Maternal-Fetal Medicine. Obstetric care consensus no. 1: safe prevention of the primary cesarean delivery. Obstet Gynecol. 2014;123(3):693-711.

12. Darmasseelane K, Hyde MJ, Santhakumaran S, Gale C, Modi N. Mode of delivery and offspring body mass index, overweight and obesity in adult life: a systematic review and meta-analysis. PLoS One. 2014;9(2):e87896.

13. Li HT, Zhou YB, Liu JM. The impact of cesarean section on offspring overweight and obesity: a systematic review and meta-analysis. Int J Obes (Lond). 2013;37(7):893-899.

14. Li HT, Zhou YB, Liu JM. Cesarean section might moderately increase offspring obesity risk. Am J Clin Nutr. 2012;96(1):215-216.

15. Flemming K, Woolcott CG, Allen AC, Veugelers PJ, Kuhle S. The association between caesarean section and childhood obesity revisited: a cohort study. Arch Dis Child. 2013;98(7):526-532.

16. Li H-T, Zhou Y-B, Liu J-M. The impact of cesarean section on offspring overweight and obesity: a systematic review and meta-analysis. Obstet Gynecol Surv. 2014;69(1):9-11. doi:10.1097/01.ogx.0000442815.27237.2a.

17. Gillman MW, Rifas-Shiman S, Berkey CS, Field AE, Colditz GA. Maternal gestational diabetes, birth weight, and adolescent obesity. Pediatrics. 2003;111(3):e221-e226.

18. Field AE, Sonneville KR, Falbe J, et al. Association of sports drinks with weight gain among adolescents and young adults. Obesity (Silver Spring). 2014;22(10):2238-2243.

19. Mayer-Davis EJ, Rifas-Shiman SL, Zhou L, Hu FB, Colditz GA, Gillman MW. Breast-feeding and risk for childhood obesity: does maternal diabetes or obesity status matter? Diabetes Care. 2006;29(10):2231-2237.

20. Oken E, Rifas-Shiman SL, Field AE, Frazier AL, Gillman MW. Maternal gestational weight gain and offspring weight in adolescence. Obstet Gynecol. 2008;112(5):999-1006.

21. Tokmakidis SP, Christodoulos AD, Mantzouranis NI. Validity of self-reported anthropometric values used to assess body mass index and estimate obesity in Greek school children. J Adolesc Health. 2007;40(4):305-310.

22. Elgar FJ, Roberts C, Tudor-Smith C, Moore L. Validity of self-reported height and weight and predictors of bias in adolescents. J Adolesc Health. 2005;37(5):371-375.

23. Strauss RS. Comparison of measured and self-reported weight and height in a cross-sectional sample of young adolescents. Int J Obes Relat Metab Disord. 1999;23(8):904-908.

24. Goodman E, Hinden BR, Khandelwal S. Accuracy of teen and parental reports of obesity and body mass index. Pediatrics. 2000;106(1, pt 1):52-58.

25. Troy LM, Hunter DJ, Manson JE, Colditz GA, Stampfer MJ, Willett WC. The validity of recalled weight among younger women. Int J Obes Relat Metab Disord. 1995;19(8):570-572.

26. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med. 2011;364(25):2392-2404.

27. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ. 2000;320(7244):1240-1243.

28. Physical status: the use and interpretation of anthropometry: report of a WHO expert committee. World Health Organ Tech Rep Ser. 1995;854:1-452.

29. Obesity: preventing and managing the global epidemic: report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894:i-xii, 1-253.

30. Michels KB, Willett WC, Graubard BI, et al. A longitudinal study of infant feeding and obesity throughout life course. Int J Obes (Lond). 2007;31(7):1078-1085.

31. Tomeo CA, Rich-Edwards JW, Michels KB, et al. Reproducibility and validity of maternal recall of pregnancy-related events. Epidemiology. 1999;10(6):774-777.

32. Colditz GA, Hankinson SE. The Nurses' Health Study: lifestyle and health among women. Nat Rev Cancer. 2005;5(5):388-396.

33. Cho E, Chen WY, Hunter DJ, et al. Red meat intake and risk of breast cancer among premenopausal women. Arch Intern Med. 2006;166(20):2253-2259.

34. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol. 2008;168(6):656-664.

35. Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. Value Health. 2010;13(2):273-277.

36. Bråbäck L, Ekéus C, Lowe AJ, Hjern A. Confounding with familial determinants affects the association between mode of delivery and childhood asthma medication—a national cohort study. Allergy Asthma Clin Immunol. 2013;9(1):14.

37. Frisell T, Öberg S, Kuja-Halkola R, Sjölander A. Sibling comparison designs: bias from non-shared confounders and measurement error. Epidemiology. 2012;23(5):713-720.

38. Almqvist C, Cnattingius S, Lichtenstein P, Lundholm C. The impact of birth mode of delivery on childhood asthma and allergic diseases—a sibling study. Clin Exp Allergy. 2012;42(9):1369-1376.

39. Khashan AS, Kenny LC, Lundholm C, Kearney PM, Gong T, Almqvist C. Mode of obstetrical delivery and type 1 diabetes: a sibling design study. Pediatrics. 2014;134(3):e806-e813.

40. Neu J, Rushing J. Cesarean versus vaginal delivery: long-term infant outcomes and the hygiene hypothesis. Clin Perinatol. 2011;38(2):321-331.

41. Musso G, Gambino R, Cassader M. Obesity, diabetes, and gut microbiota: the hygiene hypothesis expanded? Diabetes Care. 2010;33(10):2277-2284.

42. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci U S A. 2010;107(26):11971-11975.

43. Huurre A, Kalliomäki M, Rautava S, Rinne M, Salminen S, Isolauri E. Mode of delivery—effects on gut microbiota and humoral immunity. Neonatology. 2008;93(4):236-240.

44. Biasucci G, Benenati B, Morelli L, Bessi E, Boehm G. Cesarean delivery may affect the early biodiversity of intestinal bacteria. J Nutr. 2008;138(9):1796S-1800S.

45. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006;444(7122):1027-1031.

46. Ajslev TA, Andersen CS, Gamborg M, Sørensen TI, Jess T. Childhood overweight after establishment of the gut microbiota: the role of delivery mode, pre-pregnancy weight and early administration of antibiotics. Int J Obes (Lond). 2011;35(4):522-529.

47. Barros FC, Matijasevich A, Hallal PC, et al. Cesarean section and risk of obesity in childhood, adolescence, and early adulthood: evidence from 3 Brazilian birth cohorts. Am J Clin Nutr. 2012;95(2):465-470.

48. Goldani MZ, Barbieri MA, da Silva AA, Gutierrez MR, Bettiol H, Goldani HA. Cesarean section and increased body mass index in school children: two cohort studies from distinct socioeconomic background areas in Brazil. Nutr J. 2013;12(1):104.

49. Huh SY, Rifas-Shiman SL, Zera CA, et al. Delivery by caesarean section and risk of obesity in preschool age children: a prospective cohort study. Arch Dis Child. 2012;97(7):610-616.

50. Li H; Coordinating Group of Nine Cities Study on the Physical Growth and Development of Children, Capital Institute of Pediatrics. A national epidemiological survey on obesity of children under 7 years of age in nine cities of China, 2006 [in Chinese]. Zhonghua Er Ke Za Zhi. 2008;46(3):174-178.

51. Rooney BL, Mathiason MA, Schauberger CW. Predictors of obesity in childhood, adolescence, and adulthood in a birth cohort. Matern Child Health J. 2011;15(8):1166-1175.

52. Steur M, Smit HA, Schipper CM, et al. Predicting the risk of newborn children to become overweight later in childhood: the PIAMA birth cohort study. Int J Pediatr Obes. 2011;6(2-2):e170-e178.

53. Zhou L, He G, Zhang J, Xie R, Walker M, Wen SW. Risk factors of obesity in preschool children in an urban area in China. Eur J Pediatr. 2011;170(11):1401-1406.

54. Pei Z, Heinrich J, Fuertes E, et al; Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus Air Pollution and Genetics (LISAplus) Study Group. Cesarean delivery and risk of childhood obesity. J Pediatr. 2014;164(5):1068-1073.e2.

55. Barber EL, Lundsberg LS, Belanger K, Pettker CM, Funai EF, Illuzzi JL. Indications contributing to the increasing cesarean delivery rate. Obstet Gynecol. 2011;118(1):29-38.

56. Kuczmarski RJ, Flegal KM, Campbell SM, Johnson CL. Increasing prevalence of overweight among US adults: the National Health and Nutrition Examination Surveys, 1960 to 1991. JAMA. 1994;272(3):205-211.