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Does Cesarean delivery impact infant weight gain and adiposity over the first year of life?

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Abstract

Background: Potentially driven by the lack of mother-to-infant transmission of microbiota at birth, Cesarean delivery has been associated with higher offspring obesity. Yet, no studies have examined when delivery-mode differences in adiposity begin to emerge. In this study, we examine differences in infant weight and adiposity trajectories from birth to 12 months by delivery mode.

Methods: From 2013 to 2015, we recruited pregnant women into the Nurture Study and followed up their 666 infants. We ascertained maternal delivery method and infant birth weight from medical records. We measured weight, length, and skinfolds (subscapular, triceps, abdominal) when infants were 3, 6, 9 and 12 months of age. The main outcome, infant weight-for-length z score, was derived based on the WHO Child Growth Standards. We used linear regression to assess the difference at each time point and used linear mixed models to examine the growth rate for infant weight and adiposity trajectories. We controlled for maternal age, race, marital status, education level, household income, smoking status, maternal pre-pregnancy body mass index, and infant birth weight.

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Supplementary Material
Supplementary information is available at International Journal of Obesity's website

Results: Of the 563 infants in our final sample, 179 (31.8%) were Cesarean delivered. From birth to 12 months, the rate of increase in weight-for-length *z* score was 0.02 units/month (p=0.03) greater for Cesarean-delivered than vaginally-delivered infants. As a result of more rapid growth, Cesarean-delivered infants had higher weight-for-length *z* score (0.26 units, 95% CI 0.05–0.47) and sum of subscapular and triceps (SS+TR) skinfolds (0.95mm, 95% CI 0.30–1.60)—an adiposity indicator—at 12 months, compared to vaginally-delivered infants.

Conclusion: Compared to vaginal delivery, Cesarean delivery was associated with greater offspring rate of weight gain over the first year and differences in adiposity that appear as early as 3 months of age. Monitoring Cesarean-delivered infants closely for excess weight gain may help guide primordial prevention of obesity later in life.

Background

Childhood obesity has increased dramatically since 1988 and now affects 18.5% of children in the United States (US), including 13.7% aged 2 to 5 years[1]. Not only is childhood obesity associated with substantial lifelong morbidity, increased health care costs, and premature death, it is also notoriously difficult to prevent and treat. As such, there is need for early-life interventions to prevent excess weight gain before it leads to overweight and obesity.

The human microbiome is a compelling target for early-life intervention because, unlike the human genome, it is largely determined by the environment at the beginning of life and is also modifiable. Different ensembles of microbial communities, or microbiota, in the human intestine have been shown to cause weight gain of mice[2,3], possibly through modulation of gut mucosal biological and immunologic factors[4]. Cesarean delivery—one of the most common surgical procedures carried out in the US[5]— can be a life-saving intervention. However, it also deprives newborns of normal microbial colonization at birth.[6–9] Similar to childhood obesity, Cesarean delivery rates have markedly increased over the last three decades[10]. While guidelines[11] note that evidence of the long-term-consequences of Cesarean delivery on the offspring are lacking, a growing number of human studies[12–17] have linked Cesarean delivery to risk of obesity.

In light of this evidence, there is a need to understand if and when Cesarean delivery affects the growth rate and adiposity of offspring. To date, no studies have measured the growth trajectory of Cesarean versus vaginally delivered infants over the first year of life. Furthermore, no studies have examined the association between delivery mode and other measures of adiposity in infants. In the present analysis of a birth cohort of women and their offspring, our aim was to examine the association of Cesarean delivery with weight-for-length *z* score and sum of subscapular and triceps (SS+TR) skinfolds as proxies for adiposity at 4 time points through the first year of life.

Subjects and methods

Study population

Nurture is an ongoing prospective birth cohort study examining risk factors associated with infant adiposity and weight trajectories in the first year of life. Detailed cohort descriptions have been published previously.[18] From 2013 to early 2015, we recruited pregnant women between 20 and 36 weeks of gestation. We recruited women from a local private prenatal clinic and the county health department prenatal clinic in Durham, North Carolina in the US. To meet the study inclusion criteria, the infant had to be a singleton born after 28 weeks' gestation with no congenital abnormalities. Written informed consent was obtained from each woman at recruitment into the study during pregnancy and then again for participation of both mother and infant shortly after delivery.

Of the 666 mother-infant pairs who provided consent for themselves and their infants after delivery, 100 infants did not have measurement in weight-for-length *z* score or skinfolds on any visit, and 3 infants had missing data on delivery method, leaving an analytic sample of 563 mother-infant pairs. The study was approved by Duke University Medical Center IRB (human subjects committee) (Pro 00036242).

Exposure

We ascertained maternal delivery method (Cesarean; operative vaginal delivery; spontaneous vaginal delivery) from medical records. We combined operative (n=17) and spontaneous (n=367) vaginal delivery to allow for more robust statistical inference.

Outcomes

We measured weight, height and skinfold thickness at 3 (visit 1), 6 (visit 2), 9 (visit 3) and 12 (visit 4) months after birth. Infant weight was measured in light clothing without shoes by trained data collectors using a ShorrBoard Portable Length Board to nearest 1/8 inch; infant height was measured using a Seca Infant Scale to the nearest 0.1 pound; we measured infant abdomen, subscapular and triceps skinfold thicknesses to the nearest 0.2 mm using standard techniques.[19] To reduce measurement error, we conducted all measurements 3 times and used the average value. We calculated the age and sex specific weight-for-length *z* score based on the World Health Organization Child Growth Standards.[20]

The primary outcome was change in weight-for-length *z* score from birth to 12 months. Secondary outcomes included child weight-for-length *z* score, subscapular skinfolds, triceps skinfolds, abdominal skinfolds by delivery method at each visit. We also summed the subscapular and triceps skinfolds thickness as a proxy for overall fatness.

Other covariates

We collected maternal characteristics including age at delivery (continuous), race (Black or African American; White; other), marital status (married; other), highest educational achievement (high school or below; some college or above), household income (<$20,000; $20,000 to 40,000; $40,001 to 70,000; >$70,000), parity (continuous), smoking status (yes; no), any breastfeeding (ever; never), type of breastfeeding (exclusive breastfeeding; no breastfeeding [formula only], mixed feeding); length of any breastfeeding during the first year after delivery (no breastfeeding; breastfeeding <6 months; breastfeeding ≥ 6 months), and antibiotic intake during pregnancy (ever; never) from interviews and questionnaires at recruitment and during home visits.

We weighed mothers at each visit to the nearest 0.1 kg using a Tanita BWB-800 Scale and had their height measured to the nearest 0.1 cm using a Seca stadiometer. We calculated pre-pregnancy body mass index (BMI) as weight divided by height squared (kg/m^2). Women were further categorized as underweight (BMI < 18.5 kg/m^2), normal weight (BMI ≥ 18.5 & < 25 kg/m^2), overweight (BMI ≥ 25 kg/m^2 & < 30 kg/m^2) and obese (BMI ≥ 30 kg/m^2). We recorded infant characteristics including birth weight (continuous), infant gender (boys; girls), gestational age in weeks at birth (continuous) from electronic medical records. We calculated infant birth weight for gestational age *z* score based on the Intergrowth-21st standards.[21]

Data analysis

We used linear regression models to estimate the crude and the adjusted difference in weight-for-length *z* scores, skinfold thicknesses (abdomen, subscapular, triceps), and SS+TR at each visit by delivery method. We also used linear mixed-effect models with random intercepts to examine the growth rate for these adiposity trajectories from 3 to 12 months.

We defined confounders as covariates related to both the exposure (delivery method) and the outcomes (weight and adiposity trajectories) but not in the causal pathway based on the literature. Preselected potential confounders we considered included maternal age at delivery, race, marital status, highest educational achievement, household income, smoking status, pre-pregnancy BMI, and infant birth weight. We also conducted a sensitivity analysis with our confounder model additional adjusted for each of the infant feeding exposure variables. Missing values for categorical variables were treated as a separate category, and we excluded observations with missing continuous variables in the models.

We examined whether the association of delivery method and infant weight-for-length *z* score growth rate differed by potential effect measure modifiers (EMM) including any breastfeeding, maternal antibiotic use during pregnancy, infant gender and maternal pre-pregnancy BMI (we excluded the underweight group due to its small size, n=13). We tested for additive interactions by using the likelihood ratio test comparing models with two-way interactions (delivery method and age) and with three-way interactions (plus the potential EMM). The designated significance level was two-sided p-value<0.05. We performed all analyses using Stata 15.1 (Stata Corp, College Station, TX). Code is available upon request.

Results

Of the 563 women in the final analytical dataset, 394 (70.0%) had a self-reported race as Black or African American, 263 (46.7%) had a high school diploma or less, 327 (58.1%) had household incomes <20,000 USD/year and 167 (29.7%) were married.

Maternal and infant characteristics by delivery method are provided in Table 1. Of the 563 mothers in the final analytical dataset, 179 (31.8%) had Cesarean delivery, which was similar to the Cesarean rate (31.9%) in the US in 2016[22]. Mothers who experienced Cesarean delivery had higher pre-pregnancy BMI and older age at delivery compared with those who had vaginal delivery. Cesarean delivered infants had lower gestational age and higher birth weight for gestational age *z* scores. We also compared the baseline characteristics for 566 mother-infant pairs remained in the study with the 100 lost to follow-up (Table 2). Mothers who were lost to follow-up were younger and more likely to be unmarried, but otherwise mother-infant pairs were similar in characteristics at baseline.

The average number of follow-up visits was 3.3, and 367 (65.2%) completed all 4 visits. Table 2 shows the mean difference in growth parameters between Cesarean and vaginally delivered infants at each time point. At the 3-month visit, the multivariable-adjusted mean difference in weight-for-length *z* score, sub-scapular skinfolds, triceps skinfolds, abdominal skinfolds, SS+TR were 0.11 (95% CI: −0.11, 0.32), 0.23 (95% CI: −0.10, 0.57), 0.45 (95% CI: 0.09, 0.82), −0.002 (95% CI: −0.47, 0.46) and 0.68 (95% CI: 0.06, 1.31) respectively. Since that time point, the difference increased monotonically for weight-for-length *z* score and sub-scapular skinfolds; difference for other skinfolds measures increased until 6 (triceps; SS+TR) or 9 months (abdominal) and then leveled off or decreased slightly since then.

At the 12-month visit, the Cesarean delivered infants and vaginally delivered infants differed significantly in weight-for-length *z* score (0.26, 95% CI: 0.05, 0.47), scapular skinfolds (0.42, 95% CI: 0.12, 0.73), triceps skinfolds (0.52, 95% CI: 0.09, 0.95) and SS+TR (0.95, 95% CI: 0.30, 1.60) after adjustment.

The per-month change rate in infant weight-for-length *z* score from 3 to 12 months was 0.05 units (95% CI: 0.04, 0.06) for vaginally delivered infants and 0.07 units (95% CI: 0.05, 0.08) for Cesarean delivered infants (Figure 1). The weight-for-length *z* score change rate was 0.02 units/month (p=0.03) more for Cesarean delivered infants, which roughly represented a difference of 0.015 kg/month for an average-weight infant of 30 inches, resulting in a difference of 0.2 kg at 12 months. This suggests that infants who were Cesarean delivered had nearly 28.5% percent higher growth rate compared to those who were vaginally delivered. Findings did not change and remained significant (all p values < 0.05) when we further adjusted for infant feeding exposures, including ever vs. never breastfed, type of breastfeeding (exclusive breastfeeding; no breastfeeding [formula only], mixed feeding), or length of any breastfeeding during the first year of life (results not shown). There was no significant difference in change rate for scapular skinfolds (p=0.45), triceps skinfolds (p=0.77), abdominal skinfolds (p=0.60) or SS+TR (p=0.54).

In the analysis for potential EMMs (Figure 2), we found that boys had a larger difference in weight-for-length *z* score growth rate between Cesarean delivery and vaginally delivery, compared with girls (boys: 0.03/month, 95% CI: 0.01, 0.06; girls: 0.002/month, 95% CI: −0.02, 0.03; p-value for interaction: 0.02). We also found that infants born to normal weight (vs. overweight or obese) mothers had a larger difference in weight-for-length *z* score growth rate between Cesarean delivery and vaginally delivery (p-value for interaction: 0.045). We did not find evidence of differences in growth rate across different categories of any breastfeeding (p-value for interaction=0.67), or antibiotic use during pregnancy (p-value for interaction=0.37).

Discussion

In this prospective birth cohort of a relatively low-income population predominantly Black women and infants in the Southeastern US, we found that Cesarean delivery (versus vaginal delivery) was associated with accelerated weight gain over the first year of life. Furthermore, differences in skinfolds, a proxy for adiposity, began to emerge as early as 3 months of age. These associations persisted after controlling for multiple potential confounders.

Our findings are consistent with a growing body of literature linking Cesarean delivery to obesity in children and adults.[12–17] To our knowledge, our study is the first to show that in humans these differences may be due to accelerated weight and adiposity gains in the first year of life and can be detected as early as 3 months of age. A recently published experiment in mice also found that Cesarean section led to increased weight gain.[23] While the average difference between Cesarean and vaginally delivered infants in our study—approximately 200 grams at 12 months—may not seem large on an individual level, given the ubiquity of Cesarean delivery[10], even a small effect size could translate to a substantial impact on health of the population[24]. Furthermore, as shown in our figure, the differences in weight-for-length z score appear to be getting larger over time, and previous research has also shown that differences in infant weight-for-length as early as 6 months are associated with BMI z-score and overweight risk later in childhood.[25]

The accelerated growth in Cesarean delivered infants may be due to immunologic or metabolic factors that are programmed early in life by the pioneering gut microbiota. Previously we found differences in gut microbiota composition and predicted metabolic function in transitional stools of infants at 3 days of life.[9] Others have noted differences in the diversity and composition of microbiota that may persist for up to 1 or 2 years.[7,8] Cox et al. demonstrated, in mice, that regardless of whether differences in gut microbiota composition persists, early-life impacts on the developing gut microbiome can have long-consequences on excess weight gain.[26]

Delivery mode may also contribute to infant growth through its impact on stress hormones and cytokine levels. Vaginal delivery can induce a greater stress hormone response than Cesarean delivery and has been positively associated with serum levels of monocytes[27] and granulocytes[28–30]. During labour, the activation of cytokines has also been found in systemic maternal circulation.[31–33] Future longitudinal studies—with serial measurement of maternal and infant stool and blood biospecimens—are needed to determine the extent to which perturbations to the infant microbiome *versus* other factors associated with delivery (e.g. hormonal stress response) contribute to the observed differences in infant growth rate and obesity risk.

In addition to our main findings, we observed some evidence that the association of Cesarean delivery with accelerated weight gain in the first year of life was less dramatic for infants born to obese mothers and for female infants. The former observation aligns with our previous work showing birth-mode specific associations between maternal weight status and the infant microbiome.[34] However, in another study we found that the association of Cesarean delivery with odds for childhood overweight or obesity did not depend on delivery mode.[35] Our findings of effect modification by gender—suggesting the possibility of sexual dimorphism in the effect of Cesarean delivery on infant weight—is also consistent with research finding that boys are disproportionately affected by microbial programming of obesity.[36] Larger prospective studies are warranted to test the hypothesis that the effects of Cesarean delivery on the infant microbiome and weight gain may be gender-specific and potentially modified by differences in maternal weight status.

There are several limitations of our study. First, this is an observational study and although we addressed confounding by adjusting for socio-demographic factors, pre-pregnancy BMI, infant birth weight and infant feeding variables, we cannot exclude the possibility that residual confounding or confounding by indication influenced our findings. Our results persisted after adjustment for confounders and were consistent in breastfed and non-breastfed infants. However, medical management of Cesarean-delivered infants can differ, and the indication for Cesarean delivery, e.g. fetal distress, itself may cause accelerated weight gain. Second, although we observed differences in the point estimates by maternal pre-pregnancy BMI and sex, suggesting effect modification by these factors, we cannot rule out that these findings were due to the small sample size of these subgroup analyses. Birth cohorts with larger sample sizes are needed to corroborate these interesting findings. Third, attrition bias may exist, although we compared the characteristics of mother-infant pairs that remained in the study to those with those lost to follow up and found they were similar.

In conclusion, compared to vaginal delivery, Cesarean delivery was associated with greater offspring rate of weight gain in the first year along with differences in adiposity, which emerge as early as 3 months of age. Screening Cesarean delivered infants for excess weight gain may help guide primordial prevention of obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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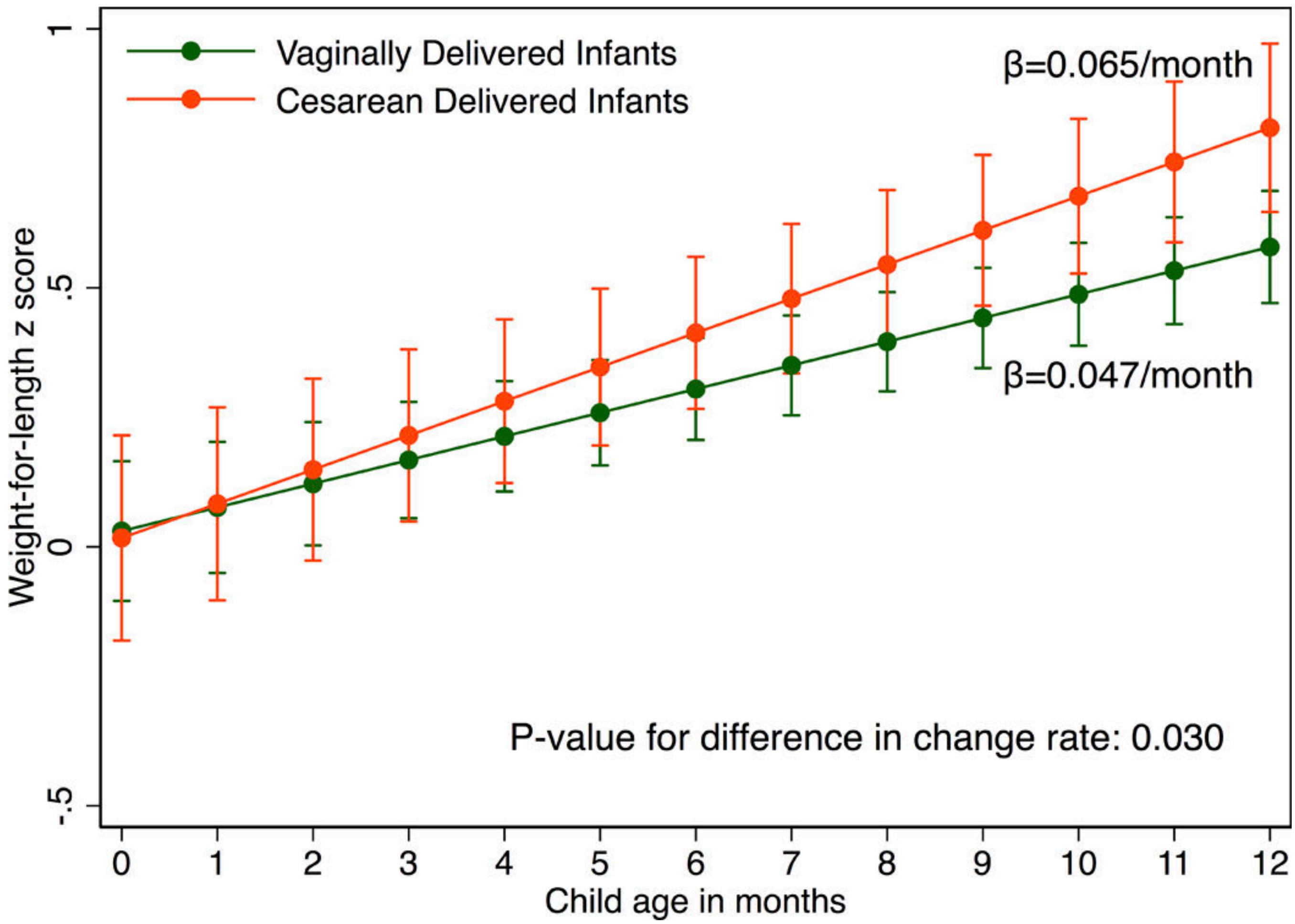

Figure 1.

Multivariable-adjusted predicted change in infant weight-for-length z score from birth to 12 months. Adjusted for maternal age at delivery, race/ethnicity, household income, educational level, marital status, smoking status, child birth weight, maternal pre-pregnancy body mass index.

Group	#n	Difference in Growth Rate Between Cesarean Delivered and Vaginally Delivered Infants	P-value for interaction
Overall	563	0.02 (0.00, 0.04)	
Any breastfeeding			0.67
Never	88	0.01 (-0.03, 0.05)	
Ever	475	0.02 (0.00, 0.04)	
Maternal pre-pregnancy BMI			0.05
Normal weight	186	0.06 (0.02, 0.09)	
Overweight or obesity	339	0.00 (-0.02, 0.02)	
Maternal antibiotic use during pregnancy			0.37
Yes	240	0.02 (0.00, 0.04)	
No	323	0.01 (-0.01, 0.04)	
Infant gender			0.02
Boys	280	0.03 (0.01, 0.06)	
Girls	283	0.00 (-0.02, 0.03)	

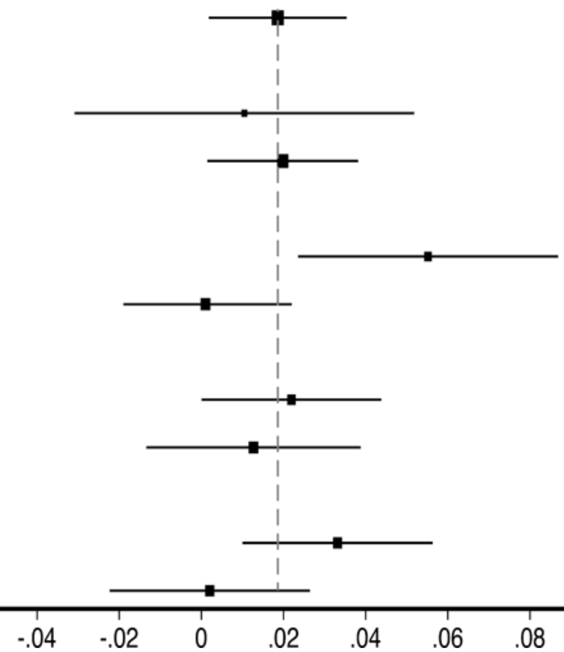

Figure 2.

Multivariable-adjusted difference in weight-for-length z score growth rate between Cesarean delivered and vaginally delivered infants by potential effect measure modifiers. Adjusted for maternal age at delivery, race/ethnicity, household income, educational level, marital status, smoking status, child birth weight, maternal pre-pregnancy body mass index.

Table 1.

Maternal and infant characteristics by delivery method (n=563)

	Delivery method		
	Cesarean Delivery (n=179)	**Vaginal Delivery (n=384)**	**p-value**
Maternal/ Household Characteristics			
Pre-pregnancy BMI, kg/m^2, mean (SD)	33.97 (10.77)	28.25 (7.81)	<0.001
Age, years, mean (SD)	28.38 (5.35)	27.09 (5.95)	0.01
Nulliparous, %			0.32
Yes	59 (33.7%)	142 (38.1%)	
No	116 (66.3%)	231 (61.9%)	
Race/Ethnicity, %			0.34
Black or African American	122 (68.2%)	272 (71.0%)	
White	35 (19.6%)	79 (20.6%)	
Other	22 (12.3%)	32 (8.4%)	
Married, %			0.67
Yes	50 (27.9%)	100 (26.2%)	
No	129 (72.1%)	281 (73.8%)	
Low educational achievement*, %			0.63
Yes	81 (45.3%)	182 (47.4%)	
No	98 (54.7%)	202 (52.6%)	
Household income per year in USD at baseline, %			0.32
<$20,000	95 (55.9%)	213 (61.6%)	
$20,001 to 40,000	40 (23.5%)	66 (19.1%)	
$40,001 to 70,000	23 (13.5%)	35 (10.1%)	
>$70,000	12 (7.1%)	32 (9.2%)	
Smoking status at baseline, %			0.53
No	130 (83.3%)	295 (85.5%)	
Yes	26 (16.7%)	50 (14.5%)	
Antibiotic intake during pregnancy, %			0.84
No	125 (69.8%)	265 (69.0%)	
Yes	54 (30.2%)	119 (31.0%)	
Any breastfeeding			0.21
Never	33 (18.4%)	55 (14.3%)	
Ever	146 (81.6%)	329 (85.7%)	
Infant Characteristics			
Gender, %			0.21
Male	96 (53.6%)	184 (47.9%)	
Female	83 (46.4%)	200 (52.1%)	
Gestational age, week, mean (SD)	38.35 (1.71)	38.70 (1.51)	0.02
Birth weight, kg, mean (SD)	3.24 (0.57)	3.19 (0.50)	0.31
Infant birth weight for gestational age z-score, mean (SD)	0.25 (1.08)	0.00 (0.99)	0.01

* Low educational achievement defined as having the highest education as middle school or below.

Table 2

Adjusted mean difference in growth parameters between Cesarean and vaginally delivered infants.

Growth parameter	At 3-month visit	At 6-month visit	At 9-month visit	At 12-month visit	p-value for difference at 12-month visit
Weight-for-length *z* score	0.11 (−0.11, 0.32)	0.11 (−0.12, 0.33)	0.19 (−0.03, 0.41)	0.26 (0.05, 0.47)	0.016
Subscapular skinfolds	0.23 (−0.10, 0.57)	0.31 (−0.05, 0.67)	0.32 (−0.02, 0.67)	0.42 (0.12, 0.73)	0.006
Triceps skinfolds	0.45 (0.09, 0.82)	0.79 (0.33, 1.25)	0.75 (0.29, 1.22)	0.52 (0.09, 0.95)	0.018
Abdominal skinfolds	0.00 (−0.47, 0.46)	0.31 (−0.21, 0.82)	0.36 (−0.12, 0.83)	0.27 (−0.17, 0.71)	0.233
Subscapular + Triceps skinfolds	0.68 (0.06, 1.31)	1.10 (0.38, 1.82)	1.09 (0.36, 1.82)	0.95 (0.30, 1.60)	0.004

[*] Adjusted for maternal age at delivery, race/ethnicity, household income, educational level, marital status, smoking status, child birth weight, maternal pre-pregnancy body mass index.

[**] P-value for difference in change rate comparing Cesarean and vaginally delivered infants from 3–12 months of age: weight-for-length z score, p=0.03; sub-scapular skinfolds, p=0.45; triceps skinfolds, p=0.77; abdominal skinfolds, p=0.60; subscapular + triceps skinfolds, p=0.54