Delivery by caesarean section and risk of obesity in preschool age children: a prospective cohort study

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ABSTRACT

Objective To examine whether delivery by caesarean section is a risk factor for childhood obesity.

Design Prospective prebirth cohort study (Project Viva).

Setting Eight outpatient multi-specialty practices based in the Boston, Massachusetts area.

Participants We recruited women during early pregnancy between 1999 and 2002, and followed their children after birth. We included 1255 children with body composition measured at 3 years of age.

Main outcome measures BMI score, obesity (BMI for age and sex ≥95th percentile), and sum of triceps plus subscapular skinfold thicknesses at 3 years of age.

Results 284 children (22.6%) were delivered by caesarean section. At age 3, 15.7% of children delivered by caesarean section were obese compared with 7.5% of children born vaginally. In multivariable logistic and linear regression models adjusting for maternal prepregnancy BMI, birth weight, and other covariates, birth by caesarean section was associated with a higher odds of obesity at age 3 (OR 2.10, 95% CI 1.36 to 3.23), higher mean BMI z-score (0.20 units, 95% CI 0.07 to 0.33), and higher sum of triceps plus subscapular skinfold thicknesses (0.94 mm, 95% CI 0.36 to 1.51).

Conclusions Infants delivered by caesarean section may be at increased risk of childhood obesity. Further studies are needed to confirm our findings and to explore mechanisms underlying this association.

What is already known on this topic

- Delivery by caesarean section has been identified as a risk factor for childhood asthma, but data on childhood obesity are limited.
- An association of caesarean section with childhood obesity would provide an important additional rationale to avoid non-medically indicated caesarean section

What this study adds

- Infants delivered by caesarean section had twofold higher odds of childhood obesity, even after adjusting for maternal body mass index, birth weight and other confounding variables.
- Expectant mothers choosing caesarean delivery in the absence of a medical indication should be aware that their children may have a higher risk of obesity

INTRODUCTION

Identifying modifiable risk factors during the perinatal period may offer promising strategies to prevent obesity and its complications throughout the life course.[1] Delivery by caesarean section has been identified as a risk factor for childhood asthma and allergic rhinitis,[2 3] but only one previous study has examined the relationship between mode of delivery and childhood obesity.[4] One potential rationale for examining the relationship between mode of delivery and childhood obesity is that, compared with vaginally born infants, infants delivered by caesarean section exhibit differences in the composition and timing of acquisition of intestinal flora.[5 6] These alterations in intestinal microbial composition in the first year of life may last throughout childhood, and may contribute to the development of obesity[7–9] and other health outcomes. Mode of delivery also has the potential to influence long-term obesity risk through effects on inflammation, immune or endocrine function that are independent of the intestinal microbiota composition.

To our knowledge, no prospective studies have specifically examined whether caesarean delivery is associated with the risk of childhood obesity. An association between caesarean birth and increased risk of childhood obesity would provide an important rationale to avoid non-medically indicated caesarean section. In the USA, the proportion of births by caesarean section increased from 20.7% in 1996 to 32% in 2007,[10] probably in part because of increased rates of caesarean birth on maternal request.[11] The study goal was to examine whether delivery by caesarean section was associated with a higher risk of childhood obesity at age 3 in a longitudinal prebirth cohort.

METHODS

Participants

From April 1999 to July 2002, we enrolled participants into Project Viva, a longitudinal prebirth

cohort of mother–offspring pairs in eastern Massachusetts, USA. Human Subjects Committees of Harvard Pilgrim Health Care, Brigham and Women's Hospital (BWH), and Beth Israel Deaconess Medical Center (BIDMC) approved study protocols,[12] and all mothers provided written informed consent.

We have previously described in detail the study population, enrolment and follow-up procedures.[12] We recruited women attending their initial prenatal visit before 22 weeks' gestational age at Harvard Vanguard Medical Associates, a multi-specialty group practice. Eligibility criteria included fluency in English and singleton pregnancy. All mothers gave birth at one of two hospitals. A trained research assistant conducted in-person study visits with the mother at the end of the first and second trimesters of pregnancy, and with both mother and child after delivery and at 6 months and 3 years after birth. At each in-person visit, we measured the infant's length/height and weight; at 3 years of age, we also measured the child's skinfold thicknesses. At 1 and 2 years postpartum, participants completed mailed questionnaires.

Of the 2128 women who delivered a live infant, 1579 were eligible for 3-year follow-up on the basis of having completed a prenatal nutrition assessment and providing consent for their children to participate. Of the 1579 participants, 182 were lost to follow-up. We collected follow-up information on 1397 participants (88% of 1579), including in-person 3-year examinations on 1292 (82%). We excluded 16 participants who lacked weight, height and skinfold measures at age 3, 1 participant who was missing exposure data, and 20 participants who were born before 34 weeks' gestational age. Thus, our sample size for analysis was 1255 mother–child pairs. For analyses examining BMI z-score, overweight and obesity outcomes, we excluded 12 participants lacking weight or height at age 3, and 6 participants with biologically implausible weight, height or BMI, leaving 1237 participants. For analyses examining skinfolds, we excluded 56 participants who did not have skinfold measurements, leaving 1199 participants. Compared with the 296 children who were eligible but not included in the present analysis, children in the present study were more likely to have mothers of white race/ethnicity (73% vs 56%) and have college-educated mothers (71% vs 54%). Among included participants, mean maternal BMI was slightly lower (24.6 vs 25.3 kg/m^2) and birth weight was slightly higher (3517 vs 3474 g) than among excluded participants. Rates of caesarean birth were similar among included (23%) and excluded (24%) participants.

Exposure: mode of delivery

We obtained information about mode of delivery from electronic hospital records. For each participant who had a caesarean section recorded on electronic birth logs, we reviewed the operative report to confirm caesarean delivery and to abstract the primary indication for operative delivery. We defined an unplanned caesarean delivery as a delivery in which the operative report described a failed induction of labour, prolonged latent phase, prolonged active phase, arrest of dilation, 'failure to progress', arrest of descent in the second stage or failed operative vaginal delivery, 'non-reassuring fetal heart rate tracing', non-reassuring testing prompting immediate caesarean delivery, cord prolapse or abruption. We defined planned caesarean deliveries as those in which participants did not undergo a trial of labour (elective repeat caesarean without trial of labour, malpresentation, placenta previa, suspected macrosomia, maternal request, or other indication precluding trial of labour). We defined mode of delivery as a two-category variable: caesarean section versus vaginal delivery. We also performed separate analyses defining mode of delivery as a three-category variable: planned caesarean section, unplanned caesarean section, and vaginal delivery. For analyses using the three-category mode of delivery, we excluded four children for whom we were unable to determine whether the caesarean section was planned or unplanned. Unlike planned caesarean section, unplanned caesarean section is frequently accompanied by prior rupture of membranes, which might allow vaginal flora to ascend into the uterus, colonising the fetus.[2] Data on the timing of rupture of membranes were not available for these analyses.

Outcome measures at age 3 years

For each child, we measured height using a research-standard stadiometer (Shorr Productions, Olney, Maryland, USA), and weight using a digital scale (Seca model 881, Seca Corporation, Hanover, Maryland, USA), from which we calculated BMI (weight in kg/(height in m)^2). We calculated age-specific and sex-specific BMI percentiles and z-scores using US national reference data.[13] We defined obesity as a BMI (kg/m^2)≥95th percentile for age and sex,[14 15] overweight as a BMI≥85th and <95th percentile for age and sex, and we used BMI<85th percentile as the comparison group. We also calculated the sum (SS+TR) and ratio (SS:TR) of the children's subscapular (SS) and triceps (TR) skinfold thicknesses, each measured using Holtain calipers (Holtain, Crosswell, UK) with adequate training and evidence of reproducibility.

Covariates

We collected sociodemographic and medical data through in-person interviews at enrolment, ages 6 months and 3 years; yearly self-administered questionnaires; and hospital and ambulatory medical records. Mothers reported their age, race/ethnicity, education, parity, prepregnancy weight and height, and paternal weight and height. We calculated gestational weight gain by subtracting prepregnancy weight from the last prenatal weight. To determine the reporting error using self-reported prepregnancy weight, we compared the weights for 170 participants who had clinic visit measurements recorded within 3 months of their last menstrual period for the index pregnancy with self-reported prepregnancy weight at the first trimester visit. The correlation coefficient between the two weights was 0.99, with underreporting of prepregnancy weight averaging 1 kg. Correlation coefficients and reporting error did not differ by maternal race/ethnicity or gestational age at enrolment into the study. We calculated gestational age at birth using the date of the last menstrual period. If the estimate of gestational age by second-trimester ultrasound assessment differed from the calculated gestational age by more than 10 days, we used the ultrasound dating. We obtained birth weight from medical records. Mothers reported number of hours their children spent in child care,[16] timing of solid food introduction,[17] breastfeeding duration, child diet,[18] television viewing[19] and physical activity habits.

Statistical analysis

We used unadjusted and multivariable linear regression models to assess the associations between caesarean delivery and BMI z-score, SS+TR and SS:TR at age 3 years. We used multinomial logistic regression to assess the associations between caesarean delivery and overweight (BMI 85th to <95th percentile)

and obesity (BMI≥95th percentile), and used <85th percentile as the comparison. In our multivariable model, we adjusted for maternal age, race/ethnicity, education and BMI; and child age, sex and birth weight. For SS:TR models, we additionally adjusted for child BMI z-score. In an additional model, we repeated the analyses defining mode of delivery as a three-category variable: planned caesarean, unplanned caesarean and vaginal delivery. We excluded from our final models potential confounders that did not change our effect estimates, including household income; paternal BMI; maternal smoking, gestational weight gain, parity and maternal glucose tolerance during pregnancy; and child gestational age at birth, initiation and duration of breastfeeding, timing of solid food introduction, energy intake and television viewing at age 2, and height at age 3. We used birth weight rather than birth weight for gestational age z-score to represent fetal size in our models, because caesarean delivery is more likely to be related to birth weight. Replacement of birth weight with birth weight for gestational age z-score in our final model made no difference to the effect estimates.

Because maternal BMI was likely to be strongly associated with both mode of delivery and child obesity, we examined potential confounding by maternal BMI in several ways. First, we examined the effect of adjustment for maternal BMI as a continuous variable and in deciles. The results were similar, so we defined maternal BMI as a continuous variable in our models. Second, we performed analyses stratified by maternal BMI status, categorised as <25 or ≥25 kg/m^2, in which we also adjusted for continuous maternal BMI within each category. We controlled for confounding by fetal size by adjustment for birth weight in our models, and by performing analyses stratified by birth weight, categorised as <3.5 kg or ≥3.5 kg.

We conducted all data analyses using SAS V.9.2.

RESULTS

Participant characteristics are shown in table 1. Of the 1255 deliveries, 22.6% were by caesarean section and 77.4% were vaginal deliveries. Mean maternal prepregnancy BMI was higher among infants delivered by caesarean section than for infants delivered vaginally. Birth weight for gestational age z-score, but not birth weight, was higher for caesarean-delivered than for vaginally delivered infants. Breastfeeding duration was shorter for infants delivered by caesarean section. Compared with vaginal delivery, caesarean delivery was associated with a higher age 3 mean BMI z-score (0.67 vs 0.39 units), and higher mean sum of SS+TR skinfolds (17.5 vs 16.5 mm). Children delivered by caesarean section were more likely to be overweight (18.9% vs 16.7%) or obese (15.7% vs 7.5%), at age 3 than those delivered vaginally (figure 1).

In multivariable models, caesarean delivery was associated with adverse age 3 adiposity outcomes (table 2). In unadjusted multinomial logistic regression analyses, caesarean delivery was associated with 2.4-fold higher odds of obesity (95% CI 1.60 to 3.62). After adjustment for maternal age, education, race/ethnicity, and child age and sex (model 1), the magnitude of the association was hardly changed (OR 2.43, 95% CI 1.60 to 3.68). Additional adjustment for maternal prepregnancy BMI and for birth weight (model 3) slightly attenuated the relationship between caesarean delivery and risk of obesity (OR 2.10, 95% CI 1.36 to 3.23). Caesarean delivery was not significantly associated with age 3 overweight; the odds ratio was 1.24 (95% CI 0.86 to 1.77) after full adjustment.

Table 1 Characteristics among 1255 mother–child pairs participating in Project Viva. Values are given as mean (SD) unless stated otherwise

	Vaginal delivery (n=971)	Caesarean delivery (n=284)	p Value
Maternal characteristics			
Age, years	32.3 (5.2)	33.1 (4.5)	0.01
Race/ethnicity, n (%)			0.55
White	712 (73.6)	198 (69.7)	
Black	114 (11.8)	39 (13.7)	
Hispanic	59 (6.1)	17 (6.0)	
Other	83 (8.6)	30 (10.6)	
College graduate, n (%)	680 (70.3)	207 (72.9)	0.39
Yearly household income >US$70 000, n (%)	588 (65.3)	168 (60.9)	0.18
Smoking during pregnancy, n (%)			0.96
Former	199 (21.0)	57 (20.8)	
During pregnancy	102 (10.8)	28 (10.2)	
Never	647 (68.3)	189 (69.0)	
Prepregnancy BMI, kg/m^2	24.3 (4.8)	25.8 (6.0)	0.0001
Gestational weight gain, kg	15.6 (5.1)	15.7 (6.0)	0.75
Paternal BMI, kg/m^2	26.2 (3.8)	27.1 (4.0)	0.001
Maternal glucose tolerance status, n (%)			0.07
Gestational diabetes	36 (3.8)	15 (5.3)	
Impaired glucose tolerance	26 (2.7)	15 (5.3)	
Transient hyperglycaemia	91 (9.5)	21 (7.5)	
Normal	808 (84.1)	230 (81.9)	
Child characteristics			
Female sex, n (%)	480 (49.4)	136 (47.9)	0.65
Gestational age at birth, weeks	39.7 (1.4)	39.6 (1.5)	0.46
Birth weight, kg	3.50 (0.50)	3.56 (0.56)	0.11
Birth weight for gestational age z-score, units	0.18 (0.94)	0.32 (1.01)	0.04
Breastfeeding initiation	838 (89.5)	224 (83.0)	0.003
Breastfeeding duration, months	6.7 (4.5)	5.6 (4.4)	0.0004
Timing of solid food introduction, n (%)			0.90
<4 months	127 (15.5)	37 (15.5)	
4–5 months	572 (69.6)	169 (70.7)	
≥6 months	123 (15)	33 (13.8)	
Energy intake at age 2 years, kcal/day	1536 (448)	1523 (409)	0.69
TV viewing at age 2 years, h/day	1.4 (1.2)	1.4 (1.1)	0.67
Age 3 characteristics			
Age at 3-year visit, months	39.5 (4.6)	39.1 (3.9)	0.19
BMI, kg/m^2	16.4 (1.5)	16.8 (1.6)	0.0003
BMI z-score, units	0.39 (1.00)	0.67 (1.07)	0.0001
BMI category, n (%)			<.0001
<85th percentile	724 (75.7)	184 (65.5)	
85th to <95th percentile	160 (16.7)	53 (18.9)	
≥95th percentile	72 (7.5)	44 (15.7)	
Sum of subscapular and triceps skinfolds, mm	16.5 (4.2)	17.5 (4.7)	0.002
Ratio of subscapular to triceps skinfolds, units	64.3 (15.7)	65.2 (15.7)	0.41
Height, cm	97.5 (4.8)	97.7 (4.5)	0.60

p Values are from χ^2 for categorical characteristics and t-test for continuous characteristics.

In the fully adjusted (model 3 covariates) linear regression models, caesarean delivery was associated with a 0.20 unit increment (95% CI 0.07 to 0.33) in age 3 BMI z-score and with a 0.94 mm increment (95% CI 0.36 to 1.51) in the sum

of skinfolds, but it was not associated with the subscapular: triceps skinfold ratio, a measure of central adiposity (β −0.18, 95% CI −2.30 to 1.94). In addition, each kg/m^2 increment in maternal BMI was associated with higher odds of child overweight (model 3 OR 1.04, 95% CI 1.01 to 1.07) and obesity (model 3 OR 1.10, 95% CI 1.06 to 1.13). Higher birth weight was also associated with child overweight (model 3 OR 1.96 per kg increment in birth weight, 95% CI 1.44 to 2.68) and obesity (model 3 OR 2.02 per kg, 95% CI 1.35 to 3.03).

In analyses stratified by maternal prepregnancy BMI (table 3), caesarean delivery was associated with a nearly threefold higher odds of obesity (OR 2.97, 95% CI 1.58 to 5.60) among children born to mothers with a normal prepregnancy BMI<25 kg/m^2. Among children born to overweight or obese mothers (prepregnancy BMI≥25 kg/m^2), caesarean delivery was associated with a somewhat elevated odds of obesity that was not statistically significant (OR 1.61, 95% CI 0.88 to 2.96).

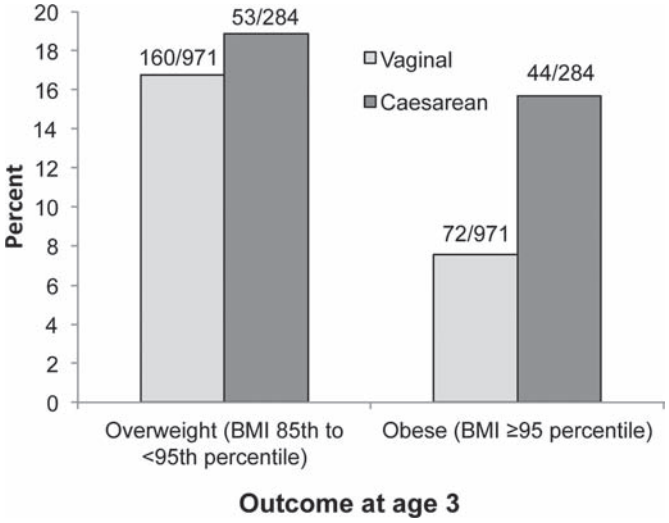

Figure 1 Association between mode of delivery and per cent overweight and obesity at age 3 among 1255 Project Viva participants.

Caesarean delivery was associated with a doubling of the odds of obesity at age 3, regardless of birth weight (table 3).

We performed additional analyses comparing the children with a planned (n=83) or unplanned (n=197) caesarean delivery with those born vaginally (n=971). In unadjusted analyses, planned caesarean section (OR 2.32, 95% CI 1.18 to 4.55) and unplanned caesarean section (OR 2.42, 95% CI 1.52 to 3.83) were associated with a similar increase in odds of obesity compared with vaginal delivery. These ORs were somewhat attenuated by adjustment for covariates in model 3: only unplanned caesarean delivery was clearly associated with a higher risk of obesity at age 3 (OR 2.19, 95% CI 1.34 to 3.55); the odds of obesity for planned caesarean delivery was less elevated and not statistically significant (model 3 OR 1.83, 95% CI 0.89 to 3.77), but the CI was wide because of a small sample size. Neither planned (OR 1.53, 95% CI 0.85 to 2.73) nor unplanned (OR 1.15, 95% CI 0.75 to 1.75) caesarean delivery was associated with odds of overweight at age 3 after covariate adjustment. Unplanned (β 0.22, 95% CI 0.06 to 0.37), but not planned (β 0.18, 95% CI −0.05 to 0.40) caesarean delivery was associated with higher mean BMI z-score. Both unplanned (β 0.70, 95% CI 0.03 to 1.36) and planned caesarean delivery (β 1.51, 95% CI 0.54 to 2.48) were associated with a higher sum of SS+TR skinfolds. Neither unplanned nor planned caesarean delivery was associated with the SS:TR skinfold ratio (data not shown).

DISCUSSION

In this prospective cohort study, we found that children delivered by caesarean section had double the odds of obesity, along with higher BMI (about 0.2 z-score units) and sum of skinfolds (about 1 mm) at age 3 compared with children who had been delivered vaginally. These associations remained even after controlling for key potential confounders, including maternal BMI and birth weight. For a 3-year-old child at the 50th percentile for weight and height, a 0.2 unit increment in BMI z-score would be equivalent to an increment of about 0.23 kg (0.5 lb).

Table 2 OR (95% CI) for obesity (BMI≥95th percentile vs <85th percentile) and overweight (BMI≥85th to <95th percentile vs <85th percentile) and regression estimates (95% CI) for the association of BMI z-score and sum of subscapular plus triceps skinfolds at age 3 years according to mode of delivery

		Outcome at age 3 years			
		Odds of overweight*	Odds of obesity*	BMI z-score* (units)	Sum of subscapular plus triceps skinfolds (mm)†
Model	Mode of Delivery	OR (95% CI)		β (95% CI)	
0	Vaginal	1.0 (ref)	1.0 (ref)	0.0 (ref)	0.0 (ref)
	Caesarean	1.30 (0.92 to 1.85)	2.40 (1.60 to 3.62)	0.27 (0.14 to 0.41)	0.96 (0.38 to 1.54)
1	Vaginal	1.0 (ref)	1.0 (ref)	0.0 (ref)	0.0 (ref)
	Caesarean	1.32 (0.92 to 1.87)	2.43 (1.60 to 3.68)	0.28 (0.14 to 0.41)	1.06 (0.48 to 1.63)
2	Vaginal	1.0 (ref)	1.0 (ref)	0.0 (ref)	0.0 (ref)
	Caesarean	1.27 (0.89 to 1.81)	2.15 (1.40 to 3.30)	0.22 (0.08 to 0.35)	0.94 (0.37 to 1.52)
3	Vaginal	1.0 (ref)	1.0 (ref)	0.0 (ref)	0.0 (ref)
	Caesarean	1.24 (0.86 to 1.77)	2.10 (1.36 to 3.23)	0.20 (0.07 to 0.33)	0.94 (0.36 to 1.51)

Model 0 unadjusted for covariates.
Model 1 adjusted for maternal age, education, race/ethnicity, and child age and sex.
Model 2 adjusted for model 1 covariates and maternal prepregnancy body mass index (BMI).
Model 3 additionally adjusted for birth weight.
ORs were calculated using multivariable multinomial logistic regression.
*For models examining overweight, obesity, and BMI z-score outcomes, model 0 includes n=1237 participants. Model 1 includes n=1234 (excluded 3 participants with missing values for education and race/ethnicity). Models 2 and 3 include n=1230 (excluded 4 participants with missing values for maternal prepregnancy BMI).
†For the subscapular plus triceps skinfolds outcome, model 0 includes n=1199 participants. Model 1 includes n=1196 (excluded 3 participants with missing values for education and race/ethnicity). Models 2 and 3 include n=1192 (excluded 4 participants with missing values for maternal prepregnancy BMI).

Table 3 The association between caesarean delivery and obesity at age 3, stratified by maternal prepregnancy BMI and birth weight

	Mode of delivery	Odds of overweight	Odds of obesity
		OR (95% CI)	
Overall	Vaginal	1.00 (ref)	1.00 (ref)
	Caesarean	1.24 (0.86 to 1.77)	2.10 (1.36 to 3.23)
Maternal BMI<25 kg/m^2 (n=811)	Vaginal	1.00 (ref)	1.00 (ref)
	Caesarean	1.12 (0.69 to 1.83)	2.97 (1.58 to 5.60)
Maternal BMI≥25 kg/m^2 (n=440)	Vaginal	1.00 (ref)	1.00 (ref)
	Caesarean	1.44 (0.83 to 2.49)	1.61 (0.88 to 2.96)
Birth weight<3.5 kg (n=629)	Vaginal	1.00 (ref)	1.00 (ref)
	Caesarean	1.15 (0.66 to 2.02)	2.29 (1.13 to 4.63)
Birth weight≥3.5 kg (n=626)	Vaginal	1.00 (ref)	1.00 (ref)
	Caesarean	1.28 (0.80 to 2.06)	2.05 (1.17 to 3.58)

We ran separate multinomial logistic regression models within each stratum. Models were adjusted for maternal age, education, race/ethnicity, and child age and sex, maternal prepregnancy body mass index (BMI) and birth weight.

Our findings suggesting that caesarean delivery may be an early life risk factor for obesity development are consistent with a small case–control study of 3–6-year-old Chinese children that reported higher odds of obesity (OR 5.23, 95% CI 1.24 to 22.04) associated with a caesarean delivery.[4] In that study of 81 obese cases and 81 normal weight controls, the authors relied largely on data collected retrospectively using parental questionnaires, and did not have data regarding maternal prepregnancy BMI. In contrast, we had a larger sample size and adjusted for multiple key confounders, including maternal prepregnancy BMI, collected prospectively during pregnancy and childhood.

In our study, we were unable to directly examine potential mechanisms underlying the association between caesarean section and child obesity. One possible mechanism is that differences in the composition of intestinal microbiota acquired at birth among caesarean and vaginally delivered newborns may contribute to their risk of obesity at age 3. Differences in child intestinal flora according to mode of delivery have been noted in the first year of life,[5 6 20–22] a period of dramatic changes in number and diversity of gut microbes as well as rapid growth. Most,[3 4 23 24] but not all[6] studies, suggest that infants delivered by caesarean section have higher stool quantities of members of the Firmicutes group, or lower quantities of the Bacteroidetes group. The Firmicutes and Bacteroidetes bacteria constitute the majority of the microbiota in the adult human intestine.[25] Data in mice and humans have shown that obese individuals display a relative abundance of Firmicutes and a lower proportion of Bacteroidetes than lean individuals.[25 26] Experiments in mice support the notion that the composition of intestinal microbiota may alter host body composition.[27] Transplantation of intestinal microbiota obtained from obese donor mice (vs lean donors) into germ-free mice resulted in substantially greater percentage increase in recipient body fat (47% vs 27%, p<0.05) and recipient intestinal microbiota with a relative abundance of Firmicutes, resembling the source microbial composition.[26] In humans, small prospective intervention studies with follow-up ranging from several weeks to a year have shown that weight loss is associated with lowering of Firmicutes levels or higher Bacteroidetes levels,[25 28 29] although not all studies are in agreement.[30] The intestinal microbiota may influence obesity development by increasing energy extracted from the diet, and by effects on host epithelial and endocrine cells that promote insulin resistance, inflammation and fat deposition.[7 27]

A few small case–control studies in Finnish children have directly examined whether intestinal microbiota composition in infancy is related to obesity in childhood.[8 9] Children who were overweight (vs normal weight) at ages 7–10 years had lower[8] or a trend towards lower[9] bifidobacterial quantities in stools collected during infancy. Stool quantities of Clostridia and Bacteroides did not significantly differ by weight status, but the small sample sizes (30 children,[9] 49 children[8]) may have limited power to detect differences. Our findings suggest a need for studies examining whether the association between caesarean delivery and child obesity is mediated by the types, quantities and functional effects of intestinal microbiota established in early life.

Other explanations for our findings are possible. Given the routine perioperative antibiotic prophylaxis accompanying caesarean delivery, caesarean delivery may be a proxy for intrapartum antibiotic use, which could influence the composition of neonatal intestinal flora, in turn influencing the development of obesity. One study that reported differences in microbiota composition by mode of delivery specifically excluded subjects who had received intrapartum or perinatal antibiotics.[21] Among 1032 Dutch infants with stool microbial composition examined at 1 month of age, maternal antibiotic use during pregnancy was not associated with infant intestinal microbiota composition;[22] antibiotic use during infancy was associated with reduced numbers of Bacteroides and bifidobacteria,[22] a pattern that may be obesogenic,[7] but other studies have not found any consistent effects of infant antibiotic use on host microbial composition.[31] In our study, we were unable to examine the relationships among caesarean delivery, perinatal antibiotic use and childhood obesity.

We hypothesised that unplanned caesarean section might be associated with a risk of child obesity intermediate between the risk associated with planned caesarean section and vaginal delivery. This hypothesis was based on the theory that the rupture of membranes, assumed to occur in most unplanned caesarean sections, would allow the fetus some exposure to vaginal flora. Instead, the evidence was contrary to the hypothesis: we found that there was little difference in the risk of obesity, mean BMI-z, and sum of SS+TR skinfolds between planned and unplanned caesarean births. Perhaps physical passage of the infant through the birth canal is more important than the presence or duration[22] of rupture of membranes in determining infant flora composition.

The mode of delivery might influence long-term obesity risk through effects on inflammation, immune or endocrine function that are independent of the intestinal microbiota composition. Labour is associated with many changes in levels of maternal and placental hormones and inflammatory cytokines, which we and others[32] have hypothesised could influence the development of obesity. Piglet offspring delivered by caesarean section had greater hepatic steatosis and altered cholesterol metabolism compared with those delivered vaginally.[33] In mice, oral exposure to lipopolysaccharide during vaginal but not caesarean birth triggered activation of gut epithelial cells.[34] Stress-response signalling associated with labour may program the long-term function of the hypothalamic–pituitary–adrenal axis,[35] or result in epigenetic modification[36 37] of key metabolic genes that might induce an obese phenotype.[38]

Strengths of this study include a well characterised cohort with adequate control for a large set of potential confounding

variables, and careful measurement of child height and weight using research standards. Our study had several limitations. To calculate maternal BMI, we relied on self-reported maternal prepregnancy weight, which we showed to be highly correlated (r=0.99) with prepregnancy clinic weights in a subset of Project Viva participants. It is possible that this correlation would be lower for the whole cohort, because participants without recorded prepregnancy clinic weights may report their weights with greater error. Our study had some loss to follow-up, raising possible selection bias. Compared with non-participants, participating mothers differed on race/ethnicity, BMI and infant birth weight. However, rates of caesarean birth were similar among included and excluded participants. Study participants had a relatively high level of education and income, which may limit generalisability. We cannot rule out the possibility of residual confounding as an explanation for our findings. We were particularly concerned about possible residual confounding by fetal size and by maternal BMI. Mean birth weight was only slightly and non-significantly higher for caesarean than for vaginally delivered infants (p=0.11, table 1), and the odds of obesity hardly changed when analyses were stratified by birth weight (table 3). The association between mode of delivery and obesity risk remained robust after adjustment for maternal BMI defined as either a categorical or a continuous variable. Moreover, the OR increased from 2.06 to 2.97 when the cohort was restricted to mothers with a normal prepregnancy BMI of <25 kg/m^2 (table 3). These findings argue against, but do not rule out, residual confounding by fetal size or maternal BMI as an explanation for our results.

The 22.1% caesarean section rate among our study mothers was similar to US national rates reported for 1999–2002.[39] From 1996 to 2007, the number of caesarean births in the USA increased to 32% of births.[10 40] One study implication is that further delineation of mechanisms explaining how caesarean section may lead to increased obesity could help with the design of targeted obesity prevention strategies. Another study implication is that prevention of child obesity may be another reason to avoid caesarean section on maternal request, which is estimated to compose between 4% and 18% of caesarean births.[11] A mother who chooses caesarean delivery on maternal request should be aware of potential health risks to her and her baby, including childhood obesity and other potential long-term risks.[2 3 32 41–43]

CONCLUSION

In this study, infants delivered by caesarean section had two-fold higher odds of childhood obesity, even after adjusting for maternal BMI, birth weight and other confounding variables. Further studies are needed to confirm our findings and to explore mechanisms underlying this association. Expectant mothers choosing caesarean delivery in the absence of an obstetrical or medical indication should be aware that their children may have a higher risk of obesity.

Contributors All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. SYH designed the research question, led data analysis and wrote the first draft of the manuscript. CAZ participated in data collection. SRS conducted the statistical analysis. MWG participated in the study design, obtained funding, and directed study operations. All authors contributed to data interpretation and to critical revision of the manuscript and approved the final version. SYH is the guarantor.

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