Int J Obes (Lond). Author manuscript; available in PMC 2021 May 16.

Published in final edited form as:
Int J Obes (Lond). 2021 January ; 45(1): 36–44. doi:10.1038/s41366-020-00709-x.

Mode of delivery, type of labor, and measures of adiposity from childhood to teenage: Project Viva

Noel T. Mueller[1,2], **Mingyu Zhang**[1,2], **Sheryl L. Rifas-Shiman**[3], **Emily Oken**[3,4], **Marie-France Hivert**[3,6,7], **Jorge Chavarro**[4,5]

[1]Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD

[2]Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins University School of Medicine, Baltimore, MD

[3]Division of Chronic Disease Research Across the Lifecourse, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA

[4]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA

[5]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA

[6]Diabetes Unit, Massachusetts General Hospital, Boston, MA

[7]Department of Medicine, Universite de Sherbrooke, Sherbrooke, Canada

Abstract

Background: Cesarean delivery has been linked with childhood obesity. Few studies have examined if this association is attenuated if there is labor prior to delivery. The objective of this current analysis was to examine the association of cesarean vs. vaginal delivery with measures of childhood adiposity, and whether the association differs by labor type (spontaneous, induced, or absent) preceding cesarean delivery.

Methods: We ascertained delivery mode and type of labor from medical records in 1443 mother-child dyads from Project Viva with adiposity measures from at least 1 follow-up visit (3369 total observations) in early childhood (median age 3.2y), mid-childhood (median 7.7y), or early teen (median 12.9y). Child adiposity outcomes were CDC age- and sex-specific body mass index (BMI) z-scores, sum of subscapular and triceps skinfold thicknesses (SS+TR; mm), and waist circumference (cm). We used linear regression models with generalized estimating equation estimates adjusted for maternal age, education, race/ethnicity, pre-pregnancy BMI, rate of gestational weight gain, and child sex and age at outcome.

Results: A total of 333 (23%) women delivered via cesarean, including 155 (11%) with spontaneous labor, 74 (5%) with induced labor, 99 (7%) with no labor, and 5 (<1%) with unknown

Corresponding author: Noel T. Mueller, Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD.

All authors declare no conflict of interest.

labor status. Compared to vaginal-delivered children, cesarean-delivered children had higher BMI-z (0.15, 95% CI: 0.04, 0.26); and non-significantly higher waist circumference (0.50 cm, 95% CI: −0.34, 1.34) and SS+TR (0.47 mm, 95% CI: −0.52, 1.46). Cesarean deliveries that were preceded by spontaneous labor were not associated with childhood BMI-z (0.08, 95% CI: −0.07, 0.23), waist circumference (−0.12 cm, 95% CI: −1.09, 0.85), or SS+TR (−0.25 mm, 95% CI: −1.44, 0.93), as compared to vaginal deliveries.

Conclusion: Cesarean delivery was associated with higher childhood BMI-z, and although waist circumference and SS+TR trended in the same direction, these associations were not significant. Cesarean delivery preceded by spontaneous labor was not associated with adiposity outcomes.

Keywords

Pediatrics; Epidemiology; Cesarean Section; Adiposity; Obesity

INTRODUCTION

Cesarean delivery is one of the most common surgical procedure carried out in the United States (U.S.) and worldwide[1]. While it is a life-saving intervention, it has also been linked with several offspring health conditions, including childhood overweight and obesity.[2–4] It is postulated that the higher offspring risk of developing obesity is because cesarean delivery deprives the newborn of exposure to maternal microbes that are evolutionarily adapted for offspring health.[5] Yet, few studies to date have examined whether this association is modified by exposure to ruptured membranes prior to cesarean delivery. Labor may occur prior to emergency cesarean deliveries and it is often accompanied by rupture of membranes, which may allow for colonization of the fetus with maternal microbiota.[6]

In the present analysis, our aim was to examine the associations of cesarean delivery with measures of adiposity (body mass index [BMI], sum of subscapular and triceps skinfold thicknesses [SS+TR], and waist circumference), and the extent to which these associations differed for cesarean deliveries preceded by different types of labor (spontaneous, induced, or absent). We used data from a pre-birth cohort of women and their offspring from early childhood (median 3.2y), mid-childhood (median 7.7y) and early teen (median 12.9y) in-person visits. We hypothesized that cesarean delivery is associated with higher adiposity in children, but also that associations for cesarean deliveries preceded by spontaneous labor are weaker because the newborns are experience the benefits of natural labor.

SUBJECTS AND METHODS

Study Population and Design

Project Viva is a pre-birth cohort study of prenatal and perinatal exposures, pregnancy outcomes, and offspring health. Between 1999 and 2002 we recruited women in their first prenatal visit at Atrius Harvard Vanguard Medical Associates, a multi-specialty group practice in eastern Massachusetts. We have published details of participant recruitment and study protocol previously.[7] Of the 2128 women who delivered a live singleton infant, we excluded from this analysis 30 participants with missing delivery mode and then 47 with missing covariates. We then excluded 608 with no early childhood, mid-childhood, or early teen outcome data. Our sample size for analysis was 1443 mother-child pairs with 3369 total outcome observations (1258 early childhood, 1092 mid-childhood, and 1019 early teen). Compared with the 1443 participants in this analysis, the 685 non-participants were less likely to have college educated mothers (56% vs. 69%) and to have annual household income exceeding $70,000 (56% vs. 63%), and maternal age was slightly lower (mean 31.1 vs. 32.1 years). Maternal pre-pregnancy BMI (mean 25.1 vs. 24.8 kg/m^2), mode of delivery (25% vs. 23% Cesarean) and child sex (47% vs. 49% female), however, were similar (Supplemental Table 1).

Mothers provided written informed consent at enrollment and for their infants after birth, and children provided verbal assent at follow-up visits. The Institutional Review Board of Harvard Pilgrim Health Care approved this study protocol.

Exposure

We obtained information about delivery mode from electronic medical records. We first defined delivery as a two-category variable: cesarean delivery vs. vaginal delivery. For participants who had cesarean delivery recorded in electronic health records, we then abstracted information on type of labor (i.e., cesarean with spontaneous labor, cesarean with induced labor, and cesarean with no labor).

Outcome measures

We measured adiposity in early childhood (median age 3.2 y), mid-childhood (median age 7.7 y), and early teen (median age 12.9 y). Child adiposity outcomes were BMI z-scores, sum of subscapular (SS) and triceps (TR) skinfold thicknesses (mm), and waist circumference (cm).

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 using weight (kg) divided by height (m) squared. We calculated age- and sex-specific BMI z-scores using CDC 2000 US national references data.[8]

We measured waist circumference to the nearest 0.1 cm with a Hoechstmass measuring tape (Hoechstmass Balzer GmbH, Sulzbach, Germany). We also measured children’s subscapular (SS) and triceps (TR) skinfold thicknesses to the nearest 0.1 mm using Holtain calipers (Holtain, Crosswell, UK) and calculated their sum (SS+TR). Research assistants followed standardized techniques and completed in-service training to ensure measurement validity (IJ Shorr; Shorr Productions).[9] We assessed measurement error (both inter-rater and intra-rater) and found it to be within published reference ranges for all measurements.[9]

Covariates

Through interviews and questionnaires, we collected information on mothers’ age, race/ethnicity, education, household income, pregnancy smoking status, parity, and date of last menstrual period (LMP). We obtained infant sex, birthweight, and date of birth from medical records. We used LMP date to calculate gestational age, but if gestational age according to

2nd trimester ultrasound differed from that according to the LMP by >10 days, we used the ultrasound result to determine gestational duration. We calculated sex-specific birthweight for gestational age z-scores using a US national reference[10]. We calculated mothers' pre-pregnancy BMI from self-reported weight (kg) divided by height (m) squared. We calculated total gestational weight gain as the difference between self-reported pre-pregnancy weight and the last clinical weight recorded within 1 month before delivery. We used electronic medical records for blood pressure and urine protein to derive physician-diagnosed preeclampsia and we used lab results from the glucose challenge test and oral glucose tolerance test during pregnancy to derive gestational diabetes. Women with pre-pregnancy BMI ≥ 30 kg/m^2 were classified as having obesity and infants with birth weight > 4000 g were defined as having macrosomia.

We also ascertained information on relevant postnatal covariates. At 6 and 12 months, we asked mothers whether they were still breastfeeding at all. If they had stopped, we asked them the children's age at cessation. In this analysis, we categorized breastfeeding duration as <12 months, ≥12 months, consistent with recommendation by the American Academy of Pediatrics[11]. At the mid-childhood visit, mothers reported on pubarchal/pubertal phenotype based on appearance of body hair and breast development for girls; and body hair, facial hair, and deepening of voice for boys. For each characteristic, mothers selected from the following options: 1= "has not yet begun", 2 = "has barely started," 3 = "is definitely underway," or 4 = "seems complete." To create the pubertal status variable, we combined the characteristics as an ordinal summary score of breast development and body hair for girls, and the mean of deepening of voice, facial hair, and body hair for boys. We then dichotomized the variable as pre-pubertal (puberty score=1) vs. pubertal (puberty score>1) as we have previously done[12].

Statistical analysis

First, we ran separate linear regression models to assess associations of delivery mode with early childhood, mid-childhood, and early teen outcomes. Next, to leverage the power of our serially collected data, we set all 3 time points together and used linear regression models with generalized estimating equations (GEE) estimates. GEE models the within-individual similarity of residuals. It uses the estimated correlation to re-estimate regression parameters and calculate robust standard errors. We tested an exchangeable and auto regressive correlation structure, and found the autoregressive structure best fit the data.

We adjusted models for potential confounders (i.e. factors associated with the exposure and outcome but on the causal pathway) and prognostic factors. In Model 1, we adjusted for maternal socio-demographic variables (maternal age, education, and race/ethnicity) along with child sex and age at outcome. In Model 2, we additionally adjusted for mother's pre-pregnancy BMI and rate of gestational weight gain, as these factors have been previously associated with both delivery mode and child adiposity. Additional adjustment for birth weight for gestational age z-score did not change the estimates. To determine the appropriateness of the GEE models, we tested an interaction with child age. We also evaluated effect modification by using the Wald chi-square test for interaction terms for maternal pre-pregnancy BMI (<25 vs. ≥25 kg/m^2), child sex, breastfeeding duration (<12 months vs. ≥ 12 months), and mid-childhood puberty status (pre-pubertal vs. pubertal; we only included mid-childhood and early adolescent outcomes in the GEE models given that early childhood outcomes were measured before the assessment of mid-childhood puberty). To determine whether labor type modified the association of cesarean delivery with outcomes, we ran a separate regression analysis of labor type only among cesarean-delivered children.

We also conducted a number of sensitivity analyses. First, we re-ran models excluding 473 (of 1443) women with relative indications of cesarean delivery (pre-eclampsia, gestational diabetes mellitus, macrosomia, and maternal obesity). Second, we ran an inverse probability weight analysis, in which we first generated weights by predicting loss to follow up using covariate data (sex, maternal age at enrollment, educational status, maternal pre-pregnancy BMI, gestational weight gain rate, birth weight for gestational age, race, and delivery mode), and then used the weights generated in our previously defined GEE model. The significance level for all tests was two-sided $P < 0.05$, and all analyses were conducted in SAS version number 9.4 (SAS Institute, Cary, NC). SAS code is available upon request.

RESULTS

Mean (standard deviation) or n (%) for pertinent participant characteristics are presented in Table 1. The mean age of mothers in the sample was 32.1 (SD: 5.2) years, with 991 (69%) having a college education, and 452 (31%) identifying as non-White. Of the 1443 mother-child pairs, 1110 (77%) had vaginal delivery, 155 (11%) had cesarean delivery with spontaneous labor, 74 (5%) had cesarean delivery with induced labor, 99 (7%) had cesarean delivery with no labor, and 5 (<1%) had cesarean delivery with unknown labor status. Mothers who had cesarean delivery had higher pre-pregnancy BMI, were more likely to have excessive gestational weight gain, and had larger babies.

Results of multivariable adjusted models using data from all three follow-up time points (early childhood, mid-childhood, early teen) are shown in Table 2. Results at each follow-up time point are shown in Supplemental Tables 2–4. In this Results section, we are showing estimates from Model 2, which were attenuated from the results in Model 1 by ~40% (BMI-z) to ~60% (waist circumference and skinfolds). Estimates from Model 1 can be found in Table 2 and Supplemental Tables 2–4.

Compared to vaginally-delivered children, cesarean-delivered children had higher BMI-z (adj-β = 0.15, 95% CI: 0.04, 0.26), and marginally higher waist circumference (adj-β = 0.50 cm; 95% CI: −0.34, 1.34) and SS+TR (adj-β = 0.47 mm, 95% CI: −0.52, 1.46) from early childhood to early teen. Associations were similar after adjustment for birth weight for gestational age z-score (data not shown). Associations were not significantly different (all p values for interaction > 0.20) by strata of maternal pre-pregnancy BMI, breastfeeding duration, or puberty status. There was, however, tendency that associations with BMI-z were stronger in males compared to females (P for interaction = 0.08; Table 3).

The adjusted differences in BMI-z comparing cesarean-delivered vs. vaginal-delivered children appeared to slightly decrease as children aged (early childhood: adj-β = 0.18, 95%

CI: 0.05 to 0.31; mid-childhood: adj-β = 0.13, 95% CI: 0.00, 0.27; early teen: adj-β = 0.11, 95% CI: −0.04, 0.25), however the test for interaction between delivery mode and age on BMI-z was not significant (P for interaction = 0.87). The adjusted differences in waist circumference and SS+TR – different from the monotonic decreasing pattern of BMI-z – decreased from early childhood to mid-childhood, but slightly increased from mid-childhood to early teen (Supplemental Tables 2–4). However, interaction terms between delivery method (cesarean vs. vaginal) and age suggested that the associations did not significantly change over time for waist circumference (P for interaction = 0.17) or SS+TR (P for interaction = 0.10).

Compared with vaginally-delivered children, cesarean-delivered children had higher BMI-z regardless of labor types experienced, with induced labor yielding the strongest adjusted difference (adj-β = 0.27, 95% CI: 0.07, 0.47), followed by no labor (adj-β = 0.16, 95% CI: −0.04, 0.35), and then spontaneous labor (adj-β = 0.08, 95% CI: −0.07, 0.23). There was a non-significant tendency for higher waist circumference among CS-delivered children with induced labor (adj-β = 0.97 cm, 95% CI: −0.82, 2.76) or no labor (adj-β = 1.07 cm, 95% CI: −0.60, 2.74), but not for children with spontaneous labor (adj-β = −0.12 cm, 95% CI: −1.09, 0.85). Similarly, SS+TR tended to be higher for cesarean-delivered children with induced labor (adj-β = 0.76 mm, 95% CI: −1.29, 2.82) or no labor (adj-β = 1.40 mm, 95% CI: −0.48, 3.27), but tended to be lower for children with spontaneous labor (adj-β = −0.25 mm, 95% CI: −1.44, 0.93. Results for the association of labor type with adiposity outcomes in cesarean delivered children only are shown in Table 3.

Results were not materially changed when we excluded indications for cesarean delivery (Supplemental Table 5) or when in our inverse probability weight models (Supplemental Table 6).

DISCUSSION

In a large (N=1443) prospective pre-birth cohort in Massachusetts, US, cesarean section accounted for 23.0% of deliveries (comparatively, in the US 31.9% deliveries were cesarean in 2018[13]) and was associated with higher offspring BMI-z from early childhood to early teen (2.8 to 16.6 years of age). Although the estimates appeared to weaken slightly over life stages, the interaction test did not shown evidence of heterogeneity with age, suggesting the effect is constant over time. The association of delivery mode and BMI-z appeared to persist regardless of the type of labor, though associations were not significant for spontaneous labor. Overall associations of delivery mode with waist circumference and sum of triceps and sub-scapular skinfolds, were not significant although they trended in the same direction as BMI-z. The associations with waist circumference and sum of triceps and sub-scapular skinfolds tended to be somewhat weaker for spontaneous labor compared with induced labor or no labor, however these associations were not statistically significant.

Numerous longitudinal studies[14–20], systematic reviews and meta-analyses[2–4] have linked cesarean delivery to excess weight gain and overweight and obesity in offspring, while some did not find such association[21] or found the associations attenuated or disappeared over time.[22–24] In 2012, we showed in Project Viva that infants delivered by cesarean delivery had higher risk of obesity, higher BMI-z, and higher SS+TR at 3 years of age[14]. In this current study, we added to our previous findings that the associations for BMI-z persisted in later years, with slight attenuation over life stages, but we did not find significant associations with SS+TR and waist circumference in mid-childhood or early teen.

Few studies have compared the association between cesarean delivery and child overweight/obesity across different labor types[18–20]. Rutayisire et al.[19] found in 8,900 Chinese children age 3–6 years that both those delivered by elective or non-elective cesarean sections were at increased risk of overweight/obesity, however, the authors did not differentiate by whether cesarean delivery was before or after the onset of labor. Li et al.[18] found in 181,380 Chinese children age 3–7 years that those born by cesarean delivery had higher risk of overweight and the risk was slightly higher for cesarean deliveries that were by request and before the onset of labor. More recently, Cai et al.[20] found in 727 Singaporean 12-month infants that elective cesarean delivery (i.e., due to advance planning such as maternal request), but not emergency cesarean delivery, was associated with higher risk of overweight. Furthermore, in the same study, nonlabor cesarean delivery (i.e., happened before labor onset and/or membrane rupture) was associated with higher risk of overweight, but not intrapartum cesarean delivery (i.e. during labor) was not. While the definitions of types of labor in these studies are vary slightly from our study (cesarean with spontaneous labor, cesarean with induced labor, and cesarean with no labor), the conclusions are largely consistent that associations are weaker or null for cesarean sections that are accompanied by labor or rupture of membranes.

The null associations observed among cesarean deliveries preceded by spontaneous labor provide some support for the hypothesis that interruption of mother-to-newborn transmission of microbiota at birth may explain, at least in part, the association of delivery mode and offspring risk of developing overweight and obesity. Indeed, the microbiome of cesarean-born neonates without labor (vs. with labor) has been found to be more dissimilar from vaginally-born neonates.[25] Recent longitudinal studies indicates that gut microbiota differs by delivery mode, including vaginally-delivered babies having higher *Bifidobacterium* and *Bacteroides spp.*, are independent of perinatal antibiotics[26] and may persist for up to 4 years.[27] These persistent differences could directly impact energy metabolism, however, even if the impacts to early-life development of the gut microbiome are transient, there is evidence that they can have lasting effects on adiposity,[28] possibly through epigenomic regulation such as disruption of epithelial histone deacetylase 3 in the intestine.[29] There is also the potential that associations between delivery mode and outcomes are driven by the biological stress response to labor, which should be explored further in future studies.

Another interesting observation from our study is that the associations between delivery mode and offspring adiposity appear to be stronger for boys than girls. This finding is consistent with our previous work showing that the accelerated rate of growth among cesarean-delivered infants is greater for males than females.[17] It is also congruent with literature showing a sexual dimorphism to microbial programming of obesity[30] and that microbiota could be necessary for sex-specific gene expression and metabolism.[31] Indeed, the growing number of sex-specific findings on this topic warrants further investigation with adequately powered epidemiologic studies and mechanistic animal experiments.

Our study has limitations. First, children born via cesarean delivery with induction of labor are likely a heterogenous group. Labor can be induced by separating the amniotic sack from the wall of the uterus; giving the women prostaglandins, which help to soften and thin the cervix; giving medications such as oxytocin to induce labor; or amniotomy (rupturing of the membranes) using a small hook. Each of these procedures may have their own effect on offspring outcomes. Unfortunately, we did not have data on the type of labor induction, so we had to group them together. Second, we had a relatively small number of cesarean-delivered infants with induced or spontaneous labor, which may have limited our statistical power to detect significant differences between groups. Third, losses to follow up may have introduced selection bias in our study. We attempted to address this possible bias by conducting a sensitivity analysis that included inverse probability weight, and the results from this analysis did not differ from the main analyses presented in this paper. Fourth, although we adjusted for many covariates, some of which attenuated our results, and conducted sensitivity analyses excluding indications for cesarean delivery that are also associated with child obesity, residual confounding is still possible as this is an observational study. Finally, our study was a majority white and higher income, and therefore may not be generalizable to other racial/ethnic groups and socioeconomic strata.

There are several strengths of our study. Our extensive collection of covariate data allowed used to examine cesarean delivery with different types of labors, which provided us further mechanistic insight into the established associations of cesarean delivery and child weight, and include child adiposity measures other than just BMI-z. The careful ascertainment of data also allowed us to adjust for a comprehensive set of potential confounders and other covariates, which minimized the potential confounding in the study, and use inverse probability weighting to address possible bias due to censoring. Finally, we covered a wide range of child age (from 2.8 to 16.6 years old), which allowed us to examine that change in weight and adiposity measures across life stages (early childhood to mid-childhood, then early teen).

In conclusion, our longitudinal study of mother-child dyads from the Boston area provides evidence that cesarean delivery is associated with higher childhood BMI-z from early childhood to early teen. There was a tendency for weaker associations with adiposity among cesarean deliveries preceded by spontaneous labor, raising the possibility that exposure to a component of labor, e.g. ruptured membranes, modifies associations of delivery mode with offspring adiposity. Intervention studies are needed to test the hypothesis that cesarean-delivered neonates exposed to their mother’s microbiota at birth have different health outcomes than those that are not exposed to their mother’s microbiota.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Source of Funding: Funding Grants from the US National Institutes of Health (R01 HD034568, R01 HD093761, UH3 OD023286, P30 DK046200). Dr Mueller is supported by the National Heart, Lung, and Blood Institute grant (K01HL141589).

REFERENCES

1. Boerma T, Ronsmans C, Melesse DY, Barros AJD, Barros FC, Juan L et al. Global epidemiology of use of and disparities in caesarean sections. Lancet (London, England) 2018; 392(10155): 1341–1348.
2. Li Ht, Zhou Yb, Liu Jm. The impact of cesarean section on offspring overweight and obesity: a systematic review and meta-analysis. International Journal Of Obesity 2012; 37: 893. [PubMed: 23207407]
3. 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. [PubMed: 24586295]
4. Kuhle S, Tong OS, Woolcott CG. Association between caesarean section and childhood obesity: a systematic review and meta-analysis. Obesity Reviews 2015; 16(4): 295–303. [PubMed: 25752886]
5. Mueller NT, Bakacs E, Combellick J, Grigoryan Z, Dominguez-Bello MG. The infant microbiome development: mom matters. Trends in molecular medicine 2015; 21(2): 109–17. [PubMed: 25578246]
6. Bager P, Wohlfahrt J, Westergaard T. Caesarean delivery and risk of atopy and allergic disesase: meta-analyses. Clinical & Experimental Allergy 2008; 38(4): 634–642. [PubMed: 18266879]
7. Oken E, Baccarelli AA, Gold DR, Kleinman KP, Litonjua AA, De Meo D et al. Cohort profile: project viva. Int J Epidemiol 2015; 44(1): 37–48. [PubMed: 24639442]
8. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z et al. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat 11 2002; (246): 1–190.
9. Louer AL, Simon DN, Switkowski KM, Rifas-Shiman SL, Gillman MW, Oken E. Assessment of Child Anthropometry in a Large Epidemiologic Study. J Vis Exp 2017; (120).
10. Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. BMC Pediatrics 2003; 3(1): 6. [PubMed: 12848901]
11. Breastfeeding and the Use of Human Milk. Pediatrics 2012; 129(3): e827. [PubMed: 22371471]
12. Perng W, Rifas-Shiman SL, Hivert MF, Chavarro JE, Oken E. Branched Chain Amino Acids, Androgen Hormones, and Metabolic Risk Across Early Adolescence: A Prospective Study in Project Viva. Obesity (Silver Spring, Md.) 2018; 26(5): 916–926.
13. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK. Births: Final Data for 2018. Natl Vital Stat Rep 2019; 68(13): 1–47.
14. Huh SY, Rifas-Shiman SL, Zera CA, Edwards JWR, Oken E, Weiss ST et al. Delivery by caesarean section and risk of obesity in preschool age children: a prospective cohort study. Archives of Disease in Childhood 2012; 97(7): 610–616. [PubMed: 22623615]
15. Mueller NT, Whyatt R, Hoepner L, Oberfield S, Dominguez-Bello MG, Widen EM et al. Prenatal exposure to antibiotics, cesarean section and risk of childhood obesity. International Journal Of Obesity 2014; 39: 665. [PubMed: 25298276]
16. Yuan C, Gaskins AJ, Blaine AI, Zhang C, Gillman MW, Missmer SA et al. Association Between Cesarean Birth and Risk of Obesity in Offspring in Childhood, Adolescence, and Early Adulthood. JAMA Pediatrics 2016; 170(11): e162385–e162385. [PubMed: 27599167]
17. Mueller NT, Zhang M, Hoyo C, Østbye T, Benjamin-Neelon SE. Does cesarean delivery impact infant weight gain and adiposity over the first year of life? International Journal of Obesity 2019; 43(8): 1549–1555. [PubMed: 30349009]
18. Li H, Ye R, Pei L, Ren A, Zheng X, Liu J. Caesarean delivery, caesarean delivery on maternal request and childhood overweight: a Chinese birth cohort study of 181 380 children. Pediatric Obesity 2014; 9(1): 10–16. [PubMed: 23512941]
19. Rutayisire E, Wu X, Huang K, Tao S, Chen Y, Tao F. Cesarean section may increase the risk of both overweight and obesity in preschool children. BMC Pregnancy and Childbirth 2016; 16(1): 338. [PubMed: 27809806]

20. Cai M, Loy SL, Tan KH, Godfrey KM, Gluckman PD, Chong Y-S et al. Association of Elective and Emergency Cesarean Delivery With Early Childhood Overweight at 12 Months of Age. JAMA Network Open 2018; 1(7): e185025–e185025. [PubMed: 30646378]
21. Rifas-Shiman SL, Gillman MW, Hawkins SS, Oken E, Taveras EM, Kleinman KP. Association of Cesarean Delivery With Body Mass Index z Score at Age 5 Years. JAMA Pediatrics 2018; 172(8): 777–779. [PubMed: 29889944]
22. Pei Z, Heinrich J, Fuertes E, Flexeder C, Hoffmann B, Lehmann I et al. Cesarean delivery and risk of childhood obesity. The Journal of pediatrics 2014; 164(5): 1068–1073.e2. [PubMed: 24508442]
23. Barros FC, Matijasevich A, Hallal PC, Horta BL, Barros AJ, Menezes AB et al. Cesarean section and risk of obesity in childhood, adolescence, and early adulthood: evidence from 3 Brazilian birth cohorts. The American journal of clinical nutrition 2012; 95(2): 465–70. [PubMed: 22237058]
24. Carrillo-Larco RM, Miranda JJ, Bernabe-Ortiz A. Delivery by caesarean section and risk of childhood obesity: analysis of a Peruvian prospective cohort. PeerJ 2015; 3: e1046. [PubMed: 26137427]
25. Chu DM, Ma J, Prince AL, Antony KM, Seferovic MD, Aagaard KM. Maturation of the infant microbiome community structure and function across multiple body sites and in relation to mode of delivery. Nat Med 2017; 23(3): 314–326. [PubMed: 28112736]
26. Reyman M, van Houten MA, van Baarle D, Bosch A, Man WH, Chu M et al. Impact of delivery mode-associated gut microbiota dynamics on health in the first year of life. Nat Commun 2019; 10(1): 4997. [PubMed: 31676793]
27. Fouhy F, Watkins C, Hill CJ, O'Shea CA, Nagle B, Dempsey EM et al. Perinatal factors affect the gut microbiota up to four years after birth. Nat Commun 2019; 10(1): 1517. [PubMed: 30944304]
28. Cox LM, Yamanishi S, Sohn J, Alekseyenko AV, Leung JM, Cho I et al. Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. Cell 2014; 158(4): 705–721. [PubMed: 25126780]
29. Whitt J, Woo V, Lee P, Moncivaiz J, Haberman Y, Denson L et al. Disruption of Epithelial HDAC3 in Intestine Prevents Diet-Induced Obesity in Mice. Gastroenterology 2018; 155(2): 501–513. [PubMed: 29689264]
30. Kozyrskyj AL, Kalu R, Koleva PT, Bridgman SL. Fetal programming of overweight through the microbiome: boys are disproportionately affected. J Dev Orig Health Dis 2016; 7(1): 25–34. [PubMed: 26118444]
31. Weger BD, Gobet C, Yeung J, Martin E, Jimenez S, Betrisey B et al. The Mouse Microbiome Is Required for Sex-Specific Diurnal Rhythms of Gene Expression and Metabolism. Cell Metab 2019; 29(2): 362–382 e8. [PubMed: 30344015]

Table 1.

Participant characteristics overall and according to mode of delivery and type of labor

Characteristic	Overall	4-category mode of delivery and type of labor				
		Vaginal	Cesarean delivery spontaneous labor	Cesarean delivery induced labor	Cesarean delivery no labor	
	1443	1110 (77%)	155 (11%)	74 (5%)	99 (7%)	P-value
Mother						
Age, years	32.1 (5.2)	32.0 (5.3)	32.1 (4.5)	32.1 (5.5)	34.0 (4.0)	0.003
Pre-pregnancy BMI, kg/m^2	24.8 (5.3)	24.5 (5.0)	25.3 (5.7)	26.9 (6.2)	26.4 (6.7)	<.0001
Race/ethnicity, %						0.12
Black	217 (15)	159 (14)	21 (14)	18 (24)	17 (17)	
Hispanic	96 (7)	74 (7)	13 (8)	2 (3)	7 (7)	
White	991 (69)	774 (70)	98 (63)	50 (68)	66 (67)	
Other	139 (10)	103 (9)	23 (15)	4 (5)	9 (9)	
College graduate, %						0.69
No	452 (31)	355 (32)	45 (29)	19 (26)	31 (31)	
Yes	991 (69)	755 (68)	110 (71)	55 (74)	68 (69)	
Nulliparous, %						<.0001
No	757 (52)	595 (54)	60 (39)	23 (31)	76 (77)	
Yes	686 (48)	515 (46)	95 (61)	51 (69)	23 (23)	
Household income >$70K, %						0.26
No	482 (37)	355 (35)	63 (43)	28 (41)	34 (35)	
Yes	836 (63)	646 (65)	84 (57)	40 (59)	64 (65)	
Smoking status, %						0.43
Never	993 (69)	759 (69)	106 (69)	52 (70)	74 (76)	
Former	284 (20)	221 (20)	32 (21)	11 (15)	19 (19)	
During pregnancy	160 (11)	126 (11)	16 (10)	11 (15)	5 (5)	
Total gestational weight gain, kg	15.6 (5.5)	15.5 (5.3)	15.9 (6.0)	17.0 (6.7)	14.8 (5.3)	0.05
Child						
Sex, %						0.79
Male	736 (51)	560 (50)	84 (54)	40 (54)	49 (49)	
Female	707 (49)	550 (50)	71 (46)	34 (46)	50 (51)	
Birthweight, gm	3483 (567)	3475 (526)	3439 (766)	3540 (623)	3597 (585)	0.12
Gestation length, wk	39.5 (1.8)	39.5 (1.7)	39.2 (2.6)	40.1 (1.9)	38.9 (1.4)	<.0001
Birthweight for gestational age z-score	0.20 (0.96)	0.16 (0.93)	0.21 (1.08)	0.23 (0.99)	0.54 (1.00)	0.003
Early childhood (median 3.2 y)						
BMI z-score	0.46 (1.03)	0.40 (1.00)	0.56 (1.02)	0.84 (1.01)	0.68 (1.19)	0.001
Waist circumference, cm	51.3 (3.7)	51.1 (3.6)	51.5 (3.3)	52.5 (4.0)	52.5 (4.9)	0.001
SS+TR, mm	16.7 (4.3)	16.5 (4.2)	16.8 (4.4)	17.5 (4.6)	18.2 (5.2)	0.003

		4-category mode of delivery and type of labor				
Characteristic	**Overall**	**Vaginal**	**Cesarean delivery spontaneous labor**	**Cesarean delivery induced labor**	**Cesarean delivery no labor**	
	1443	**1110 (77%)**	**155 (11%)**	**74 (5%)**	**99 (7%)**	**P-value**
Mid-childhood (median 7.7 y)						
BMI z-score	0.39 (1.00)	0.35 (1.00)	0.42 (0.96)	0.78 (0.89)	0.62 (1.03)	0.01
Waist circumference, cm	60.0 (8.3)	59.9 (8.1)	59.3 (7.1)	62.1 (9.6)	61.5 (10.8)	0.10
SS+TR, mm	19.9 (9.8)	19.7 (9.8)	19.2 (7.3)	21.6 (10.9)	21.9 (12.3)	0.13
Early teen (median 12.9 y)						
BMI z-score	0.38 (1.06)	0.33 (1.05)	0.42 (1.07)	0.86 (0.90)	0.54 (1.11)	0.005
Waist circumference, cm	73.3 (11.6)	72.9 (11.3)	73.2 (11.0)	76.8 (12.3)	75.3 (14.3)	0.05
SS+TR, mm	28.3 (13.7)	27.8 (13.4)	28.1 (13.6)	31.5 (15.4)	31.2 (15.8)	0.07

Abbreviations: BMI, body mass index; SS+TR, sum of subscapular and triceps skinfold thicknesses N=1443 were included in analysis cohort with vaginal delivery (N=1110) v. cesarean delivery (N=333). N=5 with cesarean deliveries had missing type of labor and were not included in this table.

Chi-square p-values for categorical characteristics; linear regression overall type-III p-values for continuous characteristics.

Table 2.

Associations of mode of delivery with measures of adiposity in children between 2.8 and 16.6 years of age in Project Viva (GEE models).

Adiposity measures	Mode of delivery	Model 1[a]		Model 2[b]	
		adj-β (95% CI)	P-value	adj-β (95% CI)	P-value
BMI z-score	Cesarean (CS) vs. vaginal	0.25 (0.13, 0.37)	<.0001	0.15 (0.04, 0.26)	0.01
	CS spontaneous labor	0.15 (−0.01, 0.31)	0.06	0.08 (−0.07, 0.23)	0.30
	CS induced labor	0.45 (0.24, 0.66)	<.0001	0.27 (0.07, 0.47)	0.01
	CS no labor	0.25 (0.04, 0.46)	0.02	0.16 (−0.04, 0.35)	0.11
	Vaginal	0.0 (ref)		0.0 (ref)	
Waist circumference, cm	Cesarean vs. vaginal	1.27 (0.36, 2.17)	0.01	0.50 (−0.34, 1.34)	0.24
	CS spontaneous labor	0.39 (−0.63, 1.40)	0.46	−0.12 (−1.09, 0.85)	0.80
	CS induced labor	2.33 (0.48, 4.18)	0.01	0.97 (−0.82, 2.76)	0.29
	CS no labor	1.85 (0.01, 3.69)	0.05	1.07 (−0.60, 2.74)	0.21
	Vaginal	0.0 (ref)		0.0 (ref)	
SS+TR, mm	Cesarean vs. vaginal	1.24 (0.19, 2.29)	0.02	0.47 (−0.52, 1.46)	0.35
	CS spontaneous labor	0.26 (−0.98, 1.49)	0.68	−0.25 (−1.44, 0.93)	0.67
	CS induced labor	2.15 (0.00, 4.29)	0.05	0.76 (−1.29, 2.82)	0.47
	CS no labor	2.15 (0.12, 4.18)	0.04	1.40 (−0.48, 3.27)	0.14
	Vaginal	0.0 (ref)		0.0 (ref)	

Abbreviations: GEE indicates generalized estimating equations; BMI, body mass index; SS+TR, sum of subscapular and triceps skinfold thicknesses.

[a.] Model 1. Adjusted for maternal age, education and race/ethnicity and child age and sex

[b.] Model 2. Model 1 + pre-pregnancy BMI and gestational weight gain rate (total kg/weeks of gestation)

Author Manuscript

Author Manuscript

Author Manuscript

Table 3.

Associations of model of delivery with measures of adiposity in children between 2.8 and 16.6 years of age in Project Viva (GEE models): Female vs. Male

	Overall		**Female**		**Male**		**Sex interaction**
	adj-β (95% CI)	**P-value**	**adj-β (95% CI)**	**P-value**	**adj-β (95% CI)**	**P-value**	**P-value**
Cesarean v. vaginal (reference)							
BMI z-score	0.15 (0.04, 0.26)	0.01	0.05 (−0.10, 0.19)	0.54	0.25 (0.10, 0.41)	0.002	0.08
Waist circumference, cm	0.50 (−0.34, 1.34)	0.24	−0.13 (−1.23, 0.98)	0.82	1.13 (−0.08, 2.34)	0.07	0.20
SS+TR, mm	0.47 (−0.52, 1.46)	0.35	−0.02 (−1.37, 1.33)	0.98	1.04 (−0.35, 2.43)	0.14	0.35

Abbreviations: GEE indicates generalized estimating equations; BMI, body mass index; SS+TR, sum of subscapular and triceps skinfold thicknesses

Multivariable model adjusted for maternal age, education and race/ethnicity, pre-pregnancy BMI, gestational weight gain rate (total kg/weeks of gestation), and child age and sex

Table 4.

Associations of mode of delivery with measures of adiposity in children between 2.8 and 16.6 years of age in Project Viva (GEE models): among cesarean delivered children only.

Adiposity measures	Mode of delivery	Model 1[a]		Model 2[b]	
		adj-β (95% CI)	P-value	adj-β (95% CI)	P-value
BMI z-score	Cesarean (CS) spontaneous labor	−0.10 (−0.36, 0.15)	0.43	−0.09 (−0.32, 0.15)	0.46
	CS induced labor	0.20 (−0.09, 0.49)	0.18	0.12 (−0.16, 0.39)	0.41
	CS no labor	0.0 (ref)		0.0 (ref)	
Waist circumference, cm	CS spontaneous labor	−1.52 (−3.65, 0.60)	0.16	−1.34 (−3.28, 0.60)	0.18
	CS induced labor	0.59 (−1.98, 3.15)	0.66	−0.02 (−2.51, 2.48)	0.99
	CS no labor	0.0 (ref)		0.0 (ref)	
SS+TR, mm	CS spontaneous labor	−1.78 (−4.12, 0.56)	0.14	−1.64 (−3.82, 0.53)	0.14
	CS induced labor	0.18 (−2.68, 3.03)	0.90	−0.54 (−3.31, 2.23)	0.70
	CS no labor	0.0 (ref)		0.0 (ref)	

Abbreviations: GEE indicates generalized estimating equations; BMI, body mass index; SS+TR, sum of subscapular and triceps skinfold thicknesses

[a.] Model 1. Adjusted for maternal age, education and race/ethnicity and child age and sex

[b.] Model 2. Model 1 + pre-pregnancy BMI and gestational weight gain rate (total kg/weeks of gestation)

P-values for 4-category exposure are pairwise (v. vaginal).