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Abstract

Background: Cesarean delivery has been associated with later adiposity, perhaps via early programming or perhaps because of residual confounding by maternal or birth characteristics.

Objectives: Examine associations of cesarean delivery with adiposity and cardio-metabolic biomarkers.

Methods: Observational analysis of 15,069 children in the PROBIT cohort in Belarus. We examined measures of child anthropometry and blood pressure at 6.5, 11.5, and 16 years and fasting blood (11.5 years).

Results: Cesarean-delivered children were slightly heavier at 6.5 (mean BMI 15.8 vs. 15.6 kg/m²), 11.5 (18.4 vs. 18.2), and 16 years (21.5 vs. 21.3). After adjustment for prenatal characteristics including maternal 3rd trimester BMI, however, we observed no association of cesarean vs. vaginal delivery with child BMI (β 0.05 kg/m²; 95%CI: -0.03, 0.14), sum of skinfolds (0.14 mm; -0.13, 0.42), waist circumference (-0.07 cm; -0.23, 0.10), obesity (OR 0.99; 0.76, 1.29), or systolic (-0.20 mmHg; -0.70, 0.30) or diastolic (-0.17 mmHg, -0.60, 0.26) blood pressure at 6.5 years; results were similar at 11.5 and 16 years. At 11.5 years, we observed a modest association of cesarean delivery with fasting insulin (0.33 mU/L; 0.00, 0.65).

Conclusions: Cesarean delivery had little or no association with adiposity or related cardio-metabolic biomarkers in childhood. Adjustment for maternal BMI attenuated all outcome effect estimates.

Introduction

Cesarean delivery rates remain high and variable across hospitals, regions and countries worldwide, with rates >40% in some settings and as low as <10% elsewhere.¹ These variations suggest that many cesarean deliveries are not medically indicated.^{2,3} A thorough understanding of the potential short- and longer-term maternal and offspring health risks associated with cesarean delivery is required to inform pre-conception counseling, medical decision-making and public health policy.

While operative delivery may be life-saving in some circumstances, adverse maternal and short-term offspring health consequences of cesarean delivery are also well-established and include greater risk of cardiac arrest, emergency hysterectomy, and newborn respiratory complications.^{4,5} Concern is growing that cesarean delivery may adversely affect long-term offspring health, including risk of atopic conditions such as asthma and allergic rhinitis.^{6,7} Cesarean delivery may also be a risk factor for child obesity.⁸⁻¹¹ Two meta-analyses, summarizing data from 24 studies, have reported a higher risk of obesity for offspring of cesarean delivery (pooled OR [95% CI] 1.22 [1.05, 1.42] and 1.33 [1.19, 1.48]).^{8,10} The relationship between mode of delivery and child health may be mediated by the effects of cesarean delivery on the development of the offspring intestinal microbiome, which may influence health either through host-microbial interactions¹² or through changes in host cell development or function.¹³ Others theorize that the absence of one or more stages of labor in cesarean delivery could program offspring endocrine function through epigenetic^{14,15} or hormonal mechanisms.^{16,17} Methodologic limitations of prior studies include potential selection bias resulting from case-control designs, small sample sizes in several studies, and lack of adjustment for maternal body composition, a key potential confounder.

Confirmation that cesarean delivery is a risk factor for child obesity would have implications for public health efforts targeting reduction in cesarean delivery, and also for identifying children at higher risk for developing obesity. Our study goal was to determine the extent to which cesarean delivery was associated with child adiposity and related cardio-metabolic biomarkers at 6.5, 11.5, and 16 years, in a large prospective Belarusian cohort of mother-child pairs, nested within the Promotion of Breastfeeding Intervention Trial (PROBIT).

Methods

Details regarding enrollment and follow-up of PROBIT have been reported in detail.¹⁸ In brief, 31 Belarusian maternity hospitals and one affiliated polyclinic (outpatient clinic for routine health care follow-up) per hospital were randomly assigned to a breastfeeding promotion intervention or to usual practice. Mothers and their term (≥ 37 week's gestation) healthy singletons weighing at least 2500 g at birth, with Apgar scores of ≥ 5 at 5 minutes, and who initiated breastfeeding, were recruited between June 1996 and December 1997.

At each polyclinic, a trained pediatrician (a single pediatrician in smaller clinics, two pediatricians in high-volume clinics) conducted interviews and physical examinations when the children reached 1, 2, 3, 6, 9 and 12 months (PROBIT I); 6.5 years (PROBIT II); 11.5 years (PROBIT III); and 16 years (PROBIT IV). Training procedures¹⁹ and details of data collection at the 6.5-year,²⁰ 11.5-year,²¹ and 16-year²² visit have been previously described. A parent or legal guardian provided written informed consent in Russian at enrollment and at follow-up visits. All children provided written assent at 11.5 and 16 years. The study was approved by institutional review boards of Harvard Pilgrim Health Care, the McGill University Health Centre Research

Ethics Board, and the Avon Longitudinal Study of Parents and Children (ALSPAC) Law and Ethics Committee, as well as by the Belarusian Ministry of Health.

Participants

Of the 17,046 mother-child pairs enrolled into PROBIT, 15,069 completed a 6.5-, 11.5-, or 16.5-year child visit. Of the 15,069 children, outcome data were available for 13,889 (81% of 17,046) at 6.5 years, 13,879 (81% of 17,046) at 11.5 years, and 13,557 (80% of 17,046) at 16 years.

Compared to the 1977 pairs unavailable for analysis, mothers of included children were slightly more likely to have completed some post-secondary education (64% vs. 61%) and less likely to have smoked during pregnancy (2.2% vs. 3.2%). Mean birth weight and cesarean delivery rates were the same among included and excluded participants (3.4 kg, 11.6% in both groups).

Exposure: mode of delivery

Mode of delivery was obtained from maternal interviews at the maternity hospital soon after delivery and defined as a two-category variable: cesarean or vaginal delivery.

Outcomes

Specially-trained pediatricians obtained anthropometric measures in duplicate; we used the mean of the two for each measure. We measured standing height at 6.5, 11.5, and 16 years with a wall-mounted stadiometer (Medtechnika, Pinsk, Belarus), and weight at 6.5 years with an

electronic digital scale (Bella 840; Seca Corporation, Hamburg, Germany). At 11.5 and 16 years, we used the Tanita TGF 300GS scale (Tanita Corporation, Japan) with foot-foot bio-impedance to measure weight, fat mass, fat-free (lean) mass, and percent body fat. We measured waist circumference above the iliac crests using a non-stretching measuring tape kept in a horizontal plane.

We calculated body mass, fat mass, and fat-free (lean) mass indices (kg/m^2). We calculated age- and sex-specific BMI percentiles using U.S. Centers for Disease Control and Prevention 2000 reference data²³ and defined obesity as BMI $\geq 95^{\text{th}}$ percentile for age and sex^{24,25} and overweight as BMI $\geq 85^{\text{th}}$ and $< 95^{\text{th}}$ percentile. We measured children's subscapular (SS) and triceps (TR) skinfold thicknesses at 6.5 and 11.5 years and calculated their sum (SS+TR) and ratio (SS:TR) as measures of overall and central adiposity, respectively.²⁶ We measured systolic and diastolic blood pressure in duplicate at 6.5 and 16 years and in triplicate at 11.5 years using a digital oscillometric device (Omron Healthcare, Milton Keynes, United Kingdom) and appropriately sized cuff.²⁰

The blood assays have been previously described.^{18,21,27,28} At 11.5 years, after a minimum 8-hour fast, we measured whole blood glucose with a hand-held glucometer (Advantage Accu-Chek Glucometer, Roche Diagnostics Ltd, Burgess Hill, UK).¹⁸ Additionally, whole blood was collected by finger prick onto Whatman 903 filter paper cards (Whatman plc, Maidstone, UK), dried and stored at -20°C for a median of 1.7 months at each polyclinic, and then transported to a central laboratory for longer-term storage at -80°C .²¹ We measured insulin (Mercodia AB, Sweden)²⁸ and adiponectin (adiponectin human ELISA, EIA4177, DRG International Inc, New Jersey)²⁷ with ELISA kits.

Covariates

From hospital medical records and parental interviews in PROBIT I, we obtained maternal date of birth, smoking during pregnancy, education, place of residence, and offspring birth weight, gestational age, and breastfeeding duration. At a later timepoint, pediatricians abstracted maternal height and weights during pregnancy from medical records and we calculated maternal 3rd trimester BMI as the last weight after 35 weeks gestation in kg divided by height in meters squared.

Statistical Analysis

We used unadjusted and multivariable random effects regression models to assess associations between cesarean delivery and outcomes at 6.5, 11.5, and 16 years. We used a mixed effects models that included a random effect to account for clustering of outcomes within polyclinics.^{30,31} We did not adjust for randomization to intervention or control because we have previously found that study arm did not predict adiposity or cardiometabolic outcomes.^{20,21,22} We used logistic regression to assess associations between cesarean delivery and overweight (BMI 85th to <95th percentile) and obesity (BMI $\geq$ 95th percentile), compared to <85th percentile. We also examined BMI $\geq$ 95th v. <95th percentile and $\geq$ 85th v. <85th percentile and associations were similar (results not shown). In our baseline model, Model 1, we adjusted for child sex and age at outcome. In multivariable Model 2, we additionally adjusted for the following baseline characteristics: maternal age, education, smoking during pregnancy, residence (urban vs. rural and east vs. west Belarus) and child gestational age at birth. Model 3 additionally adjusted for child birth weight and Model 4 additionally controlled for maternal BMI in the 3rd trimester of pregnancy. We conducted all data analyses using SAS version 9.4 (SAS Institute Inc., Cary, NC,

USA). All covariates were complete except maternal BMI in the 3rd trimester had 3,345 missing values. Therefore, we used multiple imputation to impute 50 values for each missing observation and combined model estimates using PROC MIANALYZE in SAS. An alternative approach, including only participants with recorded prenatal weight data (complete case), yielded similar results (data not shown).

Results

Participant characteristics are shown in Table 1. Of the 15,069 deliveries, 11.6% were cesarean and 88.4% were vaginal deliveries. Cesarean delivery was associated with higher maternal education level, urban residence, and higher mean maternal BMI. Compared to infants delivered vaginally, cesarean-delivered infants were more likely to be male (54.8 vs. 51.6%) and were slightly heavier at birth (mean birth weight 3.49 vs. 3.43 kg).

In unadjusted analyses, compared with children delivered vaginally, those delivered by cesarean section had a slightly higher mean BMI and sum of skinfolds and higher rates of overweight and obesity at 6.5 and 11.5 years. At 16 years, the adiposity outcomes did not differ by mode of delivery (Table 2). Mean systolic or diastolic blood pressure, fasting blood glucose, and adiponectin level at 11.5 years did not differ by mode of delivery. Mean insulin level at 11.5 years was slightly higher among cesarean-delivered children (5.8 vs. 5.5 mU/L).

Results of multivariable models are shown in Table 3. After adjustment for child sex and age (Model 1), cesarean delivery was associated with higher child BMI, sum of skinfolds, and waist circumference at 6.5 and 11.5 years. Further adjustment for maternal age, education, smoking during pregnancy, stratum-level variable, and gestational age (Model 2) and birth

weight (Model 3) slightly attenuated these relationships. Additional adjustment for maternal BMI (Model 4) rendered these associations null. At 11.5 years, cesarean delivery was associated with a 0.19 kg/m² higher FMI (95% CI 0.08, 0.30, Model 3); further adjustment for maternal BMI (Model 4) attenuated the effect estimate to 0.09 kg/m² (95% CI -0.02, 0.21). Cesarean delivery was associated with a 0.38 mU/L higher insulin level (95% CI 0.06, 0.71, Model 3); further adjustment for maternal BMI (Model 4) attenuated the effect estimate to 0.33 mU/L (95% CI 0.00, 0.65). Cesarean delivery was not associated with subscapular to triceps skinfold ratio, systolic or diastolic blood pressure, or fasting blood glucose or adiponectin levels in Models 1 to 4. All the 16-year results were null in Models 1 to 4.

In logistic regression analyses adjusting for Model 1 and 2 covariates, cesarean delivery was associated with higher odds of overweight at 6.5 years (OR 1.23, 95% CI 1.02, 1.47); after full adjustment (Model 4), the association was attenuated and the confidence interval spanned the null (OR 1.09, 95% CI 0.90, 1.31). Nor did we observe a significant adjusted association between mode of delivery and odds of obesity at 6.5 years, or with odds of overweight or obesity at 11.5 years or 16 years.

Discussion

In this large prospective cohort, cesarean delivery was associated with higher child BMI, sum of skinfolds, percent body fat, and fat mass index at 6.5 and 11.5 years after adjustment for several maternal and child characteristics; however, further adjustment for maternal BMI substantially attenuated these associations. We also found no independent association between cesarean delivery and overweight or obesity at 6.5 or 11.5 years. All associations with the 16-year outcomes were estimated with 95% CIs that spanned the null. The associations of cesarean

delivery with fasting insulin at 11.5 years was modest but remained after adjustment for maternal BMI. These results suggest little or no independent association between cesarean delivery and childhood adiposity and cardiometabolic measures, and that the associations are strongly confounded by prenatal characteristics, especially maternal BMI.

Cesarean delivery has the potential to affect obesity risk through multiple mechanisms. Animal³² and human data³³ show that the development and composition of the intestinal flora differs between cesarean-delivered vs. vaginally-delivered offspring, and these alterations have been hypothesized to lead to long-lasting effects on host metabolism and body composition. The composition of the intestinal microbial community may increase capacity to harvest dietary energy or affect host epithelial and endocrine cell function in ways that promote inflammation, insulin resistance, and fat deposition.^{12,13} Alternatively, the absence of labor-induced changes in maternal and placental hormones and inflammatory cytokines might influence the development and function of the hypothalamic-pituitary-adrenal axis,¹⁶ or epigenetically modify the expression of key genes.^{14,34}

Two studies have reported on associations of cesarean delivery with biomarkers of metabolic risk in young adults. A Brazilian cohort study found no differences in lipids, glucose, or markers of insulin resistance at age 23-25 years, despite higher BMI among young adults born by cesarean.³⁵ Among Danish young adults (age 20 years), birth by cesarean was related to higher total cholesterol and LDL cholesterol, leptin and Apo-B levels. No association was found with blood pressure, insulin, adiponectin, triglycerides, HDL cholesterol or Apo-A.³⁶ As far as we are aware, our study is the first to report on the association of cesarean delivery with several blood biomarkers related to obesity in children. Cesarean delivery was modestly associated with higher fasting insulin levels even after full adjustment, but not with glucose or adiponectin.

Cesarean delivery also was not associated with any anthropometric or bioimpedance measures of adiposity. While it is possible that cesarean delivery could affect insulin levels without affecting the other measures of adiposity and insulin sensitivity, the lack of consistent associations among the other biomarker and anthropometric outcomes raises the possibility of a chance association. In addition, even after adjusting for measured maternal and child characteristics, residual confounding by unmeasured family lifestyle factors is likely. The effect estimate for fasting insulin (0.33 mU/L) was <5% of the standard deviation, suggesting minimal clinical importance. Further studies using blood biomarkers are needed to confirm these associations.

Our inference that cesarean delivery is not associated with obesity risk is consistent with a report of 3 Brazilian cohorts with follow-up at ages 4, 11, 15, and 23 years,³⁷ a study in the Danish National Birth Cohort with follow-up at age 7 years,³⁸ and a study of age 10-11 year old Canadian children.³⁹ It differs, however, from that of a 2012 systematic review of >240,000 children based on 2 case-control and 7 cohort studies, which observed that cesarean delivery was associated with a modestly increased risk of obesity.¹⁰ The pooled odds ratios for overweight/obesity among cesarean-delivered offspring were 1.32 (95% CI 1.15, 1.51) in children, 1.24 (95% CI 1.00, 1.54) in adolescents, and 1.50 (95% CI 1.02, 2.20) in adults.¹⁰ Other subsequent cohort studies, including our own previous work in a different cohort, have also reported a higher risk of overweight or obesity in childhood^{9,11,40-43} and adulthood^{44,45} associated with cesarean delivery.

Several reasons may explain the discrepancies among studies. One important limitation of several previous studies that reported a higher risk of child or adult obesity with cesarean delivery was the lack of adjustment for maternal BMI,^{43,46-48} a key potential confounder that would likely attenuate effect estimates as shown in our findings and by others.^{39,41} In studies

without adjustment for maternal BMI, the observed associations between cesarean delivery and child obesity might plausibly be explained by confounding by maternal BMI. In our study, mothers who had undergone cesarean section (vs. vaginal delivery) had a mean BMI that was 1.2 kg/m² higher in the 3rd trimester of pregnancy. Also, we used measured weights recorded contemporaneously in the medical record. Compared to women with a normal BMI, pregnant women with overweight or obesity are estimated to be 50-100% more likely to require a cesarean delivery,⁴⁸ and are more likely to have offspring with obesity.⁵⁰ A recent study in a longitudinal U.K. cohort found that cesarean delivery was associated with a higher odds of overweight or obesity at multiple age time points ranging from 38 months to 15 years in analyses controlling for multiple confounders, including maternal pre-pregnancy BMI. However, the association was present only among children born to overweight/obese mothers, but not those born to normal-weight mothers.⁴⁰ The authors speculated that unmeasured residual confounding might be greater among children of obese mothers. Future studies analyzing this association should include careful control for maternal pre-pregnancy or pre-birth BMI.

In addition to the lack of adjustment for measured maternal BMI, published studies vary in their adjustment for other covariates, study quality, and sample size. When the meta-analysis by Li et al¹⁰ was restricted to 4 studies deemed to be of higher quality, the pooled OR was 1.18 (95% CI 1.09, 1.27), which was lower than the overall OR of 1.33 (95% CI 1.19, 1.48) based on all 9 studies. Several studies were much smaller in size than ours. The largest studies (N>25,000) with covariate adjustment that include maternal BMI have reported low⁴² or null odds ratios.³⁸

Other potential explanations for discrepant findings across studies include differences in cesarean delivery rates and obesity prevalence. In our prior study within the US Project Viva cohort, we adjusted for several of the same confounders as used in the PROBIT analyses,

including maternal BMI based on self-reported weight and height.⁹ Among Project Viva children, 22.6% were delivered by cesarean, compared with 11.6% in PROBIT; 26% of Viva children were already overweight or obese at age 3 years, compared with 13.2% at 6.5 years, 15.2% at 11.5 years, and 13.8% at 16 years in PROBIT. In Project Viva, we found that cesarean section (v. vaginal delivery) was associated with higher odds of obesity (OR 2.10, 95% CI 1.36, 3.23) and higher BMI z-score (0.20 units; 95% CI 0.07, 0.33) at age 3 years. Differences in age at the time of outcome may also explain discrepant findings, as follow-up analyses in Project Viva children at older ages did not see persistent associations into adolescence (data not published). However, Li et al¹⁰ reported similar pooled odds ratios for studies conducted in children, adolescents and adults. Different diet, physical activity, and other environmental factors that vary across study settings may have modified the observed associations between mode of delivery and child obesity. For example, it may be that effect modification exists such that a second “hit” coming from an obesogenic pre- or postnatal obesogenic environment is required to reveal the increase in childhood obesity risk related to cesarean delivery.

Study strengths include our use of a large, well-characterized, prospective cohort with little attrition; data on several obesity-related anthropometric measures and cardiometabolic biomarkers; and adjustment for many potential confounding variables. Our use of maternal BMI in the 3rd trimester of pregnancy as a proxy for pre-pregnancy BMI is a limitation since it incorporates both pre-pregnancy weight and gestational weight gain and we can’t tease out their individual effects on the association. However, both occurred temporally before our exposure. Furthermore, the fact that we based it on measured rather than self-reported or remotely-recalled values is a strength. Other limitations are that we lack information on the indication for cesarean delivery, whether the cesarean was planned or unplanned, and antibiotic use at the time of

delivery or during childhood. Finally, rates of obesity in Belarus are low compared with many other countries, so our results may not be generalizable to settings with higher prevalence of maternal or child obesity.

Conclusion

In contrast to several previous reports, cesarean delivery was not associated with a higher risk of childhood obesity, or with several other measures of cardio-metabolic risk, in this large prospective cohort of Belarusian children. Adjustment for maternal BMI attenuated all outcome effect estimates, suggesting that confounding by maternal BMI might explain some of the positive associations observed in the literature.

Conflicts of interest

Authors declare no conflicts of interest.

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Author contributions

All authors had full access to all 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. SRS and

SYH drafted the manuscript. SRS conducted the statistical analysis. RM, MK, RP, NB, KV, and EO participated in data acquisition. RM, MK, RP, NB, KV, JT, and EO provided administrative, technical, or material support. RM, MK, RP, NB, KV, and EO directed study operations. All authors contributed to data interpretation and to critical revision of the manuscript and approved the final version.

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