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Association of elective cesarean delivery with metabolic measures in childhood: A prospective cohort study in China

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Abstract *Background and aims:* Cesarean delivery may increase the risk of childhood obesity, a precursor of metabolic syndrome (MetS). We aimed to investigate the association of elective cesarean delivery (ElCD) with MetS and its components in a Chinese birth cohort.
Methods and results: This cohort included 1467 children (737 delivered by ElCD and 730 by spontaneous vaginal delivery [SVD]) who were followed up at the age of 4–7 years in 2013. MetS was defined as the presence of ≥3 components: central obesity, hypertriglyceridemia, low high-density lipoprotein (HDL), high fasting glucose, and hypertension. Of the 1467 children, 93 (6.3%) were categorized as having MetS: 50 (6.8%) delivered by ElCD and 43 (5.9%) by SVD. After multivariable adjustment, ElCD was not associated with MetS (adjusted odds ratio [AOR] 1.15, 95% confidence interval [CI] 0.74, 1.78) or certain components including hypertriglyceridemia, low HDL, and high fasting glucose but was associated with central obesity (AOR 1.33, 95% CI 1.02, 1.72) and hypertension (AOR 1.50, 95% CI 1.15, 1.96), as well as higher levels of total cholesterol (3.43 *vs.* 3.04 mmol/L; $P < 0.001$), low-density lipoprotein–cholesterol (1.77 *vs.* 1.67 mmol/L, $P = 0.002$), fasting glucose (5.08 *vs.* 5.02 mmol/L, $P = 0.022$), systolic (97.57 *vs.* 94.69 mmHg, $P < 0.001$)/diastolic blood pressure (63.72 *vs.* 62.24 mmHg, $P < 0.001$), and BMI (15.46 *vs.* 14.83 kg/m^2, $P < 0.001$) than SVD.
Conclusions: ElCD is not associated with MetS in early to middle childhood but is associated with its components including central obesity and hypertension, as well as various continuous indices.

Introduction

Metabolic syndrome (MetS) is first defined in adulthood as a cluster of metabolic abnormalities including dyslipidemia, central obesity, hypertension, and high fasting glucose. As obesity has become prevalent in children in the past decades, even in those prepubertal children [1], MetS has been already described in these populations [2]. The prevalence of childhood MetS was 5.5% in Europe [3], 8.7% in Colombia [4], 4.2%–9.2% in the United States [5–7], and 3.4%–6.6% in China [8–10]. The occurrence of MetS in

Abbreviations: MetS, metabolic syndrome; BMI, body mass index; ElCD, elective cesarean delivery; SVD, spontaneous vaginal delivery; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation; ORs, odds ratios; CIs, confidence intervals.

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children has been associated with an increased risk of developing cardiovascular diseases and type 2 diabetes in adulthood [11,12], hence making the early identification of risk factors associated with MetS a key public health priority.

Emerging evidence suggests that MetS may originate in early life [13,14]. Cesarean delivery produces dramatic changes in perinatal physiology [15,16] and may be associated with childhood obesity [17], a prominent precursor of MetS [18], though few studies have directly examined the association between cesarean birth and MetS. One study observed an association between cesarean delivery and MetS among mid-life adults [19], while two additional studies conducted in Brazilian young adults found an association of cesarean delivery with higher body mass index (BMI), systolic blood pressure, triglycerides, and fat mass but not with other metabolic measures [20,21]. No study has examined the association in early childhood, although previous studies have shown that cesarean delivery was associated with an increased risk of offspring overweight or adiposity as early as the age of 12 months [22,23]. Furthermore, unraveling the relationship between cesarean delivery and MetS has proven to be challenging owing to the potential confounding bias caused by pregnancy complications [24–26]. Exploring associations among children born by non-medically indicated elective cesarean delivery (ElCD) is one approach that could control for these potential confounding effects.

In this prospective birth cohort study, we aimed to examine the association of ElCD with MetS and its components in early to middle childhood (aged 4–7 years). Furthermore, we used non-medically indicated ElCD as the exposure to control for confounding by pregnancy complications.

Methods

Study design and participants

This cohort study involved a subsample of children whose mothers participated in a randomized controlled trial in five counties (Yuanshi, Mancheng, Fengrun, Laoting, and Xianghe) of northern China from May 2006 to April 2009 [27]. Mothers were randomly assigned to receive daily folic acid, iron-folic acid, or iron-folic acid plus 13 additional vitamins and minerals from early pregnancy to delivery. Their infants were further followed up from birth to the age of 1 year, with 17,613 of them still alive. All children had available maternal and antenatal data [27]. Between June and October 2013, follow-up examinations were performed for a limited number of participants in the original trial, focusing on children who had been born in Yuanshi and Mancheng, two adjacent counties with similar dietary habits and socioeconomic profiles. We performed two sampling campaigns among children born by ElCD or spontaneous vaginal delivery (SVD). This cohort consisted of 1362 children, selected at random, which include 182 ElCD and 364 SVD children (1:2 ratio) from Yuanshi County and 204 ElCD and 612 SVD children (1:3 ratio) from Mancheng County. Some of the selected children, particularly those born by ElCD, were lost to follow-up, which was likely to be due to migration out of the study area [28]. Subsequent inclusion of the remaining 1219 ElCD children from Mancheng County was therefore performed to ensure sufficient statistical power. Among the 2581 children in this initial cohort, 1107 were lost to follow-up due to migration outside the study area, refusal to participate, or other reasons. Therefore, this follow-up study consisted of 1474 participants, of whom seven were further excluded due to unobtainable blood samples. In total, 1467 children aged 4–7 years were left in the analysis (Figure S1). The characteristics of the included ($n = 1467$) and excluded children ($n = 1114$) are shown in Table S1. The included and excluded children had similar maternal BMI in early pregnancy, Han ethnicity, maternal micronutrient supplementation during pregnancy, gestational age, and sex but showed significant difference in terms of maternal age, educational level, farmer occupation, and birthweight. In particular, the excluded children were more likely to have been delivered by ElCD than the included children (77.9% *vs.* 50.2%, $P < 0.001$).

The study was approved by the Institutional Review Board/Human Subjects Committee at Peking University Health Science Center (IRB00001052-13008; date of approval: 12-03-2013). All parents or guardians gave written informed consent.

Exposure and covariates

Information about the mode of delivery and maternal/perinatal covariates was extracted. Modes of delivery were categorized as SVD, assisted breech, breech extraction, vacuum, forceps, ElCD (before the onset of labor), emergency cesarean delivery (after the onset of labor), or other. For ElCD, indications were further delineated based on maternal request, fetal distress, cephalopelvic disproportion, breech/transverse presentation, maternal complications, or other factors. Maternal/perinatal covariates included micronutrient supplementation, maternal age, educational level, ethnicity, occupation, BMI in early pregnancy, offspring sex, birthweight, and gestational age. Sex-adjusted birthweight-for-gestational age z scores were subsequently calculated according to the reference values of Chinese newborns [29]. At the time of follow-up, information about each child's parental hypertension, hyperlipidemia, or hyperglycemia was collected by trained staff using a standard questionnaire.

Outcomes

Anthropometric measurements

Weight and height for all children were measured by wearing light indoor clothing without shoes by using periodically calibrated scales by trained staff. BMI (kg/m^2) was calculated as weight in kilograms divided by height in meters squared. Age- and sex-specific z scores for BMI were calculated according to the growth curves for Chinese children [30]. Waist circumference was measured

with a plastic anthropometric tape midway between the lowest portion of the rib margin and the iliac crest. Resting systolic and diastolic blood pressure was measured in children in a seated position using an Omron electronic blood pressure monitor (HEM-1020; http://www.omron.com/). All anthropometric indices were measured twice, and the average was used in the analysis.

Biochemical measurements

Fasting glucose was measured in the morning using a finger-prick blood glucose monitor (Accu-Chek, Roche Diagnostics, Germany). A fasting venous blood sample was also collected from each child and processed within 4 h by centrifugation to obtain plasma. Plasma was then aliquoted and stored at −20 °C at the local hospital for ~1 month, after which it was shipped on dry ice to the Ministry of Health Key Laboratory of Reproductive Health, where it was stored at −80 °C until analysis. Total cholesterol, triglycerides, high-density lipoprotein (HDL)−cholesterol, and low-density lipoprotein (LDL)−cholesterol were measured by enzymatic colorimetric methods on a Roche/Hitachi Cobas 6000 analyzer (Roche Diagnostics GmbH, Mannheim, Germany) that could automatically calculate the analyte concentration for each sample in mmol/L. A variety of commercially available kits were used to assess total cholesterol (Cholesterol Gen.2, Roche Diagnostics GmbH, Germany), triglycerides (Triglycerides, Roche Diagnostics), HDL−cholesterol (HDL-Cholesterol plus 3rd generation, Roche Diagnostics), and LDL−cholesterol (LDL-Cholesterol plus 2nd generation, Roche Diagnostics). The intra- and inter-assay coefficients of variation were 1.1% and 1.6% for total cholesterol, 1.6% and 1.9% for triglycerides, 0.6% and 0.9% for HDL−cholesterol, and 0.9% and 1.9% for LDL−cholesterol, respectively.

MetS definition

MetS components were defined according to the criteria proposed by de Ferranti et al. [6], which were extrapolated from the Third Report of the Adult Treatment Panel National Cholesterol Education Program (NCEP-ATP III) [31]. Hypertriglyceridemia was defined as fasting triglycerides ≥1.1 mmol/L, low HDL as HDL−cholesterol <1.3 mmol/L, high fasting glucose as fasting glucose ≥6.1 mmol/L, central obesity as waist circumference >75th age- and sex-specific percentile of that for Chinese preschool children [32], and hypertension as systolic or diastolic blood pressure >90th percentile for age, sex, and height according to the clinical practice guideline for screening and management of high blood pressure in children and adolescents [33]. A child with ≥3 components was categorized as having MetS.

Another definition of MetS for prepubertal children aged 2−11 years was further applied, which was developed from the Identification and prevention of dietary- and lifestyle-induced health effects in children and infants (IDEFICS) study [3]. According to this definition, hypertriglyceridemia, high fasting glucose, central obesity, and hypertension were defined as the values > 90th percentile and low HDL as the values < 10th percentile. Children having ≥3 components would require close monitoring.

Statistical analysis

Descriptive data were presented as means (standard deviations, SD) or frequencies (%). Total cholesterol, triglyceride, HDL−cholesterol, LDL−cholesterol, fasting glucose, systolic/diastolic blood pressure, and waist circumference were natural log-transformed before analysis for greater symmetry across data, and back transformation was done to compute means and 95% CIs for these metabolic variables. Differences between ElCD-delivered and SVD-delivered children were examined using Student's *t*-test for continuous variables and chi-square test for categorical variables.

Adjusted mean values of continuous metabolic variables of the two delivery groups were estimated using multivariable generalized linear models. Univariate and multivariable logistic regression analyses were performed to estimate the crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of MetS and its components for children born by ElCD compared with those born by SVD. The covariates in multivariable analyses included maternal age (<25, 25−29, and ≥30 years), education level (high school or above, secondary, and primary or less), BMI in early pregnancy (<18.5, 18.5−24.9, and ≥25.0 kg/m^2), micronutrient supplementation (folic acid, iron-folic acid, and multiple micronutrients), sex (male and female), gestational age (<37 and ≥ 37 wks), sex-adjusted birthweight-for-gestational age z scores (classified into quartiles), age at follow-up visit (as a continuous variable), and maternal gestational weight gain that was calculated by subtracting weight at enrollment from weight at the end of pregnancy and further classified into quartiles with its missing data grouped into a separate category.

All analyses were performed with SPSS 20.0 (SPSS, Inc., Chicago, IL). Statistical tests were two-sided, with $P < 0.05$ indicative of statistical significance.

Results

The study cohort consisted of 1467 children (808 boys and 659 girls) with a mean age of 5.4 (0.7) years and a mean age- and sex-specific BMI z score of 0.10 (1.27). Of them, 737 (50.2%) children were born by ElCD and 730 (49.8%) by SVD. Maternal and children's characteristics, by mode of delivery, are presented in Table 1. The majority of characteristics were similar between groups, with the exception of a higher maternal BMI in early pregnancy and birthweight in children born by ElCD versus those born by SVD.

ElCD and dichotomous MetS components

A total of 93 (6.3%) children were categorized as having MetS: 50 (6.8%) in the ElCD group and 43 (5.9%) in the SVD group ($P = 0.482$). The MetS prevalence was higher in girls than in boys (7.7% *vs.* 5.2%, $P = 0.047$). The prevalence of children identified as having individual and clustered MetS

Table 1 Maternal and children characteristics according to mode of delivery.[a]

Characteristics	SVD (n = 730)	ElCD (n = 737)	*P* Value
Maternal			
Age at delivery, mean (SD), y	23.1 (2.2)	23.1 (2.2)	0.836
BMI at early pregnancy, mean (SD), kg/m^2	21.8 (2.3)	22.3 (2.9)	<0.001
Education, No. (%)			
High school or above	93 (12.7)	106 (14.4)	0.287
Secondary	523 (71.6)	535 (72.6)	
Primary or less	114 (15.6)	96 (13.0)	
Farmer occupation, No. (%)	702 (96.2)	701 (95.1)	0.325
Han ethnicity, No. (%)	725 (99.7)	729 (99.6)	0.660
Micronutrient Supplementation, No. (%)			
Folic acid	236 (32.3)	246 (33.4)	0.823
Iron-folic acid	251 (34.4)	243 (33.0)	
Multiple micronutrients	243 (33.3)	248 (33.6)	
Gestational weight gain, mean (SD), kg	11.0 (4.3)	11.2 (4.1)	0.517
Offspring			
Gestational age (wk), No. (%)			0.407
<37	33 (4.5)	27 (3.7)	
≥37	697 (95.5)	710 (96.3)	
Birthweight (g), No. (%)			<0.001
<2500	9 (1.2)	14 (1.9)	
2500–3999	700 (95.9)	670 (90.9)	
≥4000	21 (2.9)	53 (7.2)	
Sex, No. (%)			
Male	403 (55.2)	405 (55.0)	0.922
Female	327 (44.8)	332 (45.1)	
Sex-adjusted birthweight-for gestational age z score, mean (SD)	−0.27 (0.82)	−0.01 (0.96)	<0.001
Age at follow-up visit, mean (SD), y	5.4 (0.7)	5.5 (0.8)	0.678

ElCD, elective cesarean delivery; SVD, spontaneous vaginal delivery; SD, standard deviation; BMI, body mass index.
[a] Descriptive data are presented as mean (SD) or frequency (%). Differences between delivery modes were examined by Student's t-test for continuous variables and chi-square analyses for categorical variables.

components according to mode of delivery is shown in Fig. 1. Compared with children delivered by SVD, ElCD children exhibited a higher prevalence of central obesity (24.7% *vs.* 18.8%, $P = 0.006$) and hypertension (23.1% *vs.* 16.6%, $P = 0.002$), with no differences seen for hypertriglyceridemia (19.0% *vs.* 16.4%, $P = 0.200$), low HDL (42.1% *vs.* 41.6%, $P = 0.871$), or high fasting glucose (0.7% *vs.* 1.1%, $P = 0.394$). Additionally, prevalence of ≥1 (71.2%

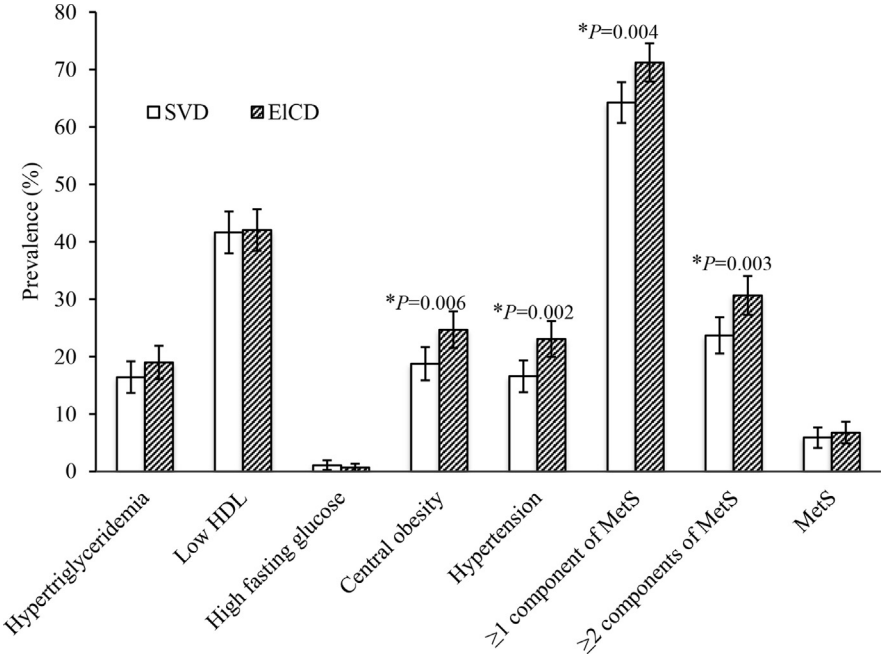

Figure 1 Prevalence estimates and 95% CIs of dichotomous MetS components by mode of delivery. *Significant differences between children born by ElCD and those by SVD ($P < 0.05$). Error bars indicate 95% CIs. CIs, confidence intervals; ElCD, elective cesarean delivery; HDL, high-density lipoprotein; MetS, metabolic syndrome; SVD, spontaneous vaginal delivery.

vs. 64.3%, $P = 0.004$) and of ≥2 MetS components (30.7% *vs.* 49.8%, $P = 0.003$) was higher in children born by ElCD than those born by SVD.

After adjustment for potential confounding factors, children born by ElCD versus those born by SVD were found to be at a higher risk for two individual MetS components: central obesity (adjusted OR 1.33, 95% CI 1.02, 1.72) and hypertension (adjusted OR 1.50, 95% CI 1.15, 1.96) (Table 2). Children born by ElCD were also at a higher risk for having ≥1 (adjusted OR 1.38, 95% CI 1.10, 1.74) and ≥2 MetS components (adjusted OR 1.41, 95% CI 1.11, 1.79). However, ElCD was not associated with an increased risk of MetS per se (adjusted OR 1.15, 95% CI 0.74, 1.78) or of its certain components, including hypertriglyceridemia (adjusted OR 1.25, 95% CI 0.95, 1.65), low HDL (adjusted OR 1.01, 95% CI 0.82, 1.26), and high fasting glucose (adjusted OR 0.58, 95% CI 0.18, 1.86).

To minimize the potential impact of genetic or perinatal confounding effects on risk estimates, sensitivity analyses were performed by excluding children whose parents reported any family history of hypertension/hyperlipidemia/hyperglycemia and by further excluding children whose delivery was indicated by maternal complications and those whose birthweight was ≥4000 g. The estimate for hypertension remained almost unchanged, while the adjusted ORs for central obesity and ≥2 MetS components successively became insignificant (Table 3). In addition, we did not find any significant interactions between sex and delivery mode (all *P* values for interaction tests >0.05).

When we repeated the main analysis using the IDEFICS definition of MetS and its components, the positive association of ElCD with hypertension (adjusted OR 1.57, 95% CI 1.15, 2.14) and ≥2 MetS components (adjusted OR 1.49, 95% CI 1.16, 1.90) persisted, while the association with central obesity and ≥1 component turned out to be insignificant (Table S2).

ElCD and continuous MetS components

Next, we examined the associations between ElCD and individual MetS components, treating clinical outcomes as continuous variables. After adjustment for multivariate confounders, children delivered by ElCD exhibited higher levels of total cholesterol (3.43 *vs.* 3.04 mmol/L, $P < 0.001$), LDL−cholesterol (1.77 *vs.* 1.67 mmol/L, $P = 0.002$), fasting glucose (5.08 *vs.* 5.02 mmol/L, $P = 0.022$), systolic blood pressure (97.57 *vs.* 94.69 mmHg, $P < 0.001$), diastolic blood pressure (63.72 *vs.* 62.24 mmHg, $P < 0.001$), and BMI (15.46 *vs.* 14.83 kg/m^2, $P < 0.001$) relative to SVD (Table 4). Triglycerides and waist circumference did not show significant difference between the two groups ($P > 0.05$). Unexpectedly, the level of HDL−cholesterol was slightly higher in children born by ElCD than in those born by SVD (1.37 *vs.* 1.32 mmol/L, $P = 0.031$). The results remained almost unchanged in sensitivity analyses after excluding children whose parents reported any family history of hypertension/hyperlipidemia/hyperglycemia and after further excluding children whose delivery was indicated by maternal complications or child birthweight ≥4000 g (Table S3).

Discussion

From this prospective cohort study of Chinese children aged 4−7 years, we concluded that ElCD was not associated with childhood MetS or several of its individual components including hypertriglyceridemia, low HDL, and high fasting glucose, but it was significantly associated with increased risks of central obesity and hypertension, as well as clustered assessments including ≥1 and ≥ 2 components. Considering continuous variables, ElCD was further associated with higher levels of various metabolic indices including triglycerides, total cholesterol, LDL−cholesterol, fasting glucose, systolic/diastolic blood pressure, and BMI.

The prevalence estimate of MetS in children aged 4−7 years was 6.3% in the present study, comparable to that of Chinese children aged 7−14 years (6.6%) reported by a previous study that used the same definition of MetS proposed by de Ferranti et al. [8]. The MetS prevalence in our study seemed to be quantitatively higher in children delivered by ElCD (6.8%) than in those by SVD (5.9%), but this difference was not statistically significant.

Table 2 Crude and adjusted ORs (95% CIs) of MetS and its dichotomous components for ElCD compared with SVD.

Outcomes	No. of Cases	Crude OR	P value	Adjusted OR[a]	P value
MetS	93	1.16 (0.76, 1.77)	0.483	1.15 (0.74, 1.78)	0.536
MetS dichotomous components					
Hypertriglyceridemia	260	1.19 (0.91, 1.56)	0.200	1.25 (0.95, 1.65)	0.109
Low HDL	614	1.02 (0.83, 1.25)	0.871	1.01 (0.82, 1.26)	0.908
Central obesity	319	1.42 (1.11, 1.82)	0.006	1.33 (1.02, 1.72)	0.033
High fasting glucose	13	0.62 (0.20, 1.89)	0.398	0.58 (0.18, 1.86)	0.362
Hypertension	291	1.51 (1.16, 1.96)	0.002	1.50 (1.15, 1.96)	0.003
≥1 MetS component	994	1.38 (1.11, 1.72)	0.004	1.38 (1.10, 1.74)	0.006
≥2 MetS components	399	1.42 (1.13, 1.80)	0.003	1.41 (1.11, 1.79)	0.005

ORs, odds ratios; CIs, confidence intervals; ElCD, elective cesarean delivery; SVD, spontaneous vaginal delivery; MetS, metabolic syndrome; HDL, high-density lipoprotein.

[a] Adjusted for maternal age, educational level, BMI in early pregnancy, gestational weight gain, micronutrient supplementation, sex, gestational age, sex-adjusted birthweight-for-gestational age z scores, and age at follow-up visit.

Table 3 Adjusted ORs (95% CIs) of MetS and its dichotomous components for ElCD compared with SVD in sensitivity analyses.[a]

Outcomes	1st sensitivity analysis (n = 1229)[b]	P value	2nd sensitivity analysis (n = 1136)[c]	P value
MetS	1.05 (0.64, 1.73)	0.844	0.86 (0.50, 1.47)	0.583
Dichotomous MetS Components				
Hypertriglyceridemia	1.33 (0.98, 1.80)	0.067	1.26 (0.92, 1.73)	0.145
Low HDL	1.01 (0.79, 1.27)	0.967	0.94 (0.74, 1.20)	0.631
Central obesity	1.24 (0.93, 1.66)	0.139	1.17 (0.86, 1.58)	0.320
High fasting glucose	0.50 (0.11, 2.17)	0.352	0.54 (0.13, 3.37)	0.416
Hypertension	1.52 (1.13, 2.06)	0.006	1.44 (1.05, 1.97)	0.024
≥1 MetS component	1.40 (1.10, 1.80)	0.007	1.31 (1.01, 1.69)	0.043
≥2 MetS components	1.32 (1.01, 1.72)	0.040	1.24 (0.94, 1.63)	0.129

ORs, odds ratios; CIs, confidence intervals; ElCD, elective cesarean delivery; SVD, spontaneous vaginal delivery; MetS, metabolic syndrome; HDL, high-density lipoprotein.

[a] Adjusted for maternal age, educational level, BMI in early pregnancy, gestational weight gain, micronutrient supplementation, sex, gestational age, sex-adjusted birthweight-for-gestational age z scores, and age at follow-up visit.

[b] Sensitivity analysis performed by excluding children whose parents reported any family history of hypertension/hyperlipidemia/hyperglycemia. Among 1467 children, parents of 1262 children had tested for the above-mentioned diseases, resulting in 33 children with and 1229 without a parental history of the diseases. The 1229 children were included in the sensitivity analysis.

[c] Sensitivity analysis performed by further excluding children whose delivery was indicated by maternal complications or child birthweight ≥4000 g. Among the 1136 children included in the 2nd sensitivity analysis, 610 were delivered by SVD without any complications and 526 by ElCD indicated by cephalopelvic disproportion (n = 5), breech/transverse presentation (n = 2), maternal request (n = 219), previous cesarean (n = 2), and other reasons (n = 298; including precious baby, advanced maternal age, and suspected macrosomia). Among the 93 excluded children, 20 were delivered by SVD indicated by macrosomia (n = 19) or premature rupture of membranes (n = 1), and 73 were delivered by ElCD indicated by fetal distress (n = 29), macrosomia (n = 41), fetal distress plus macrosomia (n = 1), and other maternal complications (n = 2).

Table 4 Adjusted mean values (95% CIs) of continuous MetS components according to mode of delivery in children.[a]

Continuous MetS components[b]	SVD (n = 730)	ElCD (n = 737)	*P* Value[c]
Triglycerides, mmol/L	0.75 (0.68, 0.83)	0.80 (0.72, 0.88)	0.025
Total cholesterol, mmol/L	3.04 (2.86, 3.24)	3.43 (3.23, 3.65)	<0.001
HDL−cholesterol, mmol/L	1.32 (1.25, 1.41)	1.37 (1.29, 1.45)	0.031
LDL−cholesterol, mmol/L	1.67 (1.56, 1.79)	1.77 (1.65, 1.89)	0.002
Glucose, mmol/L	5.02 (4.91, 5.13)	5.08 (4.97, 5.19)	0.022
Systolic blood pressure, mmHg	94.69 (92.63, 96.80)	97.57 (95.43, 99.76)	<0.001
Diastolic blood pressure, mmHg	62.24 (60.64, 63.88)	63.72 (62.07, 65.41)	<0.001
Waist circumference, cm	49.97 (49.02, 50.93)	50.20 (49.24, 51.18)	0.054
BMI, kg/m^2	14.83 (14.43, 15.23)	15.46 (15.05, 15.89)	<0.001

CIs, confidence intervals; MetS, metabolic syndrome; SVD, spontaneous vaginal delivery; ElCD, elective cesarean delivery; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index.

[a] Adjusted for maternal age, educational level, BMI in early pregnancy, gestational weight gain, micronutrient supplementation, sex, gestational age, sex-adjusted birthweight-for-gestational age z scores, and age at follow-up visit.

[b] SI conversion factors: To convert the values for glucose to mg/dL, divide by 0.0555; to covert the values for cholesterol to mg/dL, divide by 0.0259; to covert the values for triglycerides to mg/dL, divide by 0.0113.

[c] Significance for the association of delivery mode with continuous MetS components in the multivariable generalized linear models.

Only three studies have directly examined the association between cesarean delivery and metabolic measures, with inconsistent results reported [19–21]. One study using data from the 1958 National Child Development Study in Great Britain found that emergency cesarean delivery rather than ElCD was associated with adult MetS [19]. A second study conducted among Brazilian young adults found that cesarean delivery was associated with higher BMI but not with other metabolic measures; the authors suggested that the null association may have been due to the inclusion of emergency cesarean delivery [20]. The explanation could lend support by a recent study that reported a higher risk of overweight for children delivered by elective cesarean but not for those by emergency cesarean [22], which might be mainly due to absence or presence of membrane rupture and thus different in initial gut microbiome of newborns [34]. Finally, a third study found increased levels of BMI, systolic blood pressure, triglycerides, and fat mass among Brazilian young adults born by cesarean delivery versus those by vaginal delivery [21]. Inconsistencies between these results may be due to differences in cesarean subtypes, study populations, and methods used to measure MetS indices.

Our results were partially consistent with the two studies conducted among Brazilian young adults. We also found that children born by ElCD had higher levels of BMI, systolic/diastolic blood pressure, total cholesterol, LDL−cholesterol, and fasting glucose than children born by SVD. When these metabolic measures were dichotomized, ElCS was further associated with an increased risk of individual MetS components of central obesity and hypertension, as well as increased risk of clusters of ≥1 and ≥ 2 components. However, we did not find significant associations of ElCD with ≥3 components, i.e., MetS per se, or

with certain components including hypertriglyceridemia, low HDL, and high fasting glucose, at least in early childhood. Some indications for ElCD such as gestational diabetes [24], pre-eclampsia [26], and macrosomia [25] were associated with MetS or metabolic disorders in children. Therefore, we performed sensitivity analyses by excluding children whose delivery was indicated by maternal complications or macrosomia and found that the associations of ElCD with hypertension as well as most of continuous MetS indices remained. These findings suggest that the effects of ElCD are somewhat related to the cesarean delivery per se. Our results indicated that children born by ElCD might be more likely to develop metabolic disorders if they follow unhealthy lifestyles, given that they likely have increased risk of hypertension, as well as higher levels of various metabolic indices.

Several pathways may underlie the associations of ElCD with offspring metabolic measures. Variation in the gut microbiome of newborns born by ElCD versus those born by SVD is a compelling explanation. Compared with infants born by ElCD, those born by SVD acquire a greater diversity of bacterial species [15] and more beneficial intestinal microbes [35] through exposure to the maternal vaginal tract. Differences in the composition and quantity of intestinal flora may persist beyond 7 years of age [36], affecting energy uptake, absorption, and storage in the host [37], which may play a key role in the development of obesity, hypertension, and related metabolic disorders [38,39]. Other explanations for the increased risks are that infants born by ElCD exhibit a decreased rate of exclusive breastfeeding that might protect against obesity and hypertension [40–42]. Furthermore, they are also likely to have a lower level of cord blood leptin that is crucial in regulating infancy weight gain and BMI reduction in later life [16,43].

To the best of our knowledge, this is the first prospective study to examine the association of ElCD with metabolic outcomes in children. The availability of detailed prenatal information including both pregnancy-related factors and maternal and offspring characteristics made it possible for us to control for these important confounding factors. However, several limitations of our study should be taken into account. Children born by ElCD from the initial cohort were disproportionately lost to follow-up. If those lost to follow-up had different metabolic outcomes than those included in the study, our estimate of the association would be biased. In addition, the children in our study were born to mothers who participated in a randomized controlled trial, which might not be a good representative sample of the source population. Although the selection bias, if it exists, might not affect the internal validity of our results, studies with more representative populations are needed. Another limitation of this study is the relatively inadequate sample size, which may have limited our ability to detect differences in the rate of MetS between children delivered by ElCD and those by SVD. Assuming a prevalence of MetS of 5.9% in the SVD population, our sample size would have allowed us to detect the observed increase of 0.9 percentage points in the ElCD group with a 13.2% probability. Finally, information about breastfeeding was lacking, which could mediate or confound our observed association. Breastfeeding might also be a potential effect modifier that we could not assess.

In summary, this prospective cohort study showed that ElCD was not associated with early to middle childhood MetS but was associated with some of its dichotomous and continuous components, adding to a growing body of evidence indicating an association between cesarean delivery and long-term child health. Clinicians and families may wish to weigh this possibility in choosing nonessential cesarean delivery, given that the cesarean rate in China increased from 3.4% in 1988 [44] to 35% in 2014 [45], mainly due to an increase in ElCD. In addition, the findings suggested a need for possible changes in postnatal care including higher levels of physical activity and dietary modifications that might reduce MetS-related risks in cesarean-delivered children.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

YB Zhou, HT Li, and JM Liu conceived the initial research plan and conducted the research; YB Zhou analyzed all data, performed all statistical analyses, and wrote the manuscript; all authors interpreted the results and critically reviewed the manuscript; JM Liu had primary responsibility for the final content; and all authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.04.007.

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