

Association between postterm pregnancy and adverse growth outcomes in preschool-age children

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ABSTRACT

Background: Postterm pregnancy has been associated with higher risk of perinatal mortality and morbidity, but its long-term health effects on offspring are poorly understood.

Objectives: The aim of the study was to investigate the prospective associations between maternal postterm pregnancy and adverse growth outcomes in children.

Methods: The Jiaxing Birth Cohort is part of a large population-based health surveillance system in China and recruited pregnant females resident in the Jiaxing area between 1999 and 2013; newborns were followed up for a median duration of 5.8 y until they went to school. Mother–child pairs with maternal gestational information and offspring’s anthropometric data at 4–7 y old were included. Postterm pregnancy was defined as maternal gestational age ≥ 42 and < 47 wk, and its associations with offspring obesity, overweight/obesity, and thinness during childhood were determined by using Poisson regression models.

Results: Of the 101,505 included mother–child pairs, 2369 (2.3%) children were born at postterm. Children born at postterm had significantly lower BMI-for-age z score, weight-for-age z score, and height-for-age z score than those born at term; the mean difference (95% CI) was -0.11 (-0.15 , -0.06), -0.17 (-0.21 , -0.13), and -0.16 (-0.20 , -0.12), respectively. When comparing postterm with term pregnancy, the multivariable-adjusted RRs and 95% CIs among preschool-age children were 0.87 (0.68, 1.11) for obesity, 0.82 (0.72, 0.94) for overweight/obesity, and 1.18 (1.09, 1.28) for thinness, respectively. These risk estimates were robust in sensitivity analyses, but were attenuated in several subgroups stratified by age, sex, mode of delivery, and fetal distress.

Conclusions: Postterm pregnancy was associated with a higher risk of thinness, and a lower risk of overweight/obesity, as well as lower growth parameters in preschool-age children. These findings imply that postterm pregnancy may impede the long-term growth of offspring. *Am J Clin Nutr* 2022;116:482–490.

Keywords: postterm pregnancy, growth outcomes, overweight/obesity, thinness, children, birth cohort

Introduction

Postterm pregnancy, also known as prolonged pregnancy, refers to a gestational length ≥ 42 wk calculated from the first day of the last menstrual period. The prevalence of postterm pregnancy varies considerably between and within Western countries with a range from 0.4% to 11% (1–3). In China, the recent prevalence of postterm birth is reported as $\sim 1.2\%$ compared with that of 6.4% for preterm birth (4, 5). Although induction of labor at 41 weeks of gestation has been recommended in many countries to prevent postterm pregnancy, occurrence of postterm birth and related perinatal complications remain a common issue worldwide. Obstetric adverse events related to postterm pregnancy include raised risk of fetal malnutrition, respiratory distress, macrosomia, meconium aspiration syndrome, as well as higher rates of operative vaginal delivery or cesarean delivery, and even stillbirth (6–10).

Previous studies have suggested that postterm pregnancy may be associated with offspring’s growth and development (11–22). Postterm pregnancy was associated with poorer developmental outcomes including lower cognitive ability and academic achievement (11, 12), more behavioral and emotional

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Supplemental Tables 1–7 and Supplemental Methods are available from the “Supplementary data” link in the online posting of the article and from the same link in the online table of contents at <https://academic.oup.com/ajcn/>.

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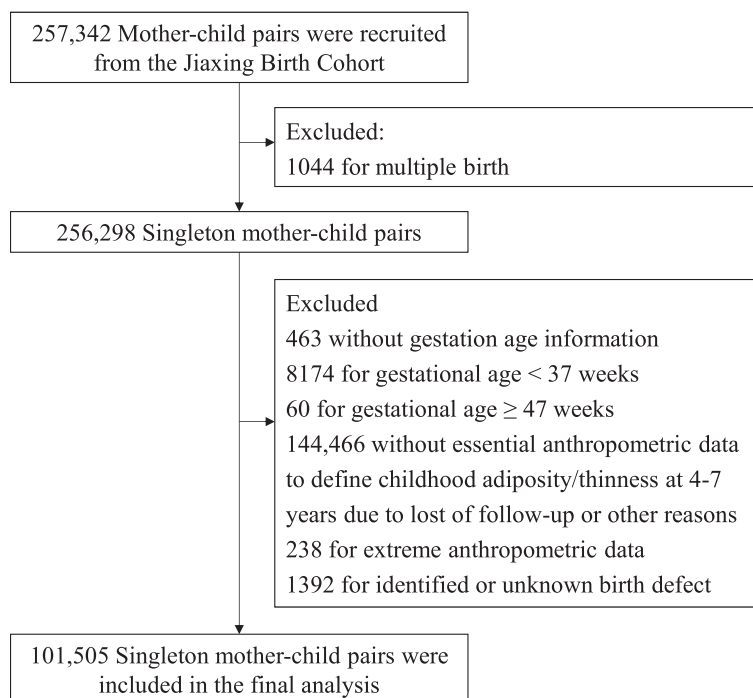


FIGURE 1 Flowchart of the study cohort for analysis.

problems (13), and higher risk of developmental vulnerability (14–16), intellectual disability (17), and cerebral palsy (18–20) in children. Nevertheless, research evidence on the association between postterm pregnancy and offspring's growth status during childhood is rare. There were only 2 studies reporting that participants born at postterm had higher BMI from early childhood to adolescence (21), and higher risk of obesity during adulthood (22), than those born at term. Given that various perinatal factors may affect the long-term growth of the offspring (23–27), the previous studies were limited by a lack of detailed assessment on potential confounders or mediators (21, 22). Taken together, the associations between postterm pregnancy and offspring's childhood growth/adiposity status remain largely unknown.

To address these knowledge gaps, we retrieved data from a large population-based cohort, the Jiaxing Birth Cohort in Southeast China, and aimed to investigate the associations between postterm pregnancy and risk of adverse growth outcomes, including adiposity (overweight or obesity) and thinness, in preschool children aged 4–7 y. For secondary research interest, we aimed to compare growth indicators including BMI-for-age z score, weight-for-age z score, and height-for-age z score between children born at postterm and term.

Methods

Study population

This study was based on the Jiaxing Birth Cohort, which was part of a large population-based health surveillance system for the Collaborative Project-China (28, 29). The cohort recruited pregnant females who were resident in the Jiaxing area of

Zhejiang province, Southeast China during 1999–2013. Pregnant females were registered during their first visit to local clinics. Maternal characteristics including sociodemographic, lifestyle, and clinical information were routinely recorded via administrated questionnaires at interview. Newborns of the recruited mothers were followed up every 3 mo in the infancy stage, every 6 mo during 1–3 y of age, and thereafter every year before they went to school at 4–7 y of age.

Among the 257,342 available mother–child pairs enrolled in the Jiaxing Birth Cohort, we excluded mother–child pairs with multiple births ($n = 1044$), leaving 256,298 singleton mother–child pairs. According to the present study design, we excluded those without maternal gestational age information ($n = 463$), and those with a preterm birth (gestational age < 37 wk) ($n = 8174$) or an extremely long gestational age (≥ 47 wk) ($n = 60$). We then excluded children without anthropometric data or loss to follow-up at 4–7 y old ($n = 144,466$), and excluded children who had extreme values of anthropometric data (calculated BMI-for-age z score > 5 or < -5) ($n = 238$). We also excluded 1392 children who had birth defects ($n = 1288$) or without information on birth defects ($n = 104$). Therefore, a total of 101,505 singleton mother–child pairs were included in the final analysis (Figure 1). The Ethics Committee of Westlake University approved the study protocol and waived the written informed consent.

Exposures

Maternal gestational age was calculated as the interval between the beginning of the last menstrual period and the birth of offspring. Postterm pregnancy was defined as maternal gestational age ≥ 42 and < 47 wk. Term pregnancy (≥ 37 and < 42 weeks of gestation) was set as the control group.

Outcomes

The primary outcome measures were adverse growth outcomes including adiposity (obesity and overweight/obesity) and thinness as the 2 opposite extremes on the spectrum of child growth. The secondary outcomes were growth indicators including BMI-for-age z score, weight-for-age z score, and height-for-age z score of children. For children aged 4–5 y, we used the 2006 WHO Child Growth Standards (30), and defined overweight and obesity as BMI-for-age z scores between 2 and 3 and >3 , respectively. For children aged 5–7 y, we used the 2007 WHO Child Growth Standards (31), and defined overweight and obesity as BMI-for-age z scores between 1 and 2 and >2 , respectively.

In children, the term “stunted” is generally used to indicate low length for age, “underweight” to indicate low weight for age, and “wasting” to indicate low weight for height (32). However, “stunted,” “underweight,” or “wasting” is not always suitable or applicable to describe malnutrition or impeded growth for children at different ages. To avoid potential confusion about the terms “stunted,” “underweight,” or “wasting” we adopted the term “thinness” which in adults indicated low BMI, and extended its use in children to represent low BMI for age. Because the BMI-for-age z scores of -1 , -2 , and -3 in children correspond to BMI of 18.5, 17, and 16.5 at age 18 y, respectively, which serve as the cutoffs for grade 1, 2, and 3 thinness in adults (33), we defined thinness as BMI-for-age z score < -1 for children in the present study.

Covariates

Covariates included calendar year of birth, maternal and paternal sociodemographic characteristics (maternal age at delivery, maternal educational level, paternal educational level, maternal employment status, and paternal employment status), maternal lifestyle factors (smoking during pregnancy and alcohol consumption during pregnancy), and maternal clinical parameters (BMI at enrollment, weight gain during pregnancy, gestational hypertension), as well as offspring characteristics (birth weight, sex, mode of delivery, and presence of fetal distress).

Statistical analysis

We summarized maternal, paternal, and child characteristics stratified by term and postterm pregnancy, and analyzed means \pm SDs for continuous variables and n (%) for categorical variables.

Poisson regression models with robust estimators of variance were used to estimate RRs and 95% CIs of adverse growth outcomes in preschool-age children born at postterm compared with those born at term. We fit the Poisson regression analysis into 3 models: 1) a model adjusted for calendar year of birth only; 2) a multivariable-adjusted model including calendar year of birth, maternal characteristics including age at delivery, BMI at enrollment, weight gain during pregnancy, gestational hypertension, smoking during pregnancy, alcohol consumption during pregnancy, educational level, and employment status, as well as paternal educational level and employment status; and 3) a multivariable-adjusted model including the covariates in model 2, plus offspring sex, birth weight, mode of delivery, and presence of fetal distress. For secondary analyses, we compared BMI-for-age z score, weight-for-age z score, and height-for-age

z score between children born at term or postterm by using linear regression models adjusted for the covariates in model 3.

We conducted subgroup analyses to test whether the main risk estimates varied across groups stratified by predefined factors including child age, sex, mode of delivery, and presence of fetal distress. The joint effects of postterm pregnancy with predefined factors were examined by including an interaction term (exposure factor \times the strata factors) in the multivariable-adjusted Poisson regression model 3.

Among the 101,505 mother–child pairs included in the present study, 9186 pairs (9.0%) had missing data for ≥ 1 covariate. Eleven covariates had missing values with rates of missingness that varied from 0.04% to 5.7% (Supplemental Table 1). We imputed missing values using multiple imputation with chained equations (Supplemental Methods). To avoid decreased statistical efficiency, the main analyses were conducted based on the imputed datasets.

To examine the robustness of our study results, we further conducted several sensitivity analyses: 1) analyses comparing postterm pregnancy with different reference categories of term pregnancy including early term pregnancy (37 0/7 weeks of gestation through 38 6/7 weeks of gestation), full-term pregnancy (39 0/7 weeks of gestation through 40 6/7 weeks of gestation), and late term pregnancy (41 0/7 weeks of gestation through 41 6/7 weeks of gestation), as defined by 1 previous study (34) (Supplemental Table 2); 2) analyses with additional adjustment for exclusive breastfeeding in the infancy stage and lifestyle factors in childhood in the Poisson regression models to test the potential mediation effect (Supplemental Table 3); 3) analyses using the International Obesity Task Force (IOTF) (35) and Chinese reference data (36) to define childhood overweight and obesity, and using BMI-for-age z score < -2 (corresponding to grade 2 thinness in adults) to define childhood thinness (Supplemental Table 4); and 4) analysis using logistic regression models to obtain effect estimates in comparison with the Poisson regression models, complete case analyses as an alternative method, and analysis including children with birth defects (Supplemental Table 5). All the statistical analyses were performed using Stata version 15.0 (StataCorp). A 2-tailed P value < 0.05 was regarded as statistically significant.

Results

Population characteristics

A total of 101,505 singleton mother–child pairs were included in the final analyses (Figure 1). Of these, 2369 (2.3%) children were born at postterm. Table 1 summarizes parental and children’s characteristics by postterm and term pregnancy status. Mothers with postterm pregnancy had a higher BMI at enrollment than those with term pregnancy. Maternal and paternal educational levels and employment status were different between term- and postterm-born children. Children born at postterm were more likely females and had higher birth weight. Interestingly, children born at postterm showed a lower percentage of cesarean delivery than children born at term, although high rates of cesarean delivery were found for both groups. Supplemental Table 6 presents characteristics of the included and excluded mother–child pairs.

TABLE 1 Maternal and offspring characteristics by postterm and term pregnancy¹

Characteristic	Mother-child pairs, <i>n</i> (%)		
	Total (<i>n</i> = 101,505)	Term pregnancy (<i>n</i> = 99,136)	Postterm pregnancy (<i>n</i> = 2369)
Maternal age, y			
<20	1786 (1.8)	1717 (1.7)	69 (2.9)
20–24	59,612 (58.7)	58,236 (58.7)	1376 (58.1)
25–29	27,791 (27.4)	27,191 (27.4)	600 (25.3)
30–34	10,509 (10.4)	10,228 (10.3)	281 (11.9)
≥35	1807 (1.8)	1764 (1.8)	43 (1.8)
Mean ± SD	25.1 ± 3.8	25.1 ± 3.8	25.0 ± 3.9
Maternal BMI at enrollment, kg/m²			
<18.5	19,195 (18.9)	18,817 (19.0)	378 (16.0)
18.5–24.9	74,821 (73.7)	73,080 (73.7)	1741 (73.5)
25.0–29.9	5830 (5.7)	5649 (5.7)	181 (7.6)
≥30.0	645 (0.6)	612 (0.6)	33 (1.4)
Missing	1014 (1.0)	978 (1.0)	36 (1.5)
Mean ± SD	20.7 ± 2.7	20.7 ± 2.7	21.2 ± 3.0
Maternal weight gain during pregnancy, kg			
	14.2 ± 5.5	14.2 ± 5.5	14.2 ± 5.6
Maternal gestational hypertension			
No	97,361 (95.9)	95,091 (95.9)	2270 (95.8)
Yes	3480 (3.4)	3403 (3.4)	77 (3.3)
Missing	664 (0.7)	642 (0.7)	22 (0.9)
Maternal educational level			
Illiterate or semiliterate	439 (0.4)	397 (0.4)	42 (1.8)
Elementary school	8916 (8.8)	8545 (8.6)	371 (15.7)
Middle school	63,823 (62.9)	62,372 (62.9)	1451 (61.3)
High school	18,590 (18.3)	18,248 (18.4)	342 (14.4)
College or above	9686 (9.5)	9524 (9.6)	162 (6.8)
Missing	51 (0.1)	50 (0.1)	1 (0.0)
Paternal educational level			
Illiterate or semiliterate	87 (0.1)	84 (0.1)	3 (0.1)
Elementary school	4486 (4.4)	4305 (4.3)	181 (7.6)
Middle school	58,632 (57.8)	57,171 (57.7)	1461 (61.7)
High school	19,585 (19.3)	19,239 (19.4)	346 (14.6)
College or above	12,923 (12.7)	12,696 (12.8)	227 (9.6)
Missing	5792 (5.7)	5641 (5.7)	151 (6.4)
Maternal employment status			
Homemaker, farmer, or manual worker	72,615 (71.5)	70,848 (71.5)	1767 (74.6)
Service personnel, or clerk	14,479 (14.3)	14,160 (14.3)	319 (13.5)
Professional or administration staff	5232 (5.2)	5156 (5.2)	76 (3.2)
Unclassified	9179 (9.0)	8972 (9.1)	207 (8.7)
Paternal employment status			
Homemaker, farmer, or manual worker	71,556 (70.5)	69,819 (70.4)	1737 (73.3)
Service personnel, or clerk	13,729 (13.5)	13,418 (13.5)	311 (13.1)
Professional or administration staff	6090 (6.0)	5994 (6.1)	96 (4.1)
Unclassified	10,058 (9.9)	9837 (9.9)	221 (9.3)
Missing	72 (0.1)	68 (0.1)	4 (0.2)
Maternal smoking during pregnancy			
No	100,556 (99.1)	98,218 (99.1)	2338 (98.7)
Yes	358 (0.4)	349 (0.3)	9 (0.4)
Missing	591 (0.6)	569 (0.6)	22 (0.9)
Maternal alcohol consumption during pregnancy			
No	100,636 (99.1)	98,290 (99.1)	2346 (99.0)
Yes	292 (0.3)	287 (0.3)	5 (0.2)
Missing	577 (0.6)	559 (0.6)	18 (0.8)
Child sex			
Females	49,075 (48.4)	47,784 (48.2)	1291 (54.5)
Males	52,430 (51.6)	51,352 (50.8)	1078 (45.5)
Birth weight, g			
	3342.4 ± 406.1	3341.3 ± 405.6	3389.8 ± 425.7
Mode of delivery			
Vaginal delivery	27,573 (27.2)	26,704 (26.9)	869 (36.7)
Cesarean delivery	73,691 (72.6)	72,196 (72.8)	1495 (63.1)

(Continued)

TABLE 1 (Continued)

Characteristic	Mother-child pairs, <i>n</i> (%)		
	Total (<i>n</i> = 101,505)	Term pregnancy (<i>n</i> = 99,136)	Postterm pregnancy (<i>n</i> = 2369)
Missing	241 (0.2)	236 (0.2)	5 (0.2)
Presence of fetal distress			
No	93,896 (92.5)	91,731 (92.5)	2165 (91.4)
Yes	6907 (6.8)	6728 (6.8)	179 (7.6)
Missing	702 (0.7)	677 (0.7)	25 (1.1)

¹Values are *n* (%) or mean ± SD.

Growth indicators

The mean ± SD BMI-for-age *z* score, weight-for-age *z* score, and height-for-age *z* score were -0.06 ± 1.07 and -0.16 ± 1.06 , 0.02 ± 0.99 and -0.15 ± 0.98 , and 0.06 ± 0.93 and -0.09 ± 0.94 for term- and postterm-born children, respectively (Figure 2). Children born at postterm had significantly lower BMI-for-age *z* score (mean difference: -0.11 ; 95% CI: $-0.15, -0.06$), weight-for-age *z* score (mean difference: -0.17 ; 95% CI: $-0.21, -0.13$), and height-for-age *z* score (mean difference: -0.16 ; 95% CI: $-0.20, -0.12$) than those born at term when of preschool age, and these differences were stable when stratified by child sex (Figure 2). In addition, children born at a large gestational age tended to have lower BMI-, weight-, and height-for-age *z* scores than those born at a small gestational age (Supplemental Table 7).

Adverse growth outcomes

Children were followed up for a median duration of 5.8 y (IQR: 5.0–6.3 y). During follow-up, 7657 (7.5%) children were identified as having overweight, 3373 (3.3%) obesity, and 17,289 (17.0%) thinness. In the Poisson regression model adjusted for calendar year of birth, postterm pregnancy was not associated with obesity (RR: 0.87; 95% CI: 0.69, 1.11), but was associated with a lower risk of overweight/obesity (RR: 0.83; 95% CI: 0.73, 0.95) and a higher risk of thinness (RR: 1.14; 95% CI: 1.05, 1.24)

(Table 2). Further adjustment for maternal sociodemographic factors and clinical parameters, and paternal sociodemographic factors, in model 2 did not obviously alter the associations (Table 2). In the multivariable-adjusted model 3, the associations of postterm pregnancy with overweight/obesity (RR: 0.82; 95% CI: 0.72, 0.94) and thinness (RR: 1.18; 95% CI: 1.09, 1.28) were even strengthened (Table 2).

Although the associations of postterm pregnancy with overweight/obesity and thinness became nonsignificant in several subgroups stratified by age, sex, mode of delivery, and presence of fetal distress, the directions remained generally consistent. Notably, the association of postterm pregnancy with overweight/obesity was strengthened in children born by cesarean delivery (RR: 0.74; 95% CI: 0.63, 0.88), whereas it became null in children born by vaginal delivery (RR: 1.00; 95% CI: 0.81, 1.24), with a significant interaction observed (*P*-interaction = 0.03) (Figure 3).

Sensitivity analysis

Most of the main risk estimates remained robust when comparing postterm pregnancy with 3 categories of term pregnancy (early, full, and late), except that the inverse association between postterm pregnancy and overweight/obesity became nonsignificant when comparing postterm with late-term pregnancy (Supplemental Table 2). The risk estimates for

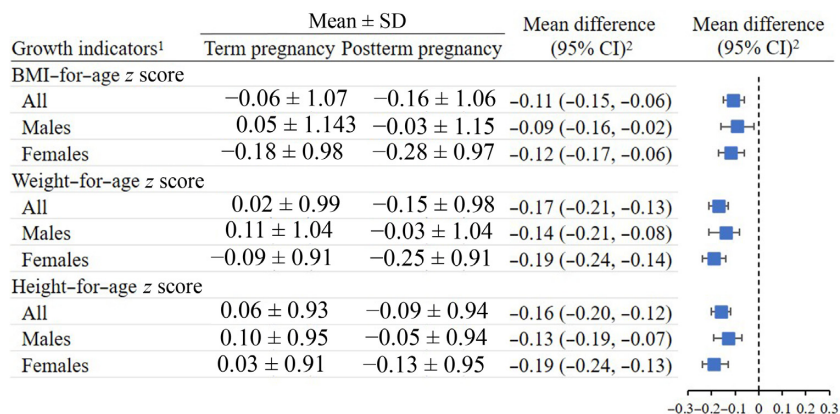


FIGURE 2 Differences of growth indicators between term- and postterm-born children. The numbers of participants born at term and postterm were 51,352 and 1078 for males, 47,784 and 1291 for females, and 99,136 and 2369 for all children, respectively. ¹BMI-for-age *z* score, weight-for-age *z* score, and height-for-age *z* score were calculated according to WHO reference data. ²Linear regression models were used to examine the differences in growth indicators between postterm- and term-born children with adjustment for calendar year of birth; maternal characteristics including age at delivery, BMI at enrollment, weight gain during pregnancy, gestational hypertension, smoking during pregnancy, alcohol consumption during pregnancy, educational level, and employment status; paternal educational level and employment status; and offspring sex, birth weight, mode of delivery, and presence of fetal distress.

TABLE 2 Associations between postterm pregnancy and risk of adverse growth outcomes in preschool-age children

Adverse growth events	<i>n</i> events/total	Person-years	RR (95% CI)		
			Adjusted model 1 ¹	Adjusted model 2 ²	Adjusted model 3 ³
Obesity					
Term pregnancy	3305/74,797	415,992	1 (Reference)	1 (Reference)	1 (Reference)
Postterm pregnancy	68/1753	9788	0.87 (0.69, 1.11)	0.83 (0.65, 1.06)	0.87 (0.68, 1.11)
Overweight/obesity					
Term pregnancy	10,822/82,314	459,930	1 (Reference)	1 (Reference)	1 (Reference)
Postterm pregnancy	208/1893	10612	0.83 (0.73, 0.95)	0.80 (0.71, 0.91)	0.82 (0.72, 0.94)
Thinness					
Term pregnancy	16,822/88,314	493,294	1 (Reference)	1 (Reference)	1 (Reference)
Postterm pregnancy	476/2161	12149	1.14 (1.05, 1.24)	1.17 (1.08, 1.27)	1.18 (1.09, 1.28)

¹Model 1 was adjusted for calendar year of birth only.

²Model 2 was adjusted for calendar year of birth; maternal characteristics including age at delivery, BMI at enrollment, weight gain during pregnancy, gestational hypertension, smoking during pregnancy, alcohol consumption during pregnancy, educational level, and employment status; as well as paternal educational level and employment status.

³Model 3 was adjusted for the covariates in model 2 plus offspring sex, birth weight, mode of delivery, and presence of fetal distress.

overweight/obesity and thinness remained robust in models with further adjustment for infant exclusive breastfeeding or childhood lifestyle factors (Supplemental Table 3). Furthermore, defining overweight/obesity by the IOTF and Chinese reference data and defining thinness as BMI-for-age *z* score < -2 did not alter the risk estimates substantially (Supplemental Table 4). Similarly, our findings remained stable in analysis using a logistic regression model, in complete case analysis, and in analysis including children with birth defects (Supplemental Table 5).

Discussion

In this large population-based birth cohort study, we found that postterm pregnancy was associated with a lower risk of overweight/obesity and a higher risk of thinness in preschool-age children. Notably, children born at postterm showed significantly lower BMI-for-age *z* scores than those born at term, characterized by both lower weight-for-age *z* scores and height-for-age *z* scores. The lower risk of overweight/obesity and higher risk of thinness likely reflected the lower growth parameters in children born at postterm, implying that postterm pregnancy might impede the long-term growth of these children.

Gestational age at birth is known to be associated with offspring's long-term health outcomes. Although a considerable number of studies have suggested that preterm birth was associated with adiposity in the later life of offspring (37), research concerning postterm pregnancy was rare. In contrast to our findings, 1 previous study suggested that postterm pregnancy led to accelerated weight gain during childhood and greater risk of obesity during adolescence in males, but not females (21). However, they did not consider any potential confounding factors, and results could also have been greatly limited by the small sample size (525 participants, 37 postterm cases). Another observational study that enrolled 211,398 Swedish females suggested that females born at postterm had greater BMI and showed increased risk of overweight and obesity with adjustment for several gestational characteristics (22). Given that various lifestyle factors and medication use during the long period from birth to adulthood could have affected the development of obesity among these female adults, a lack of assessment for these confounding factors might have eventually caused bias in that

study. Notably, there were clear sex-dependent associations for adiposity in the 2 previous studies, indicating that there might be a sex discrepancy in susceptibility to the stress associated with prolonged gestation. In contrast, the present study has considered various potential confounding factors, and the main findings were highly robust even when further adjusted for breastfeeding status during infancy and lifestyle factors during childhood. Although we observed that the inverse association between postterm pregnancy and overweight/obesity was slightly attenuated in female children, we could not demonstrate a sex-dependent association, which is likely attributable to the decreased statistical power in sex subgroups. Because of the conflicting evidence, our present negative association between postterm pregnancy and overweight/obesity should be treated with caution. More importantly, our study first demonstrated a positive association between postterm pregnancy and childhood thinness, which provides a new insight into the health consequences of postterm pregnancy, and could arouse research interest and public concern on the potential inhibiting effects of postterm pregnancy on offspring's long-term growth.

Among the potential confounding factors, postterm pregnancy-related cesarean delivery could be one of the most important because it has been reported to be highly correlated with obesity in offspring (38, 39). The present inverse association between postterm pregnancy and overweight/obesity was only evident in children born by cesarean delivery, but not in children born by vaginal delivery. The observed interaction indicated that cesarean delivery might be a potential mediator modulating the inverse association between postterm pregnancy and overweight/obesity. However, it should be also noted that the rate of cesarean delivery in our study population (72.5%) is far higher than the WHO recommended rate (<15%) (40), and coincides with a nationwide survey reporting an average rate of cesarean delivery > 60% in East China including the Jiaying area (41). The excess or non-medically indicated use of cesarean delivery in our study population might mask its mediating effects on long-term growth of offspring. The potential role of cesarean delivery in postterm pregnancy and long-term adverse growth outcomes in children should be clarified by further studies.

The mechanisms underpinning the effects of postterm pregnancy on offspring's long-term growth remain unclear, but are

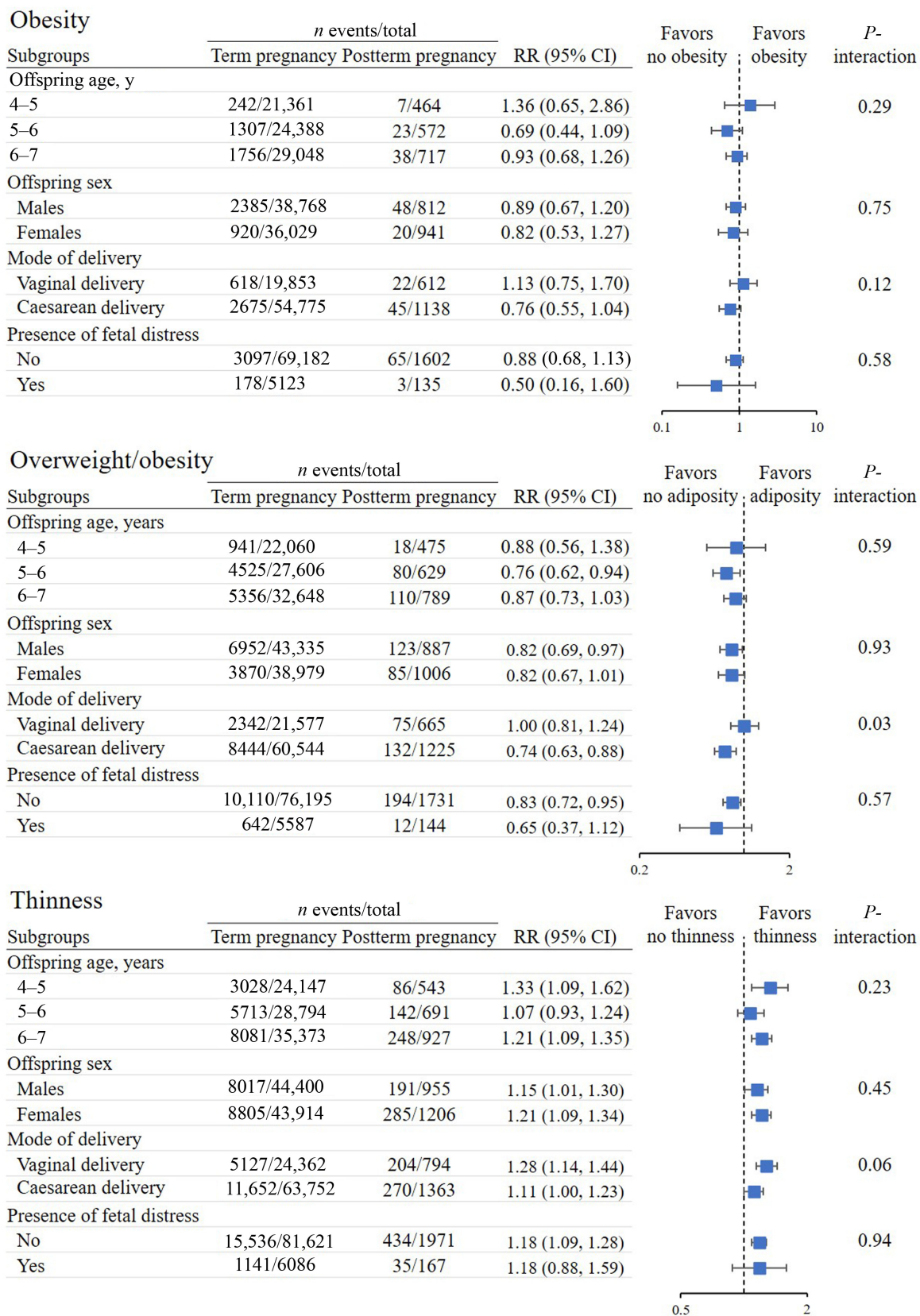


FIGURE 3 Subgroup analyses of associations between postterm pregnancy and risk of adverse growth outcomes. RRs and 95% CIs were estimated by Poisson regression model 3 with adjustment for calendar year of birth; maternal characteristics including age at delivery, BMI at enrollment, weight gain during pregnancy, gestational hypertension, smoking during pregnancy, alcohol consumption during pregnancy, educational level, and employment status; paternal educational level and employment status; and offspring sex, birth weight, mode of delivery, and presence of fetal distress.

biologically plausible. One explanation could be the degraded fetal environment caused by utero-placental insufficiency in a prolonged gestation. During this period, the oxygen content in umbilical blood is dramatically reduced, and the increased fetal exposure to physiologic stress due to lack of oxygen might eventually affect offspring's metabolic programming (42). However, the associations between postterm pregnancy and adverse growth outcomes in our study were even more robust in children without indicated fetal distress, indicating that the associations were less likely confounded by fetal distress. Another mechanism could be the placental endocrine malfunction during postterm pregnancy. A prolonged gestation caused by a disordered placental clock is generally associated with decreased placental secretion of corticotrophin-releasing hormone, which regulates the maternal and fetal hypothalamic–pituitary–adrenal (HPA) axis (43). Thus, the impeded growth of offspring born at postterm might be a consequence of altered HPA function in the early life stage. Lastly, genetic inheritance could be another underlying mechanism. A genome-wide association study has identified several intronic genetic variants in proximity to the a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13 (*ADAMTS13*), *beta-1,3-galactosyltransferase 5* (*B3GALT5*), single stranded DNA binding protein 2 (*SSBP2*), and *transketolase* (*TKT*) loci as being associated with postterm pregnancy (44). These genes are also linked to various physiologic functions including hematopoiesis (44), cell cycle, growth, proliferation, and metabolism (45, 46). These findings suggested that genetic factors could be the causes of postterm pregnancy and related adverse health outcomes. Nevertheless, these explanations are speculative, and the precise mechanisms should be elucidated by further studies.

Strengths and limitations

Our study has several strengths, including the large population-based cohort, and well-documented exposures, covariates, and outcomes. We were thus able to control for various potential confounding factors. The study also has limitations. First, over half of the mother–child pairs in the original cohort were excluded owing to missing data or loss to follow-up, which might have reduced the statistical power and introduced selection bias. Second, there was possible misclassification of outcomes in our study, because defining childhood overweight/obesity and thinness is sometimes debatable. However, our main findings were stable in sensitivity analyses using different reference data and cutoffs to define adverse growth outcomes. Third, residual confounding caused by unmeasured factors such as drug use for both mothers and children could not be eliminated. One should be cautious to treat the observed associations as evidence of a causal relation. Lastly, our findings could be region- and population-specific, and may not be applicable to other populations. Evidence from more prospective cohort studies conducted in different countries or ethnicities is needed.

Conclusion

In the present population-based birth cohort study, postterm pregnancy was associated with a higher risk of thinness, a lower risk of overweight/obesity, as well as lower growth indicators

including BMI-for-age *z* scores, weight-for-age *z* scores, and height-for-age *z* scores in preschool-age children. These findings indicate that postterm pregnancy may impede the long-term growth of offspring. Further studies are warranted to confirm the present findings and clarify the underlying mechanisms. In future, hospitals and physicians may need to implement effective strategies to prevent and manage adverse health outcomes of postterm pregnancy.

The authors' responsibilities were as follows—JT and J-SZ: designed the study; KL, XG, TH, HL, DL, and J-SZ: collected the data; JT, WG, and YF: analyzed the data; JT: drafted the manuscript; DL and J-SZ: had primary responsibility for the final content; and all authors: read and approved the final manuscript. The authors report no conflicts of interest.

Data Availability

Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval.

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