Association between maternal vitamin D status with pregnancy outcomes and offspring growth in a population of Wuxi, China

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ABSTRACT

Background and Objectives: The role of maternal vitamin D in infantile growth remains unclear. **Methods and Study Design:** Serum 25-hydroxyvitamin D [25(OH)D] concentrations were examined for pregnancies who visited the Affiliated Wuxi Maternity and Child Health Care Hospital of Nanjing Medical University from January 2016 to December 2017. Anthropometric measurements of corresponding offspring were performed from birth to 2 to 3 years old. Infantile body mass index (BMI) was transformed into age-, sex- and height- normalized Z-scores, and Latent Class Growth Mixture (LCGM) model was used to identify trajectories of BMI-Z. **Results:** Among the 329 included pregnancy women, 109 (33.13 %), 190 (57.75%) and 30 (9.12%) were defined as vitamin D deficiency [25(OH)D <30 nmol/L], insufficiency [30 nmol/L≤25(OH)D<50 nmol/L] and sufficiency [25(OH)D ≥50 nmol/L], respectively. When compared with vitamin D sufficiency, maternal vitamin D deficiency was not associated with preterm birth [odds ratio (OR)=2.69, 95% confidence interval (95% CI) =0.57-12.80], small for gestation age (OR=0.99, 95% CI=0.29-3.46), and low birth weight (OR=1.69, 95% CI=0.34-8.51). Similarly, no significant relationships were found between maternal vitamin D concentrations and anthropometric indices (such as weight, length, BMI) during 0 to 3 years old. Furthermore, LCGM model identified two patterns of offspring growth: stable moderate BMI-Z and early transient BMI-Z groups. Maternal vitamin D levels were higher in the former group than the latter (p=0.037); however, maternal vitamin D status appeared to be unrelated with offspring BMI-Z trajectories in multivariable logistic regression models. **Conclusions:** Maternal vitamin D deficiency may not be related to adverse pregnancy outcomes as well as offspring growth.

Key Words: maternal vitamin D deficiency, preterm birth, small for gestational age, low birth weight, offspring growth

INTRODUCTION

Vitamin D is well known as a fat-soluble and secosteroid hormone that maintaining skeletal health.[1] This nutrient is also involved in cell proliferation and immune regulation.[2] It is worth noting that the prevalence of vitamin D deficiency (25-hydroxyvitamin D [25(OH)D] <30 nmol/L) remains up to 32%-72.3% in pregnancies in China.[3-5] Since fetal and neonatal vitamin D status relies on the mothers, it has brought great concern about the adverse outcomes that vitamin D deficiency during pregnancy may bring.

Two recent meta-analyses of randomized controlled trials consistently reported that maternal supplementation of vitamin D may reduce the risk of infants being born small for gestational age (SGA).[6] However, the recommended dosage for preventing SGA was still under discussion.[7] Regarding low birth weight (LBW), one meta-analysis supported the beneficial effect of perinatal vitamin D supplementation,[8] but others did not.[9,10] On the other hand, a recent meta-analysis of observational studies revealed that mothers with vitamin D deficiency [25(OH)D <30 nmol/L] versus non-deficiency had statistically higher risk of LBW and SGA, but not preterm birth (PTB).[11] Nevertheless, conflicting evidence is still emerging. For example, a multicenter prospective cohort of 2813 pregnant women failed to reach a statistical significance between maternal 25(OH)D deficiency in the first trimester and risk of PTB or SGA overall.[12] A large-scale retrospective cohort study in southern China also reported that low vitamin D status in pregnant women appeared to be unrelated with PTB.[13]

Low serum vitamin D concentrations during pregnancy may influence beyond the time of birth. Several studies also managed to relate maternal vitamin D deficiency with growth of their offspring during infancy.[14-16] However, there was still evidence that prenatal vitamin D supplementation[17,18] or maternal vitamin D status[19] were not associated with offspring anthropometric outcomes. What's more, previous observation even suggested potential disadvantageous effects of high maternal vitamin D concentrations on offspring health outcomes.[20]

Above all, the relationship between maternal vitamin D status and neonatal outcomes remains equivocal. Also, the epidemiologic literatures relating maternal vitamin D concentrations and post-natal infantile growth were sparse and inconclusive. Therefore, further research is still required. Based on a mother-child paired population in Wuxi, east of China, we aimed to access the association between maternal vitamin D status with neonatal outcomes. Subsequently, the association between maternal vitamin D deficiency and offspring growth from birth until the alternate ages of 2 to 3 years were also examined.

MATERIALS AND METHODS

Ethical approval and funding

This study was approved by the ethic committee of the Affiliated Wuxi Maternity and Child Health Care Hospital of Nanjing Medical University and Soochow University. It was funded by Wuxi Municipal Science and Education Strengthening Health Engineering Medical Young Talent Project (Grant Number: QNRC091), High-level Talent Training Project of Wuxi Taihu

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Study population

From January 2016 to December 2017, enrollment was made for 480 mother-fetus pairs who visited Department of Child Health Prevention, the Affiliated Wuxi Maternity and Child Health Care Hospital of Nanjing Medical University in Jiangsu Province of China. Information for mother-child pairs were retrieved from medical records and through questionnaire interviews. After, 43 mothers who suffered liver and renal diseases that could possibly influence metabolism of vitamin D during pregnancy, were excluded. Further exclusion was made for lack of maternal vitamin D concentrations (n=93) or infant birth weight (n=15). Finally, 329 eligible mother-child pairs were included. The process on how we selected objects of the study is described in Figure 1.

Details of maternal characteristics

Basic maternal characteristics were collected, including maternal age, education level, family income level, pre-conceptional body mass index (BMI), gestational weight gain (GWG), mode of delivery, gestational complications (i.e., gestational diabetes, hypertension disorders during pregnancy, and gestational hyperlipidemia), passive smoking during pregnancy, self-reported mental conditions, vitamin D and folic acid supplementation, sleeping conditions, exercise status and season of serum sampling.

The mode of delivery was divided into two groups: vaginal and caesarean. Educational levels of pregnancy women were categorized into four groups: primary school or below, junior school, high school, and university or above. The seasons of sample collection were divided as: spring (from March to May), summer (from June to August), autumn (from September to November), and winter (from December to February).

Details of offspring characteristics

Anthropometric measurements were made for each infant at three time periods (at birth, at the age of 1 year old and at the age of 2 to 3 years old, respectively). For all measurements, duplicate measures were performed and averaged values were recorded. Weight was measured in light clothing and without shoes using a digital scale. Length was measured from top of the head to the soles of the feet using an infant mat. PTB represents live birth before 37 weeks of gestation.[21] SGA is defined as birth weight <10th percentile for gestational age

according to Chinese references.[22] LBW is used to describe newborns who are born with weight less than 2500 grams.[23]

Vitamin D supplementation and breastfeeding duration after birth were also extracted through questionnaire interviews. Breastfeeding duration was divided into four categories which were ≥6 months, 3-6 months, 0-3 months and none, respectively. For the anthropometric data, age and sex-adjusted Z-scores for weight, length and BMI were derived with reference to the World Health Organization standards for child growth.[24]

Maternal and infant 25(OH)D assessment

Detailed method for laboratory examination was described in previous report.[25] Maternal blood samples were collected once at a specific time during the interval of 11th and 29th gestational week. Subsequently, serum 25(OH)D concentrations were detected using these blood samples, and regarded as maternal vitamin D status during pregnancy. For corresponding infants, finger-sticking blood samples were collected at 1 year old. Samples were then placed directly into a 0.5mL micro-tube. Within 10 min after collection, specimens were centrifuged at 3500 rpm for 15 min. Serum samples were stored at -80°C until assay.

Serum 25(OH)D levels of the participants were detected via enzyme-linked immunosorbent assay (ELISA) according to the standard procedure in the Affiliated Wuxi Maternity and Child Health Care Hospital of Nanjing Medical University (IDS Ltd., Boldon Colliery, Tyne & Wear, UK). The inter-assay and intra-assay coefficients of variation were <10%.

According to National Osteoporosis Society, vitamin D status was assessed by 25(OH)D levels into three groups: sufficiency (≥50 nmol/L), insufficiency (30 to <50 nmol/L) and deficiency (<30 nmol/L).[26]

Identification of BMI-Z trajectories

In our study, the change patterns of BMI-Z were fitted by LCGM model by using Proc Traj in statistical analysis system (SAS) software 9.4. A censored normal model (CNORM) was considered appropriate due to the continuity of BMI-Z. We firstly compared the Bayesian Information Criterion (BIC) among models with two to five trajectories, with all functional forms set to a third-order (cubic) equation. Posterior probabilities (PP) showed the accuracy and effectiveness of the model. Therefore, we further estimated the mean PP and the percentage of subjects with PP>0.7 within each subgroup, since mean PP>0.7 and percentage>65% indicated a well classification.[27] The parameter estimates of model with 2 to

5 trajectories are given in Supplementary table 1. Thus, two trajectories were selected as the optimum model considering BIC value close to zero, relatively high mean PP and percent of PP>0.7.28 Furthermore, cubic, quadratic, and linear terms were evaluated based on their statistical significance after starting with the highest polynomial. Finally, two trajectories with cubic curve assumptions were choose out.

Statistical analysis

Continuous and categorical variables were presented as mean [standard deviation (SD)] and frequency (percentage), respectively. The distribution of maternal and infant characteristics between maternal vitamin D categories or infant growth trajectories was compared using ANOVA for continuous variables and Chi-square test for categorical variables, respectively.

For neonatal outcomes (i.e., PTB, SGA and LBW), multivariable logistic regression analysis was used to examine their associations with maternal vitamin D status; adjustments included maternal age, GWG, maternal vitamin D and folic acid supplementation, season of serum sampling, fetal sex, and complications of pregnancy (i.e., gestational diabetes, hypertension disorders during pregnancy and gestational hyperlipidemia).

To examine the association between maternal vitamin D status and newborn anthropometric parameters, multivariable linear regression analysis was performed, with the same covariates adjusted in the aforementioned logistic model. Besides, when it turned to infantile anthropometric parameters at 1 to 3 years old, birth weight, infant vitamin D levels at 1 year old and breastfeeding duration were further adjusted.

For different BMI-Z trajectories, logistic regression analysis was used to evaluate their associations with maternal vitamin D levels. Model 1 was unadjusted. Model 2 was adjusted for the same factors which controlled in multivariable logistic model for pregnancy outcomes. Model 3 additionally controlled for infantile characteristics including fetal sex, SGA, LBW, breastfeeding duration and 1-year-old infant vitamin D levels. Odds ratio (OR) and 95% confidence interval (95% CI) were calculated in logistics models.

All p values were 2-tailed and $p<0.05$ was defined as statistically significant. The software package SAS (SAS Institute Inc., NC, USA) was used for statistical analysis.

RESULTS

Characteristics of participants

In total, the study enrolled 329 mother-child pairs. Basic maternal and corresponding infantile characteristics of the study population were summarized in Table 1 according to maternal

vitamin D categories. The mean age of pregnant women was 29.68 years; while for infants following up for postnatal growth, their average age at final visit was 2.28 years. The mean±SD of maternal vitamin D levels was 35.27±11.78 nmol/L. It was found that 33.13%, 57.75% and 9.12% of the participants suffered vitamin D deficiency, insufficiency and sufficiency, respectively. Infants born to mothers with sufficient vitamin D tended to gain higher serum vitamin D concentrations in 1 years old (p<0.001).

Association between maternal vitamin D and pregnancy outcomes

In the crude model, compared with vitamin D sufficiency, vitamin D deficiency (<30 nmol/L) or vitamin D insufficiency (30 to <50 nmol/L) did not significantly increase the risk for adverse pregnancy outcomes. After the adjustment for potential confounding factors, maternal vitamin D deficiency still showed neutral association with PTB (OR=2.69,95% CI =0.57-12.8), SGA (OR=0.99, 95% CI=0.29-3.46), and LBW (OR=1.69, 95% CI=0.34-8.51). Likewise, when compared vitamin D non-deficiency (≥50 nmol/L) to deficiency (<50 nmol/L), null associations were observed for PTB, LBW and SGA in multivariable logistic regression model (Table 2).

Linear relationship between maternal vitamin D and anthropometric data

Table 3 shows the relationship between maternal vitamin D and anthropometric data. We found no statistically meaningful associations between maternal vitamin D levels and any growth indices after labor. After adjusting for maternal characteristics, no statistically significant associations were observed, including birth weight (p=0.788), length (p=0.843), BMI (p=0.778) and BMI-Z (p=0.713). Null association remained when the outcome shifted to anthropometric indices at 1 and 2 to 3 years old.

BMI-Z trajectories in the first 2 to 3 years

As illustrated in Figure 2, two distinct BMI-Z trajectories were identified. A total of 17.1% (n=56) infants were defined as early transient BMI-Z group. Infants in this group started with a low BMI-Z, and their BMI-Z continued to increase before the first year of life. The other 82.9% (n=273) infants were assigned to stable moderate BMI-Z group, which maintained the status within the alternate age of 2 to 3 years.

The baseline information for infants and mothers was presented in Table 4 according to trajectory groups. Family income levels, maternal mental conditions and maternal sleeping conditions were found to be significantly different between two trajectory groups. The early

transient BMI-Z group was more likely to include infants whose mother with gestational complications (i.e., hypertension disorders during pregnancy, gestational diabetes and gestational hyperlipidemia). As for infants born as SGA or LBW, they had a higher chance to establish a low BMI-Z before 1 year old (p<0.001). Moreover, 1-year-old infant vitamin D concentrations differed significantly between two groups (p=0.027).

Association between maternal vitamin D and offspring trajectory groups

The mean±SD for maternal vitamin D level was 31.95±11.48 nmol/L in early transient low BMI-Z group, significantly lower than that of the stable moderate group (mean±SD=35.82±11.76 nmol/L, p=0.037). However, the maternal vitamin D deficient category was not associated with BMI-Z trajectory groups in logistic regression models (Table 5).

DISCUSSION

In our study based on paired pregnant women and infants from Wuxi, eastern China, we found no significant association between maternal vitamin D deficiency and adverse neonatal outcomes, including PTB, SGA and LBW. Besides, our study also failed to show relationship between maternal vitamin D concentration and offspring anthropometric indices in the first 2 to 3 years.

Up to 33.13% of pregnant women enrolled in our study suffered vitamin D deficiency. Similarly, previous study from the same city Wuxi (located 31°N) reported that the proportion of vitamin D deficiency was 40.8% in pregnant women.[4] Another research in Guizhou (located 24°N), reported a prevalence of 38.4% for maternal vitamin D deficiency.[3] Meanwhile, the prevalence of vitamin D deficiency in pregnancies of Shanghai (located 30°N) was up to 72.3%.[5] Our study supports the view that vitamin D deficiency is highly prevalent among Chinese pregnant women.

In terms of the etiology of adverse pregnancy outcomes, one of the most common risk factors for PTB could be infection.[29] Vitamin D, through its role in antimicrobial,[30] may enable implantation and thus reducing the risk of PTB. However, in contrasting with studies resulting in supportive conclusion,[31-33] another large-scale retrospective Chinese cohort study found no association between maternal vitamin D status and PTB.[34] With regard to SGA and LBW, studies, but not all, reported that vitamin D may act through its positive role on skeletal and muscle development, and consequently reduce the risk of SGA or LBW.[35-37] Similar results were found in the interventional studies for maternal vitamin D supplementation and

its impact on birth size.[38,39] However, our current study could not infer a significant association between maternal vitamin D deficiency and SGA as well as LBW, which was in concordant with a few other studies.[40-42] Variations may be explained by the study population (high risk/general), maternal age, diet and nutrition conditions, the trimester of measurement and gestational complications, which may affect the metabolism of vitamin D. Also, differences in methods to assess vitamin D levels, season of blood sampling, vitamin D cutoffs may also contribute to the discordant results.

As for offspring growth, related studies are sparse and varied. Our study, which revealed insignificant associations, does not support the hypothesis proposed by previous studies that maternal vitamin D during pregnancy may have an impact on offspring growth patterns.[14,43] In line with our results, several studies also identified null relationships. For example, a systematic review of 30 observational studies suggested that prenatal vitamin D status was linked with offspring weight, but it failed to relate to length at early age.[19] Similarly, there was a consistent lack of effect on infant height. A two-blinded randomized clinical trial manifested no difference in height at 6 years old between intervention and placebo groups (supplementation of vitamin D with 2800IU/d versus 400IU/d).[18] To resolve the inconsistence and explore long-term growth patterns, more researches are needed.

Furthermore, we found that the association of maternal vitamin D deficiency with distinct BMI-Z trajectories in 2 to 3 years old was not significant. Infants born as SGA or LBW had a significantly lower BMI-Z in subsequent growth compared with their counterparts. This group of infants experienced a catch-up growth by 12 months. However, such accelerated growth failed to link with maternal vitamin D in our results. Conversely, some studies reported a positive relationship between a poor maternal vitamin D status and catch-up growth for their offspring.[16,44] It was explained that intentionally postnatal vitamin D supplementation for infants born to vitamin D deficient mothers may contribute to their catch-up growth. In addition to vitamin D supplementation, confounding factors such as breastfeeding duration, dietary intake and multiple nutrition status may also affect offspring postnatal growth.

Recently, the concept of vitamin D in preventing adverse pregnancy outcomes and improving offspring growth is actively discussed. Undoubtedly, vitamin D deficiency is prevalent in pregnancies globally. Strengths in our study lie in the relatively long observational period (up to 3 years old). A lot of studies performed a follow-up growth measurement for infants within 1 year old.[14,16,45] Moreover, the comprehensive maternal and infantile characteristics included in current research made it possible to control for various

potential confounding factors. Additionally, the use of LCGM model was able to observe the dynamic change trend of infant growth.

Although the current study provides a glimpse of maternal vitamin D and its effect on offspring outcomes, there remain some limitations. Firstly, the current study has a relatively small sample size, although it would have a statistical power of >70% to explore the association between vitamin D deficiency with infant outcomes. Secondly, owing to the feature of observational study, we could not confer the causal association. Thirdly, our study was performed in Wuxi, the southeastern area of China. The limited geographical environment made it difficult to represent other areas of Chinese population. Last, the single detection of vitamin D concentrations at a specific time point may make it difficult to represent the maternal nutritional status during the whole pregnancy trimesters. Therefore, further studies are warranted to address above weaknesses.

Conclusion

The results revealed that maternal vitamin D deficiency was not related to adverse pregnancy outcomes. Besides, no significant association was observed between maternal vitamin D status and offspring growth in the first 2 to 3 years. Further studies with a relatively large sample size are required for validation, especially in Chinese population.

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AUTHOR DISCLOSURE

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Table 1. Baseline characteristics for pregnant women and corresponding infants

	Overall (N=329)	Vitamin D sufficiency (n=30)	Vitamin D insufficiency (n=190)	Vitamin D deficiency (n=109)	*p*-value
Maternal characteristics					
Maternal age(years), mean (SD)	29.68 (4.42)	29.10 (4.51)	29.83 (4.36)	29.58 (4.51)	0.683
Preconception body mass index (kg/m^2), mean (SD)	21.06 (3.32)	21.16 (2.85)	21.09 (3.50)	20.98 (3.16)	0.949
Gestational weight gain(kg), mean (SD)	14.14 (7.53)	12.19 (5.61)	14.35 (7.96)	14.29 (7.16)	0.356
Mode of delivery, n (%)					0.369
Vaginal	150 (45.87)	14 (48.27)	92 (48.68)	44 (40.37)	
Caesarean	177 (54.13)	15 (51.73)	97 (51.32)	65 (59.63)	
Education level, n (%)					0.078
Primary school or below	3 (0.92)	0 (0.00)	2 (1.07)	1 (0.92)	
Junior school	18 (5.54)	1 (3.45)	9 (4.81)	8 (7.34)	
High school	40 (12.31)	6 (20.69)	14 (7.49)	20 (18.35)	
University and above	264 (81.23)	22 (75.86)	162 (86.63)	80 (73.39)	
Family income level, n (%)					0.263
Poor	19 (6.27)	2 (7.14)	13 (7.34)	4 (4.08)	
Normal	120 (39.60)	15 (53.57)	70 (39.55)	35 (35.71)	
Good	154 (50.83)	11 (39.29)	90 (50.85)	53 (54.08)	
Very good	10 (3.30)	0 (0.00)	4 (2.26)	6 (6.13)	
Season of serum sampling, n (%)					0.777
Spring	73 (22.19)	9 (30.00)	42 (22.11)	22 (20.18)	
Summer	91 (27.66)	7 (23.33)	53 (27.89)	31 (28.44)	
Autumn	85 (25.84)	7 (23.33)	46 (24.21)	32 (29.36)	
Winter	80 (24.32)	7 (23.34)	49 (25.79)	24 (22.02)	
Hypertension disorders during pregnancy, n (%)	13 (3.95)	0 (0.00)	6 (3.16)	7 (6.42)	0.192
Gestational diabetes, n (%)	81 (24.62)	6 (20.00)	45 (23.68)	30 (27.52)	0.628
Gestational hyperlipidemia, n (%)	3 (0.90)	0 (0.00)	0 (0.00)	3 (2.75)	0.047*
Passive smoking status, n (%)					0.700
Yes	245 (78.53)	23 (82.14)	143 (79.44)	79 (75.96)	
No	67 (21.47)	5 (17.86)	37 (20.56)	25 (24.04)	
Mental conditions, n (%)					0.115
Nervous	31 (9.60)	2 (6.90)	17 (9.09)	12 (11.21)	
Anxious	10 (3.10)	0 (0.00)	3 (1.60)	7 (6.54)	
Relaxed	282 (87.3)	27 (93.10)	167 (89.30)	88 (82.25)	
Vitamin D supplementation, n (%)	99 (30.94)	8 (26.67)	61 (32.62)	30 (29.13)	0.718
Folic acid supplementation, n (%)	223 (69.04)	19 (63.33)	138 (73.02)	66 (63.46)	0.186
Sleeping conditions, n (%)					0.490
Good	137 (41.64)	15 (50.0)	72 (37.89)	50 (45.87)	
Normal	166 (50.46)	14 (46.7)	102 (53.68)	50 (45.87)	
Poor	26 (7.90)	1 (3.33)	16 (8.42)	9 (8.26)	

Table 1. Baseline characteristics for pregnant women and corresponding infants (cont.)

	Overall (N=329)	Vitamin D sufficiency (n=30)	Vitamin D insufficiency (n=190)	Vitamin D deficiency (n=109)	*p*-value
Exercise state, n (%)					0.977
Yes	111 (34.91)	11 (36.67)	64 (34.78)	36 (34.62)	
No	207 (65.09)	19 (63.33)	120 (65.22)	68 (65.38)	
Neonatal characteristics					
Sex, n (%)					0.132
Male	161 (48.94)	17 (56.67)	84 (44.21)	60 (55.05)	
Female	168 (51.06)	13 (43.33)	106 (55.79)	49 (44.95)	
Weight (kg), mean (SD)	3.24 (0.60)	3.14 (0.48)	3.30 (0.59)	3.18 (0.62)	0.174
Length (cm), mean (SD)	49.7 (2.10)	49.7 (0.98)	49.7 (2.09)	49.5 (2.33)	0.704
BMI (kg/m^2), mean (SD)	13.1 (1.86)	12.7 (1.57)	13.3 (1.84)	12.8 (1.93)	0.071
Weight-Z, mean (SD)	-0.17 (1.32)	-0.38 (1.01)	-0.05 (1.29)	-0.33 (1.41)	0.363
Length-Z, mean (SD)	0.08 (1.11)	0.09 (0.55)	0.13 (1.11)	-0.02 (1.23)	0.514
BMI-Z, mean (SD)	-0.37 (1.57)	-0.68 (1.27)	-0.20 (1.53)	-0.57 (1.67)	0.073
Preterm delivery, n (%)	48 (16.55)	2 (7.69)	27 (15.79)	19 (20.43)	0.278
Small for gestational age, n (%)	46 (15.86)	4 (15.38)	23 (13.45)	19 (20.43)	0.332
Low birth weight, n (%)	37 (11.25)	3 (10.00)	18 (9.47)	16 (14.68)	0.381
1-year-old infant characteristics					
Weight (kg), mean (SD)	10.7 (1.55)	10.8 (1.42)	10.5 (1.70)	10.8 (1.28)	0.238
Length (cm), mean (SD)	76.3 (2.86)	76.5 (2.41)	76.3 (3.28)	76.3 (2.08)	0.947
BMI (kg/m^2), mean (SD)	18.3 (2.07)	18.5 (2.12)	18.0 (2.04)	18.6 (2.08)	0.040*
Weight-Z, mean (SD)	1.12 (1.23)	1.21 (1.10)	1.04 (1.35)	1.24 (1.02)	0.378
Length-Z, mean (SD)	0.60 (1.11)	0.61 (0.95)	0.63 (1.27)	0.54 (0.82)	0.797
BMI-Z, mean (SD)	1.05 (1.27)	1.16 (1.30)	0.92 (1.22)	1.26 (1.31)	0.078
Serum vitamin D levels, mean (SD)	67.02 (19.16)	72.42 (27.73)	70.22 (17.54)	59.79 (17.02)	<0.001***
Breastfeeding duration (months), n (%)					0.370
≥6	139 (43.85)	13 (44.83)	86 (46.74)	40 (38.46)	
3-6	36 (11.35)	5 (17.24)	22 (11.96)	9 (8.65)	
0-3	29 (9.15)	0 (0.00)	13 (7.07)	16 (15.38)	
0	113 (35.65)	11 (37.93)	63 (34.24)	39 (37.51)	
Vitamin D supplementation, n (%)	318 (97.85)	29 (100.00)	182 (97.33)	107 (98.17)	0.630
2-3 years old infant characteristics					
Weight(kg), mean (SD)	13.6 (1.97)	14.0 (1.76)	13.3 (1.93)	13.9 (2.02)	0.023*
Height(cm), mean (SD)	92.5 (5.28)	93.8 (5.55)	91.6 (4.91)	93.8 (5.55)	0.002**
BMI (kg/m^2), mean (SD)	15.8 (1.47)	15.9 (1.41)	15.8 (1.57)	15.8 (1.31)	0.875
Weight-Z, mean (SD)	0.34 (0.98)	0.54 (0.89)	0.31 (1.02)	0.32 (0.92)	0.521
Height-Z, mean (SD)	0.39 (0.90)	0.61 (0.99)	0.37 (0.91)	0.35 (0.86)	0.386
BMI-Z, mean (SD)		0.22 (1.06)	0.10 (1.20)	0.12 (1.00)	0.883

Table 2. Multivariable logistic analysis of association between maternal vitamin D status and pregnancy outcomes[†]

25(OH)D categories	Preterm birth				Small for gestational age			
	Event (%)	Crude OR (95%CI)	Adjusted OR (95%CI)	Adjusted *p*-value	Event (%)	Crude OR (95%CI)	Adjusted OR (95%CI)	Adjusted *p*-value
Category I								
Sufficiency (<30 nmol/L)	9.92%	1.00	1.00		9.02%	1.00	1.00	
Insufficiency (30 to <50 nmol/L)	59.50%	2.25 (0.52-10.1)	2.15 (0.47-9.85)	0.549	60.6%	0.86 (0.27-2.71)	0.60 (0.18-2.01)	0.209
Deficiency (<30 nmol/L)	30.58%	3.08 (0.67-14.2)	2.69 (0.57-12.8)	0.209	30.33%	1.41 (0.44-4.59)	0.99 (0.29-3.46)	0.563
Category II								
Non-deficiency (≥50 nmol/L)	9.92%	1.00	1.00		9.02%		1.00	
Deficiency (<50 nmol/L)	91.08%	4.90 (0.61-18.2)	4.60 (0.55-16.8)	0.167	91.98%	1.27 (0.45-5.30)	1.14 (0.32-4.75)	0.876

25(OH)D categories	Low birth weight			
	Event (%)	Crude OR (95%CI)	Adjusted OR (95%CI)	Adjusted *p*-value
Category I				
Sufficiency (<30 nmol/L)	9.25%	1.00	1.00	
Insufficiency (30 to <50 nmol/L)	58.90%	0.94 (0.26-3.41)	0.96 (0.20-4.70)	0.541
Deficiency (<30 nmol/L)	31.85%	1.55 (0.42-5.71)	1.69 (0.34-8.51)	0.286
Category II				
Non-deficiency (≥50 nmol/L)	9.25%	1.00	1.00	
Deficiency (<50 nmol/L)	91.75%	3.16 (0.41-20.7)	2.02 (0.26-18.8)	0.483

[†]All models were adjusted for: maternal age, gestational weight gain, maternal vitamin D and folic acid supplementation, season of serum sampling, fetal sex, and complications of pregnancy including gestational diabetes, hypertension disorders during pregnancy and gestational hyperlipidemia.

Table 3. Linear correlations between maternal vitamin D levels and offspring growth indices

Parameters	Crude β estimate (SE)	Crude *p* value	Adjusted β estimate (SE)	Adjusted *p* value
At birth (n=329)				
Weight, kg	0.003 (0.003)	0.312	-0.015 (0.056)	0.788
Length, cm	0.010 (0.011)	0.288	-0.040 (0.200)	0.843
BMI, kg/m^2	0.009 (0.009)	0.319	-0.050 (0.175)	0.778
BMI-Z	0.008 (0.007)	0.272	-0.055 (0.148)	0.713
At 1 year old (n=329)[†]				
Weight, kg	-0.007 (0.003)	0.362	0.027 (0.133)	0.855
Length, cm	0.006 (0.013)	0.636	-0.093 (0.221)	0.659
BMI, kg/m^2	-0.016 (0.010)	0.100	0.122 (0.163)	0.544
BMI-Z	-0.010 (0.006)	0.093	0.070 (0.122)	0.449
At 2 to 3 years old (n=286)[‡]				
Weight, kg	-0.007 (0.010)	0.499	0.165 (0.191)	0.138
Height, cm	-0.044 (0.027)	0.103	0.927 (0.530)	0.067
BMI, kg/m^2	0.009 (0.008)	0.249	-0.031 (0.145)	0.784
BMI-Z	0.005 (0.006)	0.368	0.005 (0.116)	0.973

[†]Model at birth was adjusted for: maternal age, GWG, maternal vitamin D and folic acid supplementation, season of serum sampling, fetal sex, and complications of pregnancy including gestational diabetes, hypertension disorders during pregnancy and gestational hyperlipidemia.

[‡]Models at 1 to 3 years old were additionally adjusted for birth weight, infant vitamin D levels at 1 year old and breast-feeding duration

Table 4. Baseline information of study population stratified by BMI Z-score trajectories

	Overall (N=329)	Stable moderate BMI Z-score (n=273)	Early transient low BMI Z-score (n=56)	*p*-value
Maternal characteristics				
Serum vitamin D concentrations during pregnancy (nmol/L), mean (SD)	35.26 (11.78)	35.82 (11.76)	31.95 (11.48)	0.037*
Maternal age (years), mean (SD)	29.69 (4.42)	29.73 (4.49)	29.40 (3.96)	0.641
Preconception body mass index (kg/m^2), mean (SD)	21.06 (3.32)	21.11 (3.38)	20.75 (3.00)	0.491
Gestational weight gain(kg), mean (SD)	14.14 (7.53)	14.05 (7.70)	14.71 (6.37)	0.586
Mode of delivery, n (%)				0.889
Vaginal	147 (45.94)	125 (45.79)	22 (46.81)	
Caesarean	173 (54.06)	148 (54.21)	25 (53.19)	
Education level, n (%)				0.496
Primary School or below	3 (0.92)	3 (1.10)	0 (0.00)	
Junior school	18 (5.54)	14 (5.13)	4 (7.69)	
High school	40 (12.3)	36 (13.19)	4 (7.69)	
University and above	264 (81.2)	220 (80.59)	44 (84.62)	
Family income level, n (%)				0.037*
Poor	19 (6.27)	13 (5.00)	6 (13.95)	
Normal	120 (39.60)	108 (41.54)	12 (27.91)	
Good	154 (50.83)	132 (50.77)	22 (51.16)	
Very good	10 (3.30)	7 (2.69)	3 (6.98)	
Hypertension disorders during pregnancy, n (%)	13 (3.95)	7 (2.48)	6 (12.77)	<0.001***
Gestational diabetes, n (%)	81 (24.62)	64 (22.70)	17 (36.17)	0.047*
Gestational hyperlipidemia, n (%)	3 (0.91)	1 (0.35)	2 (4.26)	0.009**
Passive smoking status, n (%)				0.727
Yes	245 (78.53)	209 (78.87)	36 (76.60)	
No	67 (21.47)	56 (21.13)	11 (23.40)	
Mental conditions, n (%)				0.036*
Nervous	30 (9.43)	22 (8.06)	8 (17.78)	
Anxious	9 (2.83)	6 (2.20)	3 (6.67)	
Relaxed	279 (87.74)	245 (89.74)	34 (75.55)	
Vitamin D supplementation, n (%)	99 (30.94)	84 (30.77)	15 (31.91)	0.875
Folic acid supplementation, n (%)	223 (69.04)	182 (65.94)	41 (87.23)	0.004**
Sleeping conditions, n (%)				0.038*
Good	137 (41.64)	118 (43.22)	19 (33.93)	
Normal	166 (50.46)	139 (50.92)	27 (48.21)	
Poor	26 (7.90)	16 (5.86)	10 (17.56)	
Exercise state, n (%)				0.663
Yes	111 (34.91)	94 (34.43)	17 (37.78)	
No	207 (65.09)	179 (65.57)	28 (62.22)	
Neonatal characteristics				
Preterm delivery, n (%)	48 (16.55)	38 (15.45)	10 (22.73)	0.231
Small for gestational age, n (%)	46 (15.86)	12 (4.88)	34 (77.27)	<0.001***
Low birth weight, n (%)	37 (11.25)	7 (2.48)	30 (63.83)	<0.001***
Infantile characteristics				
1-year-old serum vitamin D concentrations (nmol/L), mean (SD)	67.02 (19.16)	67.98 (18.86)	61.29 (20.09)	0.027*
Breastfeeding duration (months), n (%)				0.124
≥6	139 (43.85)	121 (44.32)	18 (40.91)	
3-6	36 (11.36)	35 (12.82)	1 (2.27)	
0-3	29 (9.14)	23 (8.42)	6 (13.64)	
0	113 (35.65)	94 (34.43)	19 (43.18)	
Vitamin D supplementation, n (%)	318 (97.85)	271 (97.48)	47 (100.00)	0.271

Table 5. Association between maternal vitamin D and infant BMI-Z trajectory groups

25(OH)D categories	Stable moderate BMI Z-score, n (%)	Early transient low BMI Z-score, n (%)	Model 1 †	
			OR (95%CI)	*p*-value
Category I				
Sufficiency (≥50 nmol/L)	22 (8.06)	8 (14.3)	1.00	-
Insufficiency (30 to <50 nmol/L)	154 (56.4)	36 (64.3)	1.18 (0.33-4.21)	0.535
Deficiency (<30 nmol/L)	97 (35.5)	12 (21.4)	2.28 (0.63-8.20)	0.066
Category II				
Non-deficiency (≥50 nmol/L)	22 (8.06)	8 (14.3)	1.00	-
Deficiency (<50 nmol/L)	251 (91.9)	48 (85.7)	1.55 (0.45-5.34)	0.485

25(OH)D categories	Model 2‡		Model 3§	
	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value
Category I				
Sufficiency (≥50 nmol/L)	1.00	-	1.00	-
Insufficiency (30 to <50 nmol/L)	1.21 (0.26-5.71)	0.577	1.38 (0.14-13.9)	0.432
Deficiency (<30 nmol/L)	2.49 (0.52-11.9)	0.091	6.29 (0.58-68.5)	0.395
Category II				
Non-deficiency (≥50 nmol/L)	1.00	-	1.00	-
Deficiency (<50 nmol/L)	1.71 (0.38-7.75)	0.484	5.10 (0.51-50.6)	0.164

†Model 1 was unadjusted;
‡Model 2 was adjusted for maternal age, GWG, maternal vitamin D and folic acid supplementation, season of serum sampling, complications of pregnancy including gestational diabetes, hypertension disorders during pregnancy and gestational hyperlipidemia;
§Model 3 was additionally adjusted for fetal sex, SGA, LBW, breastfeeding duration and 1-year-old infant vitamin D status

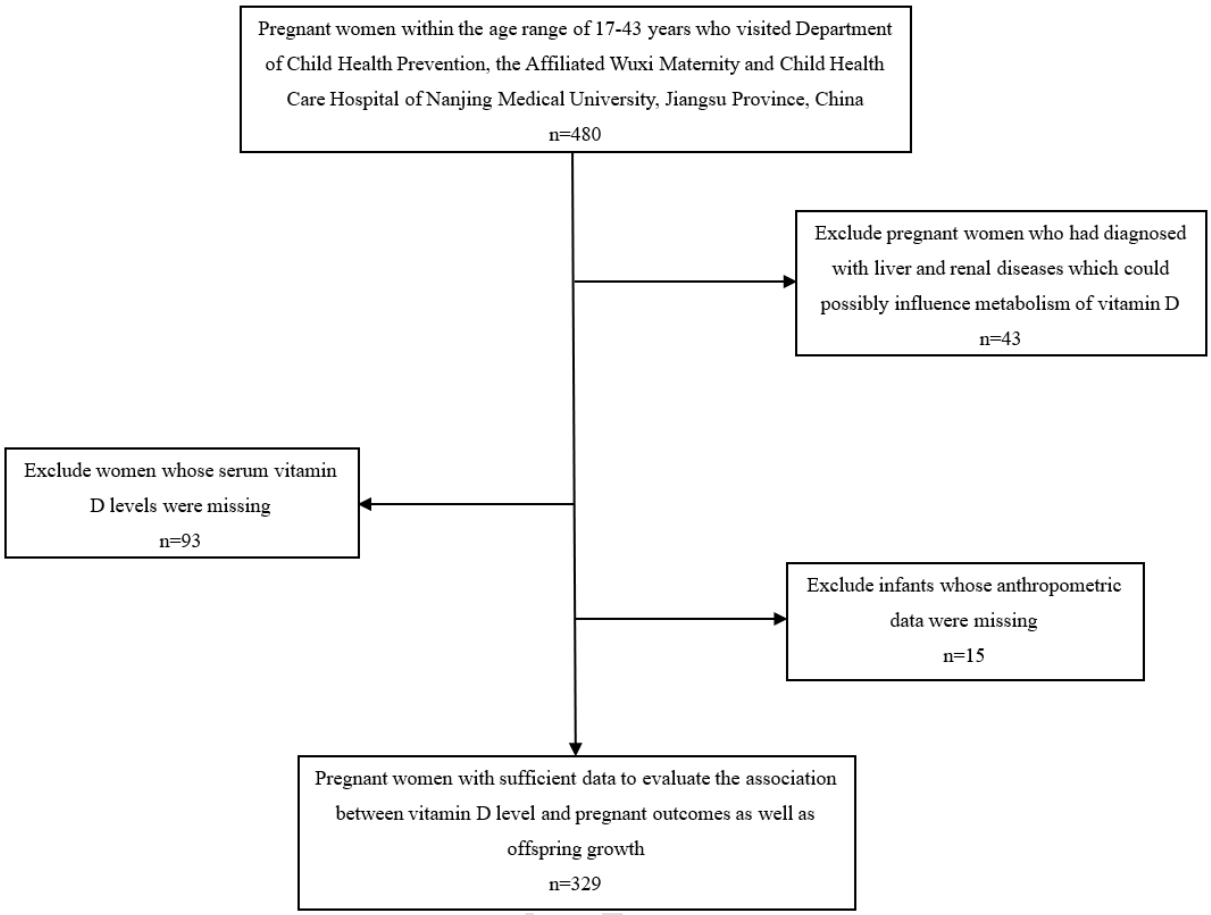

Figure 1. Flow chart for selection process of the study

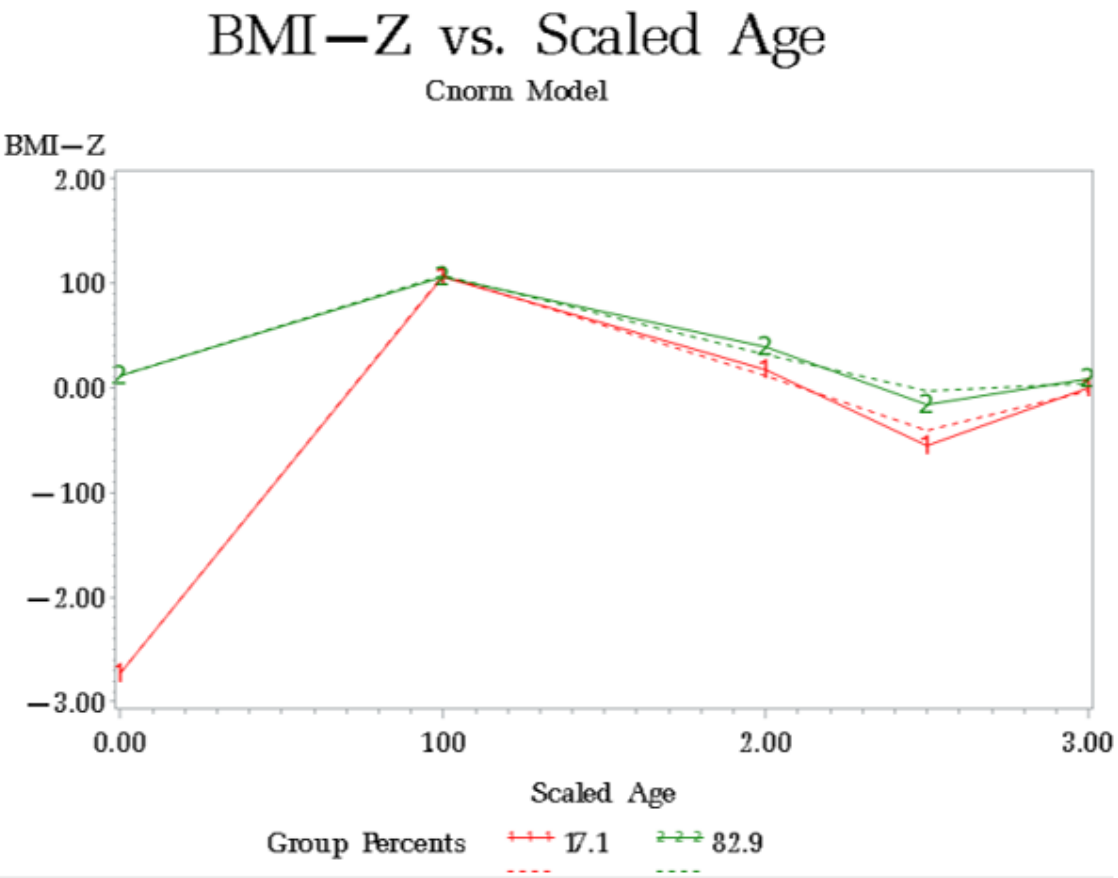

Figure 2. Modelling offspring growth trajectory in the first 3 years by LCGM. Red line stands for early transient BMI-Z, and green line stands for stable moderate BMI-Z

Supplementary table 1. Statistical characteristics for separate LCGM models

No. Latent classes	Polynomial degree	BIC (N=329)	Likelihood	Group precents	Mean posterior probabilities	Posterior probabilities > 0.7 (%)
1	Quadratic	-1760.99	-1749.40	100.00	1	-
2	Linear	-1828.86	-1808.57	21.9/78.1	0.89/0.64	82.2/16.8
2	Quadratic	-1752.74	-1726.65	19.5/80.5	0.79/0.92	68.5/92.7
2	Cubic	-1718.99	-1687.11	17.1/82.9	0.84/0.94	78.7/94.7
3	Linear	-1837.69	-1805.81	11.8/46.4/41.8	0.68/0.91/0.90	41.8/92.7/91.8
3	Quadratic	-1732.87	-1692.30	21.2/78.0/0.8	0.83/0.92/0.91	72.4/92.2/100
3	Cubic	-1724.20	-1674.93	16.2/70.2/13.7	0.83/0.88/0.69	75.0/85.8/41.5
4	Linear	-1847.09	-1803.62	3.00/48.0/37.2/11.8	0.70/0.96/0.85/0.69	40.0/95.7/83.5/42.9
4	Quadratic	-1740.98	-1685.92	19.0/63.9/0.60/16.4	0.79/0.83/1.00/0.68	69.5/73.2/100/35.4
4	Cubic	-1711.70	-1645.04	18.1/15.9065.4/0.60	0.84/0.73/0.86/1.00	76.4/55.6/80.6/100
5	Quadratic	-1745.79	-1676.24	19.7/0.30/62.3/0.60/17.1	0.81/1.00/0.83/1.00/0.68	76.3/100/70.2/100/44.2