

Cord Blood Vitamin D and Neurocognitive Development Are Nonlinearly Related in Toddlers^{1,2}

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Abstract

Background: Little is known about the relation between vitamin D status in early life and neurodevelopment outcomes.

Objective: This study was designed to examine the association of cord blood 25-hydroxyvitamin D [25(OH)D] at birth with neurocognitive development in toddlers.

Methods: As part of the China-Anhui Birth Cohort Study, 363 mother-infant pairs with complete data were selected. Concentrations of 25(OH)D in cord blood were measured by radioimmunoassay. Mental development index (MDI) and psychomotor development index (PDI) in toddlers were assessed at age 16–18 mo by using the Bayley Scales of Infant Development. The data on maternal sociodemographic characteristics and other confounding factors were also prospectively collected.

Results: Toddlers in the lowest quintile of cord blood 25(OH)D exhibited a deficit of 7.60 (95% CI: –12.4, –2.82; $P = 0.002$) and 8.04 (95% CI: –12.9, –3.11; $P = 0.001$) points in the MDI and PDI scores, respectively, compared with the reference category. Unexpectedly, toddlers in the highest quintile of cord blood 25(OH)D also had a significant deficit of 12.3 (95% CI: –17.9, –6.67; $P < 0.001$) points in PDI scores compared with the reference category.

Conclusions: This prospective study suggested that there was an inverted-U-shaped relation between neonatal vitamin D status and neurocognitive development in toddlers. Additional studies on the optimal 25(OH)D concentrations in early life are needed. *J Nutr* 2015;145:1232–8.

Keywords: cord blood, vitamin D, 25-hydroxyvitamin D, cognitive development, infant

Introduction

Vitamin D deficiency is common in pregnant women in many countries throughout the world (1–4). Studies from a variety of populations have shown that maternal vitamin D deficiency is associated with an increased risk of gestational diabetes, pre-eclampsia, and small-for-gestational-age infants (5, 6).

There is increasing evidence that vitamin D deficiency in early life may be linked to adverse neurodevelopment outcomes. Rodent studies have confirmed that low maternal vitamin D during pregnancy was linked to atypical behavior among adult offspring

(7) and has important ramifications for the developing brain including enlarged lateral ventricles, thinner cortex, and more cell proliferation (8). Epidemiologic evidence indicates that prenatal lower vitamin D status may be associated with adverse neuropsychiatric outcomes including schizophrenia (9) and autism (10).

Recently, 2 prospective longitudinal studies demonstrated a link between maternal vitamin D deficiency in early pregnancy and delayed neurocognitive development including language impairment (11), mental development, and psychomotor development (12). It has been confirmed that levels of 25-hydroxyvitamin D [25(OH)D]⁸ in cord blood closely correlated with maternal serum status (13, 14). Low levels of maternal 25(OH)D in the first and second trimester, which are known to be a critical period for

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⁸ Abbreviations used: BSID-CR, Bayley Scales of Infant Development of China Revision; GWG, gestational weight gain; MDI, mental development index; PDI, psychomotor development index; 25(OH)D, 25-hydroxyvitamin D.

the developing nervous system (15), may underpin the link between the exposure timing of pregnancy and offspring neurodevelopment outcomes.

However, the brain undergoes tremendous growth beginning early in gestation and continuing into the postnatal period. Various parts of the brain develop at different times and have different windows of vulnerability, both prenatally and postnatally, based on the temporal and regional maturation mediated through a multitude of developmental processes (15). If there is a causal relation between maternal vitamin D status in early gestation and neurodevelopment outcomes in offspring, it is plausible that infant vitamin D status at birth may also be linked to neurodevelopment outcomes in later life. However, this hypothesis has not been confirmed in humans.

In this prospective follow-up study in Anhui, China, where there was a high prevalence of maternal vitamin D deficiency, we examined the link between neonatal status of 25(OH)D and the neurocognitive development in children aged 16–18 mo.

Methods

Study design and participants. This study was nested within a prospective China-Anhui Birth Cohort Study (16). The details of subject recruitment are shown in Figure 1. Briefly, 2552 pregnant women who gave birth in the Hefei Maternal and Child Health Hospital between January and September 2008 were recruited, and 1491 cord blood samples were collected at birth. Women with delivery before 32 wk of gestation, pregnancy with assisted reproductive technology, multiple gestations, history of abnormal pregnancy, complications with pregnancy (including diabetes mellitus, hypertension, abnormal heart function, glandula thyroidea disease, intrahepatic cholestasis of pregnancy, and moderate or severe anemia), stillbirth, or birth defect were excluded from the study. One thousand two hundred sixty-six eligible participants were interviewed by telephone at 3 mo postpartum, and data about

breastfeeding and maternal postnatal depressive symptoms among 1027 participants were obtained. During 16–18 mo, the neurocognitive development was evaluated in a computer-generated random sample of 500 toddlers. One hundred thirty-seven mother-infant pairs refused the test of neurocognitive development. Finally, we obtained full data including prenatal data, cord blood samples, and cognitive ability assessments in toddlers among 363 mother-infant pairs. The study was approved by the Ethics Committee of the Anhui Medical University, and informed consent was obtained from the participants.

25(OH)D measurement in cord blood. Cord blood samples were collected immediately after delivery. Plasma samples were centrifuged and promptly refrigerated at -4°C and then transferred, within 12 h, to -80°C freezers. Concentrations of 25(OH)D were measured by using the commercial radioimmunoassay kits (DiaSorin Stillwater) according to the manufacturer's instructions. The limit of detection is 3.75 nmol/L. Intra-assay and interassay CVs were 8.8% and 11.1%, respectively. Cord blood concentrations of 25(OH)D were analyzed as both continuous and categorical variable with quintiles.

Neurocognitive development assessment. When children were at 16–18 mo of age, the neurocognitive development was evaluated by using the Bayley Scales of Infant Development of China Revision (BSID-CR) (17) in a standard test situation. Four certified examiners blinded to clinical data performed the examinations. All examiners had previous experience with the BSID-CR. The primary outcome measures were the mental developmental index (MDI) and psychomotor development index (PDI). Similar to the Bayley Scales of Infant Development second edition, the BSID-CR generates a raw score that is converted to the standardized MDI and PDI (both have a mean of 100 and SD of 15), which were corrected for the amount of prematurity. BSID-CR has been validated in a Chinese population of infants with the overall reliability coefficients for both mental and psychomotor scales being >0.95 (17).

Confounding factors. Information on essential potential confounders was collected from medical records or interviews in this prospective follow-up study. Maternal sociodemographic characteristics included age, education (≤ 9 and >9 y of completed schooling), and household incomes (<2000 , 2000 – 4000 , and >4000 yuan renminbi/mo; <300 , 300 – 600 , and >600 US\$/mo). Maternal health status included prepregnancy BMI, gestational weight gain (GWG), and parity (nulliparae or multiparae). Prepregnancy BMI was calculated on the basis of the height routinely measured at the clinic visit and on the prepregnancy weight obtained at interview. The amount of GWG was determined by subtracting the prepregnancy weight from the measured weight recorded at the last prenatal visit before delivery. Prepregnancy lifestyle included maternal alcohol consumption, father's smoking, and father's alcohol consumption for a period up to 6 mo before pregnancy. Birth outcomes included infant sex, gestational age, birth weight, and season of birth. Gestational age (in completed weeks) was calculated on the basis of the difference between the date of the last menstrual period and the date of delivery. Season of birth was designated as winter (December, January, and February), spring (March, April, and May), summer (June, July, and August), or autumn (September, October, and November). Information about breastfeeding and maternal postnatal depressive symptoms were collected via telephone interview 3 mo after delivery. The definitions of breastfeeding referred to the criteria of the WHO. Maternal postnatal depressive symptoms were assessed by using the Edinburgh Postnatal Depression Scale (Chinese version).

Statistical analysis. Differences between participants in this study and the whole cohort were examined using chi-square tests. Means and proportions for the characteristics of the participants across the quintiles of cord blood 25(OH)D concentrations were provided. The trends of MDI and PDI across quintiles of cord blood 25(OH)D concentrations were estimated by using a linear regression model. The means of the quintiles were fitted as continuous variables to estimate the trend of variables across quintiles in a linear regression model. Differences of MDI and PDI in toddlers by the characteristics of mother-infant pairs were evaluated using linear regression models.

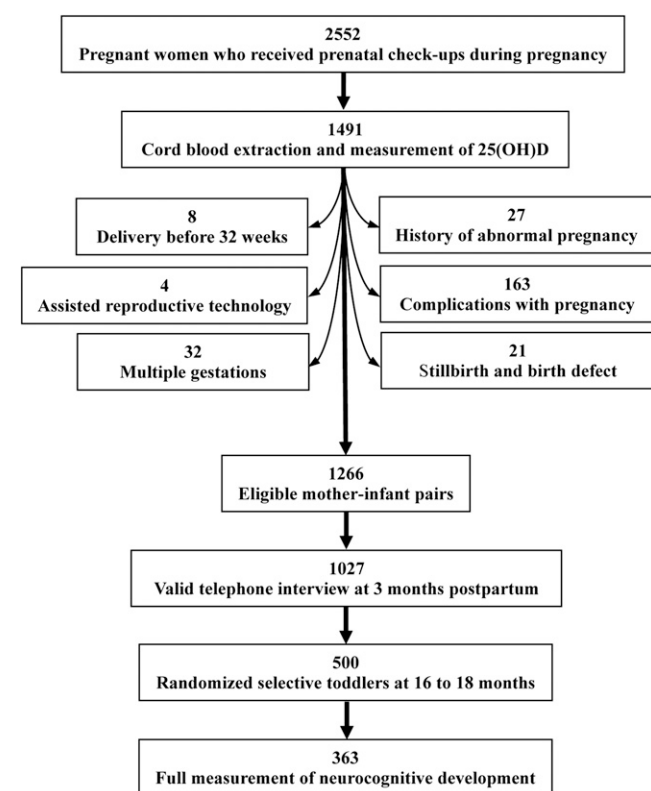


FIGURE 1 Flow diagram for subject recruitment in the prospective follow-up study. 25(OH)D, 25-hydroxyvitamin D.

The adjusted associations of cord blood 25(OH)D concentrations with MDI and PDI were examined by using multivariable regression models after adjustment for potential confounding factors: maternal sociodemographic characteristics (age, education, and income), health status (prepregnancy BMI, GWG, and parity), prepregnancy lifestyle (maternal alcohol consumption and father's smoking and alcohol consumption), birth outcomes (gestational week, birth weight, infant sex, and season of birth), breastfeeding, and maternal depressive symptoms at 3 mo postpartum. A nonlinear trend in MDI and PDI scores across the quintiles of cord blood 25(OH)D concentrations was observed. Next, the nonlinear relations of cord blood 25(OH)D concentrations with MDI and PDI were fitted in nonlinear regression models using a sine function. The goodness-of-fit of the models was checked for adequacy. Additionally, sensitivity analyses were performed to confirm the link between cord blood 25(OH)D concentrations and neurocognitive development.

Values in the text are regression coefficients (95% CI). Significance level was set at a value of $P = 0.05$ (2 tailed). All statistical analyses were performed with SPSS statistical software, version 21.0.

Results

The characteristics of participants in this study were similar to those of the whole cohort in terms of sociodemographic factors, prepregnancy lifestyle, health status, and birth outcomes, except for maternal education of >9 y (91.7% in current study

vs. 77.0% in the remainder of the cohort; $P < 0.001$) and primiparae (95.3% in current study vs. 84.8% in the remainder of the cohort; $P < 0.001$).

Table 1 shows the characteristics of 363 mother-infant pairs. The incidence of vitamin D deficiency (<50 nmol/L) was 78.8% in newborns. Most mothers in this study completed >9 y of school education, had middle-level incomes (>2000 yuan renminbi/mo), and were primiparae. Additionally, with increasing quintiles of cord blood 25(OH)D concentrations, the percentage of fathers who consumed alcohol (P -trend = 0.001) and births during summer or autumn (P -trend < 0.001) increased, whereas the proportion of low household incomes (P -trend < 0.001), multiparae (P -trend = 0.022), and breastfeeding at 3 mo postpartum (P -trend = 0.002) decreased. However, there was no significant linear trend in MDI ($P = 0.72$) and PDI ($P = 0.10$) scores across the quintiles of cord blood 25(OH)D concentrations.

Table 2 shows the associations of neurocognitive development with characteristics of mother-infant pairs in bivariate analyses. MDI was significantly associated with maternal age ($P = 0.004$), education ($P = 0.030$), incomes ($P = 0.025$), prepregnancy BMI ($P = 0.035$), GWG ($P = 0.046$), season of birth ($P < 0.001$), and breastfeeding at 3 mo postpartum ($P = 0.014$). PDI was significantly associated with maternal age ($P = 0.033$), education ($P = 0.011$), GWG ($P = 0.037$), infant sex ($P = 0.014$), and postnatal depressive symptoms ($P = 0.045$).

TABLE 1 Characteristics of the cohort according to cord blood 25(OH)D concentration¹

Characteristic	Cord blood 25(OH)D concentrations						<i>P</i> -trend ²
	All subjects (<i>n</i> = 363)	Quintile 1 (<i>n</i> = 72)	Quintile 2 (<i>n</i> = 73)	Quintile 3 (<i>n</i> = 73)	Quintile 4 (<i>n</i> = 73)	Quintile 5 (<i>n</i> = 72)	
Cord blood 25(OH)D, nmol/L							
Mean $\pm$ SD	37.2 $\pm$ 17.4	15.3 $\pm$ 4.28	26.3 $\pm$ 3.00	36.0 $\pm$ 2.49	45.1 $\pm$ 3.13	63.4 $\pm$ 11.6	
Range	5.56–111	5.56–20.8	20.8–30.9	31.0–39.8	39.9–51.0	51.3–111	
Sociodemographic characteristics							
Maternal age, y	27.6 $\pm$ 2.52	27.5 $\pm$ 2.89	27.5 $\pm$ 2.18	27.5 $\pm$ 2.71	27.8 $\pm$ 2.48	27.7 $\pm$ 2.34	0.41
Maternal education <9 y, <i>n</i> (%)	30 (8.3)	8 (11.1)	12 (16.4)	0 (0.0)	2 (2.7)	8 (11.1)	0.11
Maternal income <2000 yuan RMB, <i>n</i> (%)	44 (12.1)	18 (25.0)	13 (17.8)	9 (12.3)	2 (2.7)	2 (2.8)	<0.001
Health status							
Prepregnancy BMI, kg/m ²	20.1 $\pm$ 2.45	20.1 $\pm$ 3.20	20.4 $\pm$ 2.15	20.5 $\pm$ 2.72	19.6 $\pm$ 2.02	20.0 $\pm$ 1.87	0.25
Multiparae, <i>n</i> (%)	17 (4.7)	8 (11.1)	5 (6.8)	0 (0.0)	0 (0.0)	4 (5.6)	0.022
GWG, kg	17.5 $\pm$ 5.12	18.1 $\pm$ 6.15	18.7 $\pm$ 4.68	18.1 $\pm$ 4.85	18.3 $\pm$ 4.95	16.0 $\pm$ 4.57	0.11
Prepregnancy lifestyle, ³ <i>n</i> (%)							
Maternal alcohol consumption ⁴	75 (20.7)	14 (19.4)	14 (19.4)	17 (23.3)	21 (28.8)	9 (12.5)	0.78
Father's smoking ⁵	93 (25.6)	18 (25.0)	18 (24.7)	15 (20.5)	23 (31.5)	19 (26.4)	0.31
Father's alcohol consumption ⁴	287 (79.1)	50 (69.4)	56 (76.7)	52 (71.2)	65 (89.0)	64 (88.9)	0.001
Birth outcomes							
Male infant, <i>n</i> (%)	181 (49.9)	37 (51.4)	35 (47.9)	33 (45.2)	48 (65.8)	28 (38.9)	0.71
Gestational weeks	39.1 $\pm$ 1.20	38.8 $\pm$ 1.03	39.4 $\pm$ 1.38	39.2 $\pm$ 1.14	39.0 $\pm$ 1.22	39.1 $\pm$ 1.18	0.79
Birth weight, g	3390 $\pm$ 400	3428 $\pm$ 381	3450 $\pm$ 375	3429 $\pm$ 485	3370 $\pm$ 368	3272 $\pm$ 360	0.18
Birth during summer or autumn, <i>n</i> (%)	187 (51.5)	6 (8.3)	26 (35.6)	41 (56.2)	51 (69.9)	63 (87.5)	<0.001
Breastfeeding at 3 mo postpartum, <i>n</i> (%)	199 (54.8)	39 (54.2)	54 (74.0)	38 (52.1)	35 (47.9)	33 (45.8)	0.002
Postnatal depressive symptoms ⁶	7.6 $\pm$ 4.0	7.5 $\pm$ 3.7	7.5 $\pm$ 3.2	7.6 $\pm$ 4.4	7.7 $\pm$ 4.8	7.5 $\pm$ 3.8	0.49
Neurocognitive development in toddlers ⁷							
MDI	105 $\pm$ 11.4	103 $\pm$ 11.4	105 $\pm$ 11.8	104 $\pm$ 11.7	106 $\pm$ 10.8	104 $\pm$ 11.6	0.72
PDI	104 $\pm$ 14.2	102 $\pm$ 13.5	105 $\pm$ 14.5	109 $\pm$ 13.3	106 $\pm$ 12.8	98.2 $\pm$ 14.6	0.10

¹ Values are means $\pm$ SDs or *n* (%) or range; *n* = 363. GWG, gestational weight gain; MDI, mental development index; PDI, psychomotor development index; RMB, renminbi; 25 (OH)D, 25-hydroxyvitamin D.

² Test for trend based on Mantel-Haenszel chi-square test for categorical variables and linear regression for continuous variables.

³ Prepregnancy lifestyle means lifestyle for the period up to 6 mo before pregnancy.

⁴ Alcohol consumption was defined as any alcohol consumption.

⁵ Father's smoking was defined as >6 cigarettes daily.

⁶ Measured at 3 mo postpartum.

⁷ Measured at 16–18 mo postpartum.

TABLE 2 Associations of the characteristics of mother-infants pairs with neurocognitive development in toddlers ($n = 363$)¹

Characteristic	MDI		PDI	
	β (95% CI)	<i>P</i>	β (95% CI)	<i>P</i>
Sociodemographic characteristics				
Maternal age, y	0.69 (0.23, 1.15)	0.004	0.63 (−0.05, 1.21)	0.033
Maternal education, y				
Low (≤ 9)	Ref		Ref	
High (> 9)	4.74 (0.47, 9.00)	0.030	6.91 (1.62, 12.2)	0.011
Maternal income, yuan RMB				
Low (< 2000)	Ref		Ref	
Medium (2000–4000)	1.46 (−2.62, 5.53)	0.48	0.12 (−4.87, 5.12)	0.96
High (> 4000)	5.30 (0.69, 9.91)	0.025	1.11 (−5.60, 7.81)	0.74
Health status				
Prepregnancy BMI	−0.52 (−1.00, −0.04)	0.035	−0.35 (−0.95, 0.25)	0.24
GWG, kg	−0.23 (−0.46, −0.01)	0.046	−0.30 (−0.59, −0.02)	0.037
Parity				
Primipara	Ref		Ref	
Multipara	−1.51 (−7.09, 4.08)	0.59	−4.90 (−11.8, 2.02)	0.16
Pregpregnancy lifestyle ²				
Maternal alcohol consumption				
None	Ref		Ref	
Any	1.08 (−1.84, 3.99)	0.46	2.52 (−1.10, 6.13)	0.17
Father's smoking				
None	Ref		Ref	
1–5 cigarettes daily	0.15 (−3.14, 3.43)	0.92	0.69 (−3.42, 4.80)	0.74
> 6 cigarettes daily	0.34 (−2.44, 3.12)	0.80	−0.60 (−4.14, 2.92)	0.73
Father's alcohol consumption				
None	Ref		Ref	
Any	−1.26 (−4.16, 1.64)	0.39	0.17 (−3.43, 3.78)	0.92
Birth outcomes				
Infant sex				
Male	Ref		Ref	
Female	0.15 (−2.21, 2.51)	0.90	3.67 (0.76, 6.58)	0.014
Gestational weeks	−0.30 (−1.28, 0.69)	0.55	0.12 (−1.10, 1.35)	0.84
Birth weight, kg	0.00 (−0.00, 0.01)	0.17	0.00 (−0.01, 0.01)	0.94
Season of birth				
Summer–autumn	Ref		Ref	
Winter–spring	4.49 (2.17, 6.81)	< 0.001	1.75 (−1.18, 4.69)	0.24
Breastfeeding at 3 mo postpartum				
Yes	Ref		Ref	
No	−3.67 (−6.60, −0.74)	0.014	0.88 (−2.75, 4.51)	0.63
Postnatal depressive symptoms ³	−0.30 (−0.87, 0.29)	0.28	−0.71 (−1.40, −0.01)	0.045

¹ GWG, gestational weight gain; MDI, mental development index; PDI, psychomotor development index; Ref, reference; RMB, renminbi.² Pregpregnancy lifestyle means lifestyle for the period up to 6 mo before pregnancy.³ Measured at 3 mo postpartum.

Toddlers in the third and fourth quintile of cord blood 25 (OH)D concentrations were chosen as the PDI and MDI reference category, respectively, because they were the highest MDI or PDI scores. **Figure 2** shows the differences in the neurocognitive development in toddlers across the quintiles of 25(OH)D concentrations in cord blood. In the multivariable linear models, toddlers in the lowest quintile showed a reduction of 7.60 (95% CI: −12.4, −2.82; $P = 0.002$) and 8.04 (95% CI: −12.9, −3.11; $P = 0.001$) points in the MDI and PDI scores, respectively, in comparison with the reference category after adjustment for confounding factors. Unexpectedly, toddlers in the highest quintile of cord blood 25(OH)D concentrations also had a significant deficit of 12.3 (95% CI: −17.9, −6.67; $P < 0.001$) points in PDI scores, compared with the reference category.

A nonlinear trend in MDI and PDI scores across the quintiles of cord blood 25(OH)D concentrations was observed. We further fitted the nonlinear regression model using a sine function to best display the dose-response relation between the variables of interests. The solid black line shows the best-fit analysis for the association of cord blood 25(OH)D concentrations with the MDI (adjusted $R^2 = 0.94$, $P = 0.005$) and PDI (adjusted $R^2 = 0.91$, $P = 0.009$; **Figure 3**). The model fitted the data well because the residuals were randomly distributed.

We also undertook various sensitivity analyses to further explore the link between cord blood 25(OH)D concentrations and neurocognitive development. We examined this relation when the third and fourth quintiles were pooled as the reference category. Toddlers in the lowest quintile had a deficit of 5.58 (95% CI: −9.40, −1.75;

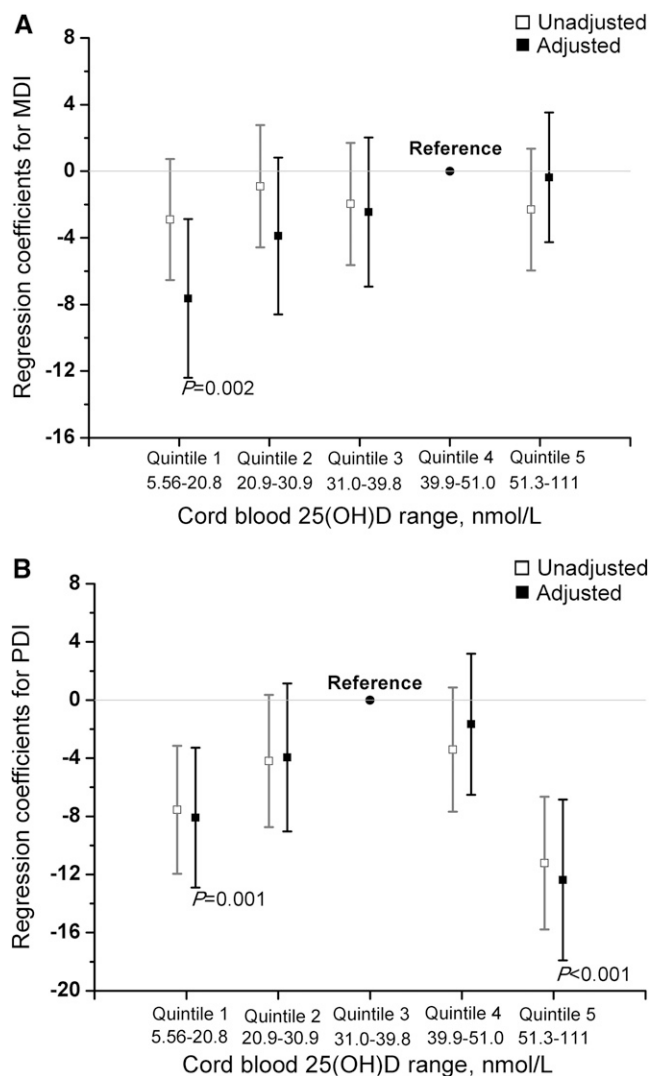


FIGURE 2 Differences in the MDI (A) and PDI (B) in toddlers by quintile of cord blood 25(OH)D concentration. Linear models were performed without and with adjustment for maternal sociodemographic characteristics, health status, prepregnancy lifestyle, birth outcomes, breastfeeding, and maternal depressive symptoms at 3 mo postpartum. Regression coefficients and 95% CIs were illustrated. MDI, mental development index; PDI, psychomotor development index; 25(OH)D, 25-hydroxyvitamin D.

$P = 0.004$) and 7.43 (95% CI: $-11.9, -2.97$; $P = 0.001$) points in the MDI and PDI scores, respectively, compared with the reference category. Similarly, the PDI scores of toddlers in the highest quintile remained significantly lower ($\beta = -4.00$; 95% CI: $-5.52, -2.49$; $P < 0.001$) than that in the reference category.

Discussion

The impacts of maternal vitamin D deficiency during early pregnancy on neuropsychologic development in offspring have been identified in 2 previous prospective longitudinal studies (11, 12). However, the development of the brain starts early in gestation and continues into the postnatal period. In humans, the growth rate of the human diencephalon peaks around the time of birth, whereas the peak rate of growth of the cerebellum is ~ 7 mo of age (18). The forebrain cortical structures of the neocortex and hippocampal formation develop primarily during

the fetal period; differentiation and synaptogenesis within and between these cortical structures and their subcortical afferents continue into the postnatal period. Myelination occurs later in development than proliferation and migration of neuronal populations and continues to progress through to adolescence in humans (19, 20).

Consistent with our hypothesis, this prospective follow-up study provided the first evidence that toddlers with lower levels of cord blood 25(OH)D were at a greater risk of delayed mental ($P = 0.002$) and psychomotor development ($P = 0.001$), because their MDI and PDI scored approximately 8 points lower than that in the reference category. Our findings further confirmed that lower neonatal vitamin D status at birth, not just during early pregnancy, still has negative impacts on later neurocognitive development. Similar effects of vitamin D status during fetal stage to birth on brain development may indicate a higher susceptibility of the brain to vitamin D deficiency during early lifetime periods. It is notable that there was a high level of vitamin D deficiency among newborns in this study. The potential public health implications of our findings are of immense importance, given the high prevalence of vitamin D deficiency in China as well as the magnitude of the effect on later impairment of neurocognitive development.

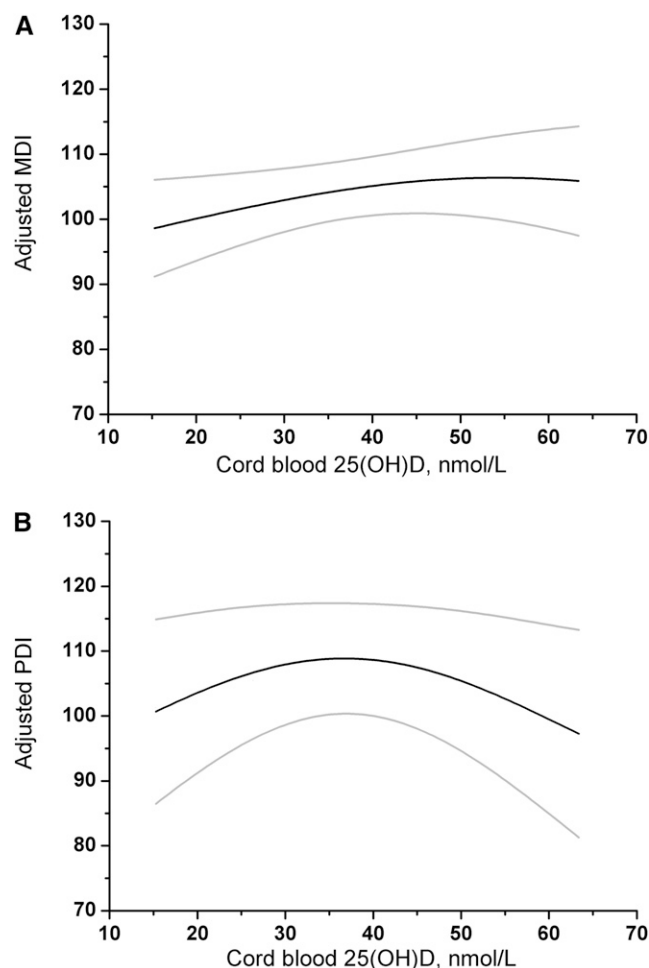


FIGURE 3 The nature of the association of cord blood 25(OH)D concentration with MDI (A) and PDI (B) in toddlers. The solid black line shows the best-fit analysis for the association of cord blood 25(OH)D concentrations with the MDI and PDI, which were tested by fitting the data to a sine function in a nonlinear regression model. The solid gray line denotes 95% CI. MDI, mental development index; PDI, psychomotor development index; 25(OH)D, 25-hydroxyvitamin D.

Unexpectedly, our findings also suggest that toddlers with the highest quintile of cord blood 25(OH)D concentrations also had a significantly increased risk of delayed psychomotor development ($P < 0.001$), with a deficit of ~12 points, compared with that in the reference group. The results of this study show that there is an inverted-U-shaped relation between cord blood 25(OH)D concentrations and later psychomotor development. The increased health risk with vitamin D levels in the upper range has also been previously observed among studies examining the risk of fetal growth restriction (21), allergic response (22, 23), lower-extremity function (24), frailty status (25), and cardiovascular disease (26, 27), as well as all-cause mortality (28). A case-control study from a Danish population-based cohort suggested that both low and high concentrations of neonatal vitamin D are associated with increased risk of schizophrenia (29). A recent prospective cohort study (30) showed that the offspring of mothers with very high circulating 25-hydroxycholecalciferol concentrations tended to have smaller head circumference ($P = 0.038$).

Concerning biologic plausibility, there is a lack of data about why high concentrations of vitamin D have adverse health effects. The mechanisms underlying the influence of high levels of vitamin D on motor development might be different from those of vitamin D deficiency, which might be related to suffering from rickets (31). We speculate that the neurodevelopmental impairment associated with high levels of vitamin D may result from the toxic (32) or proinflammatory (33) effect of vitamin D or genetic susceptibility to vitamin D (34). In the motor cortex of the monkey, synaptogenesis continues for several months postnatally, and then decreases until puberty (35). Postnatal myelination in humans, with increasing white matter density for the internal capsule (which is a fiber tract involved in motor function), proceeds into childhood. The late maturation of these pathways is related to ongoing increases in diameter and/or myelination of axons at least through birth to adolescence (20). Therefore, the developmental processes of special brain areas concerning the motor cortex may be disturbed by vitamin D in the upper concentration range during birth to several months postpartum, which may be the temporal window of vulnerability. The different effects of high levels of vitamin D on mental and psychomotor development may be explained by that various vulnerability of developmental processes that ontogeny of different parts of the brain occurs at different times during the prenatal and postnatal period (15). However, we could not exclude the possibility that the impaired psychomotor development associated with high concentrations of cord blood 25(OH)D may also be related to increasing exposure to organic pollutants or stress of hot weather (36–38). We recommend caution in this interpretation of the finding from observational epidemiology. Additional human or animal studies may be able to address these issues.

Based on the results of this study, the optimal levels of neonatal vitamin D with respect to later neurocognitive development outcomes might range from ~30 to 50 nmol/L (the third and fourth quintile range in this study), which appears somewhat low in light of recent recommendations (38). The Endocrine Society has defined 25–50 nmol/L as vitamin D deficient for bone-related health (39). However, consistent with our finding, a previous study suggested the optimal level of neonatal 25(OH)D for later schizophrenia risk ranged from 40.5 to 50.9 nmol/L (29). To date, optimal 25(OH)D levels in the neonate for brain-related outcomes have not yet been defined. However, our findings and other emerging evidence (11, 12) suggest that further studies on the optimal 25(OH)D levels in early life for various developmental outcomes, especially brain-related outcomes, are needed.

This study has 3 major strengths. First, to our knowledge, this is the first study examining the association between neonatal

vitamin D concentrations and the later neurodevelopment. Second, a nonlinear relation between neonatal vitamin D concentrations and later neurocognitive development was found using a sine function in a nonlinear regression model. Finally, to investigate the effects of neonatal vitamin D status on the later neurocognitive development, perinatal, prenatal, and postnatal covariates were controlled for through the use of multi-variable regression models.

However, some limitations should also be acknowledged in this study. First, although the sample of recruited participants during pregnancy was large, the final sample size in this study was relatively small. The selection bias was inevitable. The findings of this study need to be validated in other prospective cohort studies with larger samples. Second, we mainly focus on the effect of vitamin D at birth on the later neurodevelopment. However, the effect of vitamin D during pregnancy, especially early pregnancy, which is another critical window in the developmental progress of the brain, was neglected in this study. Third, dietary information during pregnancy and infancy was unavailable; thus, the effect of these variables on neurodevelopment in toddlers was unable to be examined. The lack of information about rickets also may confound the relation between delayed motor development and vitamin D deficiency in this study. Fourth, there is mixed evidence about the effects of maternal 25(OH)D concentrations on cognitive development (39, 40); therefore, further longitudinal cohort studies are needed to determine the long-term effects of vitamin D on neuropsychologic development. Additionally, participants in the current study were more likely to be primiparae and have higher education levels, which may limit the generalization of our findings. However, there was no evidence that the association between vitamin D status in early life and later neurodevelopment differed with parity or maternal education levels.

In conclusion, this prospective study found a nonlinear association between neonatal vitamin D concentrations and later neurocognitive development in toddlers. If the association is causal, it could have important implications for neonatal medicine and public health policy.

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