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Spain

Mental and Psychomotor Development

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Pediatrics 2012;130:e913; originally published online September 17, 2012;
DOI: 10.1542/peds.2011-3289

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Circulating 25-Hydroxyvitamin D₃ in Pregnancy and Infant Neuropsychological Development

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KEY WORDS

child development, cognition, infancy, intelligence, vitamin D

ABBREVIATIONS

CI—95% confidence intervals

FP—fractional polynomial

25(OH)D₃—25-hydroxyvitamin D₃

*Drs Morales and Guxens contributed equally to this work.

Dr Sunyer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; Drs Morales, Guxens, Sunyer were responsible for study concept and design; Drs Guxens, Llop, Tardón, Ibarluzea, Espada, and Sunyer were responsible for acquisition of data; Drs Morales and Guxens were responsible for drafting of the manuscript; Drs Llop, Rodríguez-Bernal, Tardón, Riaño, Ibarluzea, Lertxundi, Espada, Rodríguez, and Sunyer were responsible for critical revision of the manuscript for important intellectual content; Dr Guxens was responsible for statistical analysis; and Drs Ibarluzea, Tardón, and Sunyer obtained funding.

www.pediatrics.org/cgi/doi/10.1542/peds.2011-3289

doi:10.1542/peds.2011-3289

Accepted for publication May 16, 2012

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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WHAT'S KNOWN ON THIS SUBJECT: Adequate vitamin D status in mothers during pregnancy may influence the health status of offspring later in life. Growing evidence based on animal studies is linking vitamin D to brain development and functioning, but studies in humans are lacking.

WHAT THIS STUDY ADDS: This large-scale prospective pregnancy cohort study examines the association between maternal circulating 25-hydroxyvitamin D₃ concentrations in pregnancy and offspring neuropsychological development. Higher circulating concentration of 25-hydroxyvitamin D₃ in pregnancy was associated with improved mental and psychomotor development in infants.

abstract

OBJECTIVE: To investigate whether circulating 25-hydroxyvitamin D₃ [25(OH)D₃] concentration in pregnancy is associated with neuropsychological development in infants.

METHODS: The Spanish population-based cohort study Infancia y Medio Ambiente Project recruited pregnant women during the first trimester of pregnancy between November 2003 and February 2008. Completed data on 1820 mother-infant pairs were used. Maternal plasma 25(OH)D₃ concentration was measured by high-performance liquid chromatography in pregnancy (mean 13.5 ± 2.1 weeks of gestation). Offspring mental and psychomotor scores were assessed by trained psychologists at age 14 months (range, 11–23) by using the Bayley Scales of Infant Development. β -Coefficients with 95% confidence intervals (CIs) of mental and psychomotor scores associated with continuous or categorical concentrations of maternal plasma 25(OH)D₃ were calculated by using linear regression analysis.

RESULTS: The median plasma value of 25(OH)D₃ in pregnancy was 29.6 ng/mL (interquartile range, 21.8–37.3). A positive linear relationship was found between circulating concentrations of maternal 25(OH)D₃ concentrations in pregnancy and mental and psychomotor scores in the offspring. After adjustment for potential confounders, infants of mothers with 25(OH)D₃ concentrations in pregnancy >30 ng/mL showed higher mental score ($\beta = 2.60$; 95% CI 0.63–4.56) and higher psychomotor score ($\beta = 2.32$; 95% CI 0.36–4.28) in comparison with those of mothers with 25(OH)D₃ concentrations <20 ng/mL.

CONCLUSIONS: Higher circulating concentration of maternal 25(OH)D₃ in pregnancy was associated with improved mental and psychomotor development in infants. *Pediatrics* 2012;130:e913–e920

Vitamin D deficiency is a public health issue worldwide.¹ Growing evidence based on animal studies is linking vitamin D to brain development and functioning.^{2,3} Potential effects of vitamin D during brain development include neurotrophic actions,⁴ neuroprotective effects,^{5,6} and changes in brain structure and gene expression.^{7,8} It is unknown how evidence from animal studies translates to humans, but it is possible that vitamin D status during brain development affects cognitive functioning later in life.

Studies in humans examining the effects of blood concentrations of 25-hydroxyvitamin D₃ [25(OH)D₃] on brain development and cognitive functioning are limited and inconclusive. Several studies in middle-aged and older adults have shown positive associations between serum concentrations of 25(OH)D₃ and cognitive function.^{9–18}

Epidemiological studies examining whether circulating concentration of 25(OH)D₃ in early life is associated with brain development and cognitive function are scarce. To date, only 2 prospective studies have assessed the association of vitamin D status in pregnancy, measured as circulating concentrations, with cognitive function in offspring.^{19,20} Gale et al¹⁹ found no association between maternal serum 25(OH)D₃ concentrations during late pregnancy (32 weeks) and childhood cognitive function at 9 years of age in 178 mother-child pairs. More recently, a prospective study conducted on 743 mother-child pairs reported insufficient maternal serum 25(OH)D₃ concentrations, measured at 18 weeks pregnancy, to be significantly associated with offspring language impairment at 5 and 10 years of age.²⁰ Moreover, a larger cross-sectional study (*N* = 1676) reported null associations of circulating vitamin D concentrations with cognitive function in adolescents (age 12–17 years).^{21,22}

Given the emerging evidence on developmental origins of health and disease paradigm,²³ examining the association between vitamin D status in pregnancy and neuropsychological development in early life can be particularly relevant, because windows of unique vulnerability and susceptibility to prenatal influences are inherent in the developing brain more than in the brain of an adult,²⁴ and consequences of a halted or inhibited developmental process can be permanent owing to little potential for later repair. We assessed whether circulating maternal 25(OH)D₃ concentration in pregnancy, a good marker of vitamin D availability to tissues and reliable indicator of vitamin D status,²⁵ is associated with offspring neuropsychological development in infancy.

METHODS

Design and Study Population

Data come from 4 prospective population-based pregnant cohort studies in Spain embedded in the INfancia y Medio Ambiente (Environment and Childhood) Project (www.proyectoima.org).²⁶ In brief, between November 2003 and February 2008, a total of 2644 women who fulfilled the inclusion criteria (≥ 16 years of age, intention to deliver at the reference hospital, no problems of communication, singleton pregnancy, and no assisted conception) were recruited during the first prenatal visit in 4 areas of study: Valencia (39°N latitude, *n* = 855), Sabadell (41°N latitude, *n* = 657), Gipuzkoa (42°N latitude, *n* = 638), and Asturias (43°N latitude, *n* = 494). Overall, 2505 (97%) women were followed until child's birth. Circulating 25(OH)D₃ concentrations in pregnancy were determined in 2389 women, and, among them, neuropsychological assessment was performed in 2112 (89% of eligible) infants. Exclusion criteria were birth at < 37 weeks of gestation (*n* = 82), unknown gestational age (*n* = 16), underlying pathology (*n* = 17),

poor-quality neuropsychological assessment (*n* = 124), and missing information on potential covariates (*n* = 53). Ultimately, 1820 (86% of eligible) mother-infant pairs were analyzed (Fig 1). The study was approved by the ethical committees of the centers involved in the study, and written informed consent was obtained from the parents of all children.

Assessment of Maternal Circulating 25(OH)D₃ Concentrations

A single maternal blood specimen was drawn during pregnancy (mean, 13.5 ± 2.1 weeks of gestation). Most blood draws (88%) were done during the second trimester of pregnancy (from 12 to 23 weeks of gestation), with 11.6% during the first trimester (< 12 weeks of gestation), and $< 1\%$ late in pregnancy (from 24 to 36 weeks of gestation). Samples were processed immediately and stored from -70 to -80°C until analysis. Maternal plasma concentrations of 25(OH)D₃ were quantified by high-performance liquid chromatography method by using a BioRAD kit according to Clinical and Laboratory Standard Institute protocols.²⁷ Detection limit was 5 ng/mL, and interassay coefficient of variation was 4.5%. The assay was validated by German Programmes of External Evaluation of Quality (DGKL-RFB-Referenzinstitut für Bionalytik), and results were satisfactory in 100% of the cases.

Assessment of Infant Neuropsychological Development

Neuropsychological development was assessed at age 14 months (range, 11–23 months) by using the Bayley Scales of Infant Development that assess age-appropriate mental (163 items) and psychomotor (81 items) development.²⁸ All testing was done by specially trained psychologists. Interobserver differences were quantified, and 3 sets of quality

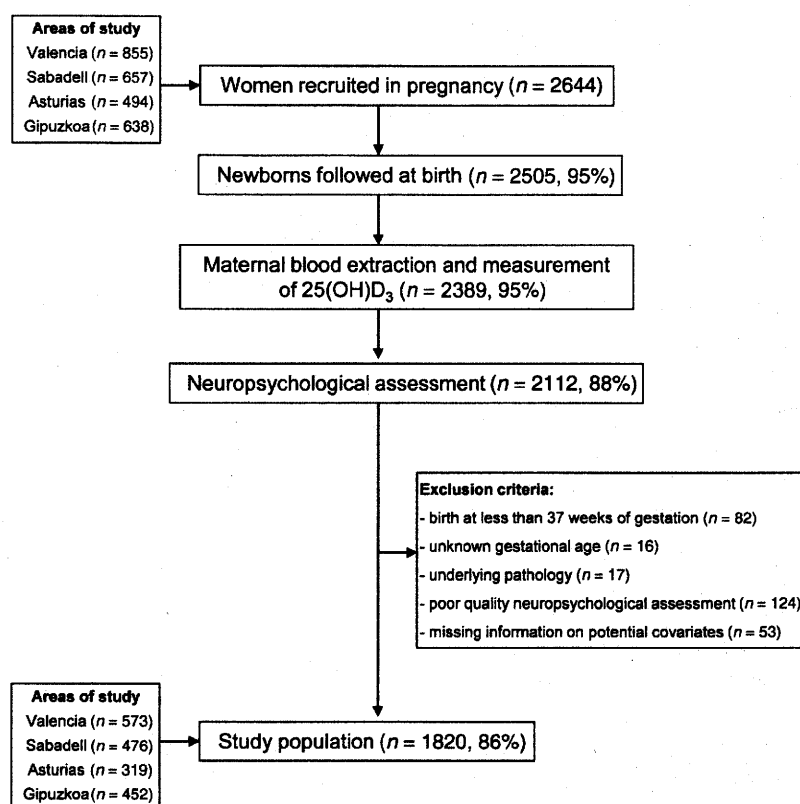


FIGURE 1
Flowchart of study population.

controls were undertaken. The inter-rater reliability, estimated by intraclass correlation, was 0.90 for mental scale and 0.96 for psychomotor scale. Furthermore, internal consistency determined by the Cronbach α -coefficient was 0.70 for mental scale and 0.73 for psychomotor scale. Raw scores were standardized for child's age in days at testing by using a parametric method for the estimation of age-specific reference intervals.²⁹ Normal distribution was adopted as starting point for model building. The parameters of the distribution (M and S curves, for the mean and SD, respectively) were modeled as a fractional polynomial (FP) function of age. FP models for the M and S curves were found by grid search of the powers in P by using Generalized Least Squares. The powers were selected from a small predefined set $P = \{-3, -2, -1, -1/2, 0, 1/2, 1, 2, 3\}$ allowing up to FP with degree 3. Once

the best powers in FP models have been chosen, the regression coefficients were estimated by maximum likelihood. Residuals were then standardized to a mean of 100 points with a SD of 15 points to homogenize the scales.

Potential Confounders

Based on previous knowledge, the following were considered a priori potential confounding factors because of their possible associations with maternal circulating 25(OH)D₃ concentration and neuropsychological test scores: child's gender, birth weight, maternal age, parity, maternal country of origin, parental social class, maternal education level, maternal pre-pregnancy BMI, and maternal smoking and alcohol consumption during pregnancy. Questionnaires during the first trimester of pregnancy obtained information about parity (0 vs 1 or more), maternal age, maternal country of birth (Spanish

versus foreign), parental social class (defined as maternal or paternal occupation during pregnancy based on the highest social class by using a widely used Spanish adaptation of the international ISCO88 coding system) (I–II, managers/technicians; III, skilled; IV–V, semiskilled/unskilled), maternal education level (primary or less, secondary, university degree), and maternal pre-pregnancy BMI based on measured height at recruitment and pre-pregnancy self-reported weight (normal weight/underweight [≤ 24.99], overweight [$25–29.99$], obese [≥ 30]). Information on maternal smoking (no versus yes) and alcohol consumption during pregnancy (no versus yes, defined as consumption of alcohol beverages at least 1 time/month) was collected through questionnaires during the third trimester. All questionnaires were administered face-to-face by trained interviewers. Information related to child's gender, birth weight, and gestational age was obtained from clinical records.

Statistical Analysis

Maternal circulating 25(OH)D₃ concentrations were normally distributed. Clinically defined 25(OH)D₃ cut points were used: <20 ng/mL (reference group), 20 to 30 ng/mL, and >30 ng/mL.³⁰ Differences in baseline characteristics of participants across categories of maternal 25(OH)D₃ concentrations were compared by using χ^2 tests for categorical variables, analysis of variance for continuous variables with normal distribution, and Kruskal-Wallis tests for variables with skewed distributions. To adjust for month at blood collection, 2 approaches were used. In the first approach, we used “deseasonalization” of 25(OH)D₃ concentrations. In this approach seasonality of 25(OH)D₃ was tested by fitting the data to a sine function with a period of 12 months in a nonlinear regression cosinor model.³¹ Then, the predicted 25(OH)D₃ concentrations based on month at

blood collection for each subject, derived from the sinusoidal model, were subtracted from the actual observed value. Subsequently, the overall mean was added and the resulting deseasonalized 25(OH)D₃ concentrations were analyzed. In the second approach, we used raw 25(OH)D₃ concentrations for the regression analysis in which we adjusted for month at blood collection. The results of these 2 approaches were essentially the same. Thus, the results using deseasonalized 25(OH)D₃ concentrations are presented in the main article, and the results using raw 25(OH)D₃ concentrations and adjusting for month are presented in the supplemental material (Supplemental Table 3). Linear dose-response relationship between maternal 25(OH)D₃ concentrations during pregnancy and infant neuropsychological development scores was assessed by using adjusted generalized additive models by graphical examination and likelihood ratio.³² To examine the relationship between infant neuropsychological development and maternal 25(OH)D₃ concentrations, we used multivariable linear regression models. We treated circulating concentrations of 25(OH)D₃ as continuous (effect per 10 ng/mL) and clinically defined categories. Analyses were first adjusted for area of study (base model). Next, a fully adjusted model included child's gender, birth weight, maternal country of origin, maternal age, parental social class, maternal education level, parity, maternal pre-pregnancy BMI, and maternal smoking and alcohol consumption in pregnancy. There was no evidence that the associations of maternal 25(OH)D₃ concentrations with infant's neuropsychological scores differed between genders (all *P* values for interaction >0.2), and all results are presented for both genders combined. To preclude potential residual confounding, we assessed whether the associations were consistent across strata defined by maternal pre-pregnancy BMI, parental

social class, and maternal education level. Analyses were conducted by using Stata software, version 11.1 (StataCorp, College Station, TX) and R statistical package version 2.13.0.

RESULTS

The study population included 49.7% male children and 58% firstborn. Ninety-two percent of mothers were born in Spain, and maternal mean age at child birth was 31.9 (4.2) years. Twenty-two percent of mothers had a low educational level (primary or less) and 33% were from high social class. Twenty-six percent of women were overweight/obese before pregnancy. Sixteen percent of women reported tobacco smoking and 19.6% alcohol consumption during pregnancy. Compared with excluded participants, those who were included in the present analysis showed higher birth weight, had higher social class, and mothers tended to smoke less during pregnancy, but did not differ in

other main baseline characteristics (Supplemental Table 4).

The median plasma value of 25(OH)D₃ in pregnancy was 29.6 ng/mL (interquartile range, 21.8–37.3). A total of 356

(19.5%) pregnant women had vitamin D deficiency [25(OH)D₃ concentration

<20 ng/mL], and 574 (31.5%) had vitamin D insufficiency [25(OH)D₃ concentration 20–30 ng/mL]. The characteristics

of participants according to clinically defined cutoff points of circulating 25(OH)D₃ concentrations during pregnancy are shown in Table 1. Concentrations of circulating 25(OH)D₃ in pregnancy differed among areas of study, with Valencia area showing the highest concentrations and Asturias the lowest concentrations. Increasing trends across the clinically defined 25(OH)D₃ categories were observed for maternal age, parity, and maternal alcohol consumption. Decreasing trends across the categories of 25(OH)D₃ were found for lower parental social class and education level,

TABLE 1 Characteristics of Participants According to Maternal Circulating 25(OH)D₃ Concentrations in Pregnancy

	Serum 25(OH)D ₃ Concentration			<i>P</i> Value Trend
	<20 ng/mL (<i>n</i> = 356)	20–30 ng/mL (<i>n</i> = 574)	>30 ng/mL (<i>n</i> = 890)	
Area of study				
Valencia (39°N latitude)	20.2	29.6	37.2	<.001
Sabadell (41°N latitude)	30.3	23.2	26.4	
Gipuzkoa (42°N latitude)	24.7	27.2	23.4	
Asturias (43°N latitude)	24.7	20.0	13.0	
Child's gender (male)	51.1	50.2	48.8	.722
Birth weight, g	3300 (435)	3283 (419)	3302 (419)	.685
Maternal age at child's birth, y	31.5 (4.5)	31.6 (4.1)	32.2 (4.0)	.004
Parity (1 or more)	36.8	41.6	44.3	.053
Maternal country of birth (non-Spanish)	9.0	6.8	7.4	.460
Parental social class				
I/II Managers/technicians	28.4	30.7	36.0	.037
III Skilled manual/nonmanual	26.1	27.5	26.5	
IV/V Semiskilled/unskilled	45.5	41.8	37.5	
Maternal education level				
Primary or less	23.9	22.1	22.3	.273
Secondary	43.5	43.6	39.4	
University degree	32.6	34.3	38.3	
Maternal pre-pregnancy BMI				
Normal weight/underweight (<24.99)	68.3	74.0	75.6	.086
Overweight (25–29.99)	22.5	19.0	16.6	
Obese (≥30)	9.3	7.0	7.8	
Smoking at third trimester (yes)	20.2	16.4	13.9	.022
Alcohol during pregnancy (yes)	18.0	16.4	22.4	.013

Values are percentages for categorical variables and mean (SD) for continuous variables.

among smokers and overweight mothers.

Maternal plasma concentrations of 25(OH)D₃ showed a seasonal distribution ($P < .05$, Fig 2). Maximum fitted concentrations of maternal plasma 25(OH)D₃ were observed in blood samples collected in August, and concentrations reached their nadir in February (Fig 2).

A positive linear relationship was found between circulating concentrations of maternal 25(OH)D₃ in pregnancy and both mental (Fig 3A) and psychomotor (Fig 3B) development scores in the offspring. In multivariable models, each 10 ng/mL increase in 25(OH)D₃ in pregnancy resulted in up to 0.79 and 0.88 points increase in mental and psychomotor development scores in offspring, respectively (Table 2). In the basic model with adjustment for area of study, infants of mothers with 25(OH)D₃ concentrations >30 ng/mL showed an advantage of 3.17 and 2.42 points in the mental and psychomotor scores, respectively, in comparison with those of mothers with 25(OH)D₃ concentrations <20 ng/mL (model 1) (Table 2). Although attenuated, these associations remained significant after adjustment for potential confounders including child's gender, birth weight, maternal country of origin, maternal age, parental socioeconomic status, maternal education level, parity, maternal pre-pregnancy BMI, and

maternal smoking and alcohol consumption in pregnancy (model 2) (Table 2).

In addition, the associations did not differ according to maternal pre-pregnancy BMI, maternal social class or education level (all P values for interactions >0.1).

DISCUSSION

To our knowledge this is one of the first large-scale prospective pregnancy cohort studies to examine the association between maternal circulating 25(OH)D₃ concentrations in pregnancy and offspring neuropsychological development in infancy. Higher concentrations of circulating 25(OH)D₃ in pregnancy were associated with improved mental and psychomotor scores. Infants of mothers with 25(OH)D₃ concentrations >30 ng/mL (clinically considered as optimal levels) showed an advantage of 2.6 and 2.3 points in mental and psychomotor scores, respectively, in comparison with those of mothers with 25(OH)D₃ concentrations <20 ng/mL (considered as deficient levels). The association remained significant after adjusting for a wide range of potential confounding and intermediate factors.

The main strengths of this study include its population-based prospective design and large sample size as well as examination of the associations with

plasma measurements of 25(OH)D₃ concentration, a reliable indicator of vitamin D status that also quantifies the outdoor exposure, rather than dietary reports that are likely to be influenced by reporting bias. Possible confounding was addressed in multivariable analyses adjusted for a wide range of potential confounding factors. Finally, we found a strong positive linear relationship at lower concentrations of maternal circulating 25(OH)D₃ (below 50–60 ng/mL), which supports the robustness of the findings; however, the generalization of this assumption at higher concentrations is limited owing to the small number of observations (ie, "sparse data bias").

The study has some limitations. First, only a single 25(OH)D₃ measurement per subject was available that could not reflect maternal long-term status during the entire pregnancy. Dealing with misclassification of estimated long-term vitamin D exposure by season of blood draw was accounted estimating deseasonalized 25(OH)D₃ concentrations based on a sinusoidal model. Second, we did not assess the effect of circulating 25(OH)D₂ concentrations, but, normally, majority of the 25(OH)D is in D₃ form. Third, the lack of information of infant's vitamin D status is another limitation. Fourth, we could not measure 25(OH)D₃ concentrations in all recruited subjects, which made selection bias possible. Participants were more likely to be female and parents had higher social class and education level; however, there was no evidence that the association between circulating maternal 25(OH)D₃ concentrations in pregnancy and infant's neuropsychological scores differed between genders, parental social class, or maternal education level. Fifth, parental intelligence, an important determinant of infant mental development, was not evaluated. However, parental education level and social class did not confound or modify

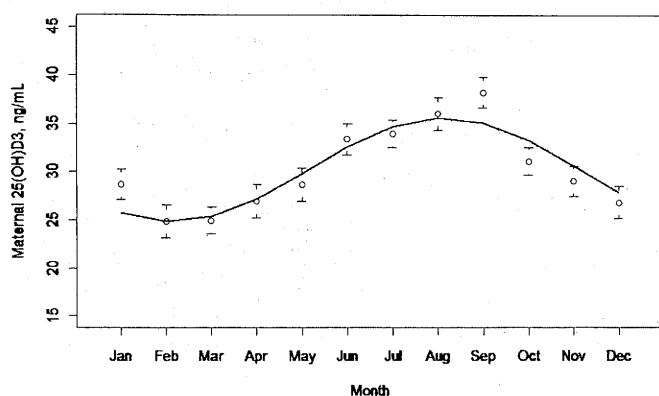


FIGURE 2

Fitted sinusoidal model for observed maternal circulating concentration of 25(OH)D₃ superimposed on plot of observed monthly mean and 95% CI values for 25(OH)D₃ concentration among 2112 participants in the INMA Project.

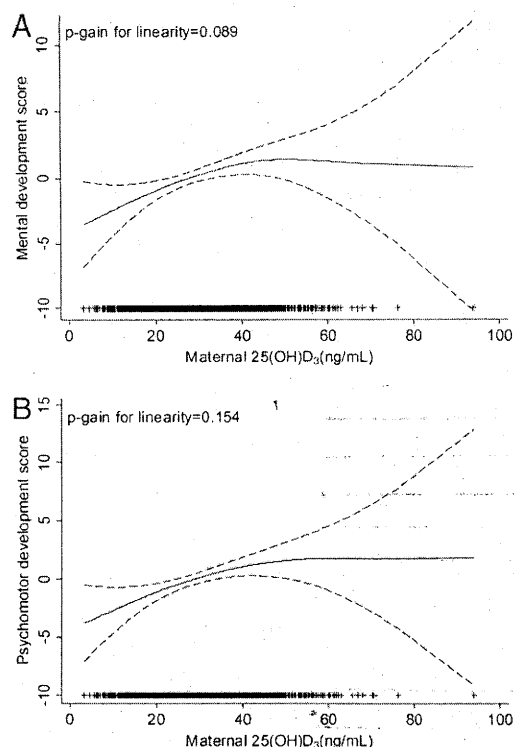


FIGURE 3

The relation (and 95% CI) of maternal circulating concentration of 25(OH)D₃ in pregnancy* (ng/mL) with mental (A) and psychomotor (B) developmental scores in infants. *Deseasonalized maternal 25(OH)D₃ concentrations based on month at blood collection for each subject derived from the sinusoidal model. General additive models adjusted for area of study, child's gender, birth weight, maternal country of origin, maternal age, parental social class, maternal education level, parity, maternal pre-pregnancy BMI, and maternal smoking and alcohol consumption in pregnancy. The symbols (+) on the x axis indicate 25(OH)D₃ observations.

TABLE 2 Association Between Maternal Circulating 25(OH)D₃ Concentrations^a in Pregnancy and Neuropsychological Scores in Infants (*n* = 1820)

	Model 1 ^b		Model 2 ^c	
	β	(95% CI)	β	(95% CI)
Mental development score				
Continuous variable (per 10 ng/mL)	0.99	(0.33 to 1.65)	0.79	(0.14 to 1.45)
Categories (ng/mL)				
<20	Ref.		Ref.	
20–30	2.14	(0.08 to 4.19)	1.89	(–0.14 to 3.91)
>30	3.17	(1.19 to 5.16)	2.60	(0.63 to 4.56)
Psychomotor development score				
Continuous variable (per 10 ng/mL)	0.94	(0.29 to 1.60)	0.88	(0.22 to 1.54)
Categories (ng/mL)				
<20	Ref.		Ref.	
20–30	0.80	(–1.21 to 2.83)	0.86	(–1.16 to 2.88)
>30	2.42	(0.47 to 4.37)	2.32	(0.36 to 4.28)

^a Deseasonalized maternal 25(OH)D₃ concentrations based on month at blood collection for each subject derived from the sinusoidal model.

^b Adjusted for area of study.

^c Adjusted for area of study, child's gender, birth weight, maternal country of origin, maternal age, parental social class, maternal education level, parity, maternal pre-pregnancy BMI, and maternal smoking and alcohol consumption in pregnancy.

the associations, but their inclusion in the model cannot completely eliminate possible residual confounding by

parental intelligence. Finally, we did not account for maternal physical activity and outdoor exposures (indicators of

maternal fitness), which may result in some residual confounding.

Two previous prospective studies have assessed the effect of maternal serum 25(OH)D₃ concentrations in pregnancy on offspring neurodevelopment.^{19,20} The first study based on 178 mother-child pairs reported no association between circulating maternal 25(OH)D₃ concentrations, measured at 32 weeks of pregnancy, and offspring cognition performance at age 9 years.¹⁹ However, in accordance with our results Whitehouse et al²⁰ have recently reported insufficient maternal serum 25(OH)D₃ concentrations, measured at 18 weeks pregnancy, to be associated with offspring language impairment at 5 and 10 years of age in a prospective study on 743 mother-child pairs. Lack of power in the Gale et al¹⁹ study and differences in timing measurements (exposure and outcome) could explain controversial results between studies. Measurement of 25(OH)D₃ concentrations in Gale et al¹⁹ study was performed in late pregnancy (median 32 weeks), whereas Whitehouse et al study and the current study determined 25(OH)D₃ concentrations earlier in pregnancy (mean, 18 and 13 weeks of gestation, respectively). Our results suggest that optimal concentrations of circulating 25(OH)D₃ as early as 13 weeks of gestation may have an impact on neuropsychological development in infancy, and vulnerability of the developing brain to vitamin D deficiency may be manifested early in pregnancy. The similarity in the effect magnitude of vitamin D deficiency in pregnancy on mental and psychomotor skills points out that different brain areas are affected and strengthen the idea that effects may occur during early development when brain structures begin to form and are thus vulnerable to damaging influences.²⁴ Furthermore, deficiencies in neuromotor development are associated with processes occurring early in fetal life.^{33,34}

Studies assessing vitamin D status on cognitive functioning beyond childhood are scarce. A large population-based cross-sectional study conducted on 1676 adolescents aged 12 to 17 years has reported null association of different domains of cognitive function with 25(OH)D₃ concentrations.^{21,22} However, the cross-sectional design and the different timing at outcome assessment make the comparison with our study difficult. Nevertheless, our results are consistent with previous studies conducted in elderly adults. Seven cross-sectional studies have reported lower concentrations of circulating 25(OH)D₃ to be associated with higher risk of cognitive impairment.^{9–11,13–15,18} Moreover, 3 cohort studies conducted on adults 65 years of age or older have also reported a trend for an independent association between lower circulating 25(OH)D₃ concentrations and odds of cognitive decline.^{12,16,17} Similar effects of vitamin D status on brain development and aging could indicate a higher susceptibility of the brain to vitamin D deficiency during these lifetime periods. The biological basis for the association of vitamin D with cognitive function comes

from evidence of the ubiquitous presence of vitamin D receptors and 1,α-hydroxylase (the terminal rate-limiting enzyme in the synthesis of calcitriol) in the rodent fetal and adult brain³⁵ and in the adult human brain.³⁶ Moreover, 25(OH)D₃ crosses the blood-brain barrier and it is also synthesized in the brain.³⁶ Developmental vitamin D deficiency has been shown to modify the expression of multiple genes and proteins in brain tissue from offspring including neurotrophic factors and mitochondrial, cytoskeletal, and synaptic proteins.^{8,37} In humans, there is some limited evidence for a relationship between vitamin D inadequacy and diverse neuropsychiatric conditions including multiple sclerosis,³⁸ depression,³⁹ schizophrenia,^{40,41} and Alzheimer disease.⁴² However, the evidence derived from animal studies strongly suggests a crucial role of vitamin D in brain development and critical brain functions,^{2,3} normal neurogenesis,⁷ learning ability and behavior.^{43–45}

CONCLUSIONS

In this prospective cohort higher circulating 25(OH)D₃ in pregnancy was

associated with improved mental and psychomotor development in infants. Efforts to maintain an adequate vitamin D status in pregnancy could make a positive impact on infants' neuropsychological development if the associations are causal. Moreover, given the magnitude of vitamin D deficiency worldwide among pregnant women, the present results have important public health implications, and population-level consequences of vitamin D deficiency in pregnancy on brain development may be more profound in settings with higher prevalence of vitamin D deficiency. Additional studies are warranted to assess long-term effects of maternal vitamin D status in pregnancy on neuropsychological development in offspring.

ACKNOWLEDGMENTS

The authors particularly thank all the participants for their generous collaboration. A full roster of the INMA Project Investigators can be found at http://www.proyecto-inma.org/presentacion-inma/listado-investigadores/en_listado-investigadores.html.

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: This study was funded by grants from Instituto de Salud Carlos III and Spanish Ministry of Health (Red INMA G03/176; CB06/02/0041; FIS 97/0588; 00/0021-2, PI061756; PS0901958; FIS-FEDER 03/1615, 04/1509, 04/1112, 04/1931, 05/1079, 05/1052, 06/1213, 07/0314 and 09/02647; FIS-PI041436, FIS-PI081151, FIS-PI06/0867 and FIS-PS09/00090), Conselleria de Sanitat Generalitat Valenciana, Generalitat de Catalunya-CIRIT 1999SGR 00241, Department of Health of the Basque Government (2005111093 and 2009111069), the Provincial Government of Gipuzkoa (DFG06/004 and DFG08/001), and Fundación Roger Torné.

TABLE 1 Characteristics of Participants According to Maternal Circulating 25(OH)D₃ Concentrations in Pregnancy

	Serum 25(OH)D ₃ Concentration			P Value Trend
	<20 ng/mL (n = 356)	20–30 ng/mL (n = 574)	>30 ng/mL (n = 890)	
Area of study				
Valencia (39°N latitude)	20.2	29.6	37.2	<.001
Sabadell (41°N latitude)	30.3	23.2	26.4	
Gipuzkoa (42°N latitude)	24.7	27.2	23.4	
Asturias (43°N latitude)	24.7	20.0	13.0	
Child's gender (male)	51.1	50.2	48.8	.722
Birth weight, g	3300 (435)	3283 (419)	3302 (419)	.685
Maternal age at child's birth, y	31.5 (4.5)	31.6 (4.1)	32.2 (4.0)	.004
Parity (1 or more)	36.8	41.6	44.3	.053
Maternal country of birth (non-Spanish)	9.0	6.8	7.4	.460
Parental social class				
I/II Managers/technicians	28.4	30.7	36.0	.037
III Skilled manual/nonmanual	26.1	27.5	26.5	
IV/V Semiskilled/unskilled	45.5	41.8	37.5	
Maternal education level				
Primary or less	23.9	22.1	22.3	.273
Secondary	43.5	43.6	39.4	
University degree	32.6	34.3	38.3	
Maternal pre-pregnancy BMI				
Normal weight/underweight (<24.99)	68.3	74.0	75.6	.086
Overweight (25–29.99)	22.5	19.0	16.6	
Obese (≥30)	9.3	7.0	7.8	
Smoking at third trimester (yes)	20.2	16.4	13.9	.022
Alcohol during pregnancy (yes)	18.0	16.4	22.4	.013

Values are percentages for categorical variables and mean (SD) for continuous variables.

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