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Vitamin D in Fetal Development: Findings From a Birth Cohort Study

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Birth cohort studies provide an invaluable resource for studies of the influence of the fetal environment on health in later life. It is uncertain to what extent maternal vitamin D status influences fetal development. Using an unselected community-based cohort of 901 mother-offspring pairs (the Western Australian Pregnancy Cohort [Raine] Study), we examined the relationship between maternal vitamin D deficiency at 18 weeks' pregnancy and long-term health outcomes of offspring who were born in Perth, Western Australia (32° South), in 1989–1991. Vitamin D deficiency (serum 25-hydroxyvitamin D [25(OH)D] <50 nmol/L) was present in 36% (323 of 901) of the pregnant women. After adjusting for relevant covariates, maternal vitamin D deficiency during pregnancy was associated with impaired lung development in 6-year-old offspring, neurocognitive difficulties at age 10, increased risk of eating disorders in adolescence, and lower peak bone mass at 20 years. In summary, vitamin D may have an important, multifaceted role in the development of fetal lungs, brain, and bone. Experimental animal studies support an active contribution of vitamin D to organ development. Randomized controlled trials of vitamin D supplementation in pregnant women with long-term follow-up of offspring are urgently required to examine whether the correction of vitamin D deficiency in pregnant women is beneficial for their offspring and to determine the optimal level of maternal serum 25(OH)D for fetal development.

The concept that health and disease in later life are partly determined in utero was first introduced by Barker in the 1980s when he showed that low birth weight babies are at greater risk of developing coronary heart disease later in life.¹ The developmental origins of health and disease hypothesis suggests that the early environment in pregnancy can determine structural, metabolic, physiologic, and behavioral development and modify response patterns that influence future disease susceptibility.² The evidence for preprogramming of disease during fetal life is being explored through the establishment of cohort studies that recruit and study pregnant women and then monitor their offspring during childhood, adolescence, and into adulthood.

Our studies have concentrated on serum 25-hydroxyvitamin D levels (25(OH)D) during pregnancy as a measure of vitamin D adequacy and the long-term implications for the health of the offspring. Many reviews support a need for vitamin D sufficiency in pregnancy but have concentrated on the benefits associated with reducing adverse pregnancy and birth outcomes such as gestational diabetes, preeclampsia, bacterial vaginosis, and small-for-gestational-age infants.³ We address longer term benefits of vitamin D sufficiency during pregnancy. We summarize the outcomes of our longitudinal analyses of children born to women with various levels of serum 25(OH)D measured when they were 18 weeks pregnant. In accordance with the guidelines of the Institute of

abstract

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Dr Hart conceptualized and designed the study, coordinated maternal 25(OH)D measures and drafted the initial manuscript; Drs Whitehouse and Kusel conceptualized and designed the study and coordinated maternal 25(OH)D measures; Dr Lucas and Ms Anderson analyzed ultraviolet radiation data; Drs Walsh, Zosky, Whitehouse, Zhu, and Allen lead analyses of maternal vitamin D levels and their associations with child and adolescent health measures; Ms Mountain manages the Raine Study; and all authors contributed to the writing of the report and approved the final manuscript as submitted.

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Medicine,⁴ we define vitamin D deficiency as serum 25(OH)D levels <50 nmol/L. We document the extensive impact that vitamin D deficiency in pregnancy can have on lung, brain, and bone development as subsequently measured in the children during childhood, adolescence, and early adulthood.

THE RAINE PROSPECTIVE BIRTH COHORT

The Western Australian Pregnancy Cohort (Raine) Study is an unselected, community-based cohort.

Predominantly Caucasian women (~90%) were recruited at approximately gestational age 18 weeks and delivered their offspring between 1989 and 1991 in Perth, Western Australia (32°South).⁵ At this time, vitamin D supplementation in a concentrated form or in food was rare and not specifically sought from the mothers. We analyzed associations between the mother's serum 25(OH)D levels at 18 weeks' gestation and longer term outcomes in their offspring in childhood, adolescence, and early adulthood. Of importance, the emphasis was on changes that reflect organ development (eg, lung capacity, language ability, peak bone mass) and that may predispose, in some cases, to ill health later in life. One hundred twenty-one mother-offspring pairs were consistent across the 5 published substudies collated here as a summative review.⁶⁻¹⁰ Studies were approved by the Human Research ethics committees at King Edward Memorial Hospital, Princess Margaret Hospital, and the University of Western Australia, Perth, Australia.

Serum 25(OH)D concentration was measured by immunoassay (Immunodiagnostic Systems Ltd, Fountain Hills, AZ); a subset of samples was reassayed by using the reference method of isotope-dilution liquid chromatography/tandem mass spectrometry and showed strong agreement ($r^2 = 0.87$) with no

evidence of analytical interference.⁷ Maternal serum 25(OH)D levels were normally distributed. Approximately 36% (323 of 901) of the pregnant women were vitamin D-deficient, which compares favorably with the reported prevalence of vitamin D deficiency in pregnancy, which ranges from 33% to 98% worldwide.¹¹ Only 3% of mothers (29 of 901) were defined as severely vitamin D deficient, that is, 25(OH)D <25 nmol/L, and 18% (162 of 901) had vitamin D levels >75 nmol/L.

ASSOCIATIONS OF BONE, LUNG, AND BRAIN DEVELOPMENT WITH SERUM 25(OH)D LEVELS

First, maternal vitamin D deficiency at 18 weeks (which is an important time in fetal lung development)¹² was associated with reduced lung function in children at 6 years of age.⁶ In this substudy of 260 mother-offspring pairs, there was a significant positive association between maternal serum 25(OH)D levels and Z scores for forced vital capacity (FVC). The effects on lung measures titrated with vitamin D levels after adjusting for confounders. Children from mothers who were vitamin D deficient had an estimated mean FVC Z score 0.10 lower than children born to mothers who had levels between 50 and 75 nmol/L. These children, in turn, had a mean estimated FVC Z score 0.23 lower than children born to mothers with 25(OH)D levels >75 nmol/L.⁶ Maternal vitamin D deficiency at 18 weeks also correlated with current wheeze in 6-year-old offspring (genders combined) and an increased risk of asthma in boys.⁶ There were no significant associations found with atopy measurements; this study suggests that an association of vitamin D deficiency with respiratory disease is due to an impact on lung development.⁶

Second, in consideration of brain development, maternal vitamin D deficiency at 18 weeks' gestation was significantly associated with reduced

neurocognitive development in the offspring, including language impairment at ages 5 and 10,⁷ increased risk of having an eating disorder in adolescence,⁸ and more autistic-like behaviors in early adulthood.⁹ In the study of language impairment in 743 mother-offspring pairs, multivariable regression analyses, incorporating a range of confounding variables (maternal age at conception, maternal education, family income, maternal smoking during pregnancy, offspring parity, season of blood collection), found that the risk of pregnant women who had 25(OH)D levels within the lowest quartile of the distribution (≤ 46 nmol/L) having a child with clinically significant language difficulties was increased close to twofold compared with women within the highest quartile of the 25(OH)D distribution (>70 nmol/L).⁷ In a follow-up investigation, 406 offspring of mothers with measured 25(OH)D levels at 18 weeks' gestation completed the Autism-Spectrum Quotient, a measure of autistic-like traits in the general population, in early adulthood. Offspring of mothers with 25(OH)D levels <50 nmol/L were at increased risk for high scores (≥ 2 SD above the mean) on the Attention Switching subscale of this measure, denoting behaviors consistent with the autism phenotype.⁹ Finally, eating disorder symptoms were assessed in offspring aged 14, 17, and 20 years in 526 white mother-child dyads.⁸ Using multivariate logistic regression models, lower maternal vitamin D status was a significant predictor of eating disorder risk in female offspring. Having a serum 25(OH)D level in the lowest quartile (<46 nmol/L) was associated with a twofold increase in odds for having an eating disorder by age 20 years (95% confidence interval [CI] for odds ratio = 1.03–5.27) relative to concentrations in the highest quartile (>71.4 nmol/L). These results were obtained after adjusting for

sociodemographic characteristics, BMI, depressive symptoms, maternal education, and season of birth.⁸ There was a nonsignificant increased odds, and suggestion of trend, for the second and third 25(OH)D quartiles.

Third, with respect to development of bone, the organ historically associated with vitamin D, we examined total bone mineral content and bone mineral density by dual energy x-ray absorptiometry in the adult offspring of 341 mothers. Maternal vitamin D deficiency at 18 weeks' gestation was associated with lower peak bone mass among their children at 20 years of age.¹⁰ Specifically, we found a reduction of 2.7% in total body bone mineral content and 1.7% lower total body bone mineral density (after accounting for season of sample collection and maternal and offspring factors) compared with offspring of vitamin D-sufficient mothers.¹⁰ The results are consistent with a previous birth cohort study in which maternal vitamin D status was determined at 34 weeks' gestation and bone mineral density measured in the offspring at 9 years of age,¹³ but not with a second study in which maternal vitamin D status was determined at various stages of pregnancy and the offspring studied at 9 to 10 years of age.¹⁴ We chose to measure bone mineral density in the offspring at 20 years of age because this represents a time of skeletal maturity, when the influence of growth-related confounders is least.¹⁵ Achievement of optimal peak bone mass is considered the best protection against age-related bone loss.¹⁵ From our results, it is biologically plausible that maternal vitamin D deficiency in pregnant women may influence fracture risk of their offspring decades later.

The outcomes in the described studies are summarized in Table 1. An analysis of the maternal serum 25(OH)D levels of the substudies in comparison with the total cohort for whom maternal serum 25(OH)D

TABLE 1 Summary of the Associations of Organ Development of the Offspring With Maternal Serum 25(OH)D Levels From 5 Separate Studies (*N* = 901)

Organ	Measure	Age at Measure	<i>n</i>	Association
Lung	Z scores ⁶ FVC	6 y	260	Positive
Brain	Language scores ⁷	5, 10 y	743	Positive
	Eating disorder risk ⁸	14, 17, 20 y	526	Negative
	Autism-Spectrum Quotient ⁹	Early adulthood	406	Negative
Bone	Peak bone mass ¹⁰	20 y	341	Positive

levels were measured showed significantly higher mean 25(OH)D levels for participants in the lung function studies (60.2 nmol/L, 95% CI 58.0–62.5) and those for language development (59.5 nmol/L, 95% CI 58.1–60.8) than for the total cohort (57.9 nmol/L). Because this mean measure for all mothers for whom 25(OH)D was measured was close to inclusion in the 95% CI for levels measured in the substudies, we concluded that any bias in those studied in the substudies was minor.

STUDIES IN EXPERIMENTAL ANIMALS

Is a physiologic role for vitamin D in the development of fetal lung, brain, and bone biologically plausible? Animal studies suggest that it is and support an active involvement by vitamin D in organ development in utero. Studies from our laboratory detected deficits in lung function and altered lung structure in 2-week-old progeny from vitamin D-deficient female mice.¹⁶ Vitamin D-deficient rats deliver babies with altered brain structures consistent with increased risk of schizophrenia development.¹⁷ Finally, although some animal studies have suggested that the mineralization of the fetal skeleton is independent of vitamin D,¹⁸ others have observed skeletal mineralization defects in fetuses born from vitamin D-deficient or vitamin D receptor-null mothers on normal calcium diets.¹⁹ The caveat is that if the intervention was dietary or mice without vitamin D receptors were used, vitamin D deficiency in the animals was extreme, causing the animals to be highly (or totally) vitamin D deficient. Nonetheless,

these studies give some support to vitamin D as an important mediator of optimal lung, brain, and bone development.

IS VITAMIN D OR EXPOSURE TO UV RADIATION RESPONSIBLE FOR THE OBSERVED ASSOCIATIONS?

In humans, circulating vitamin D is mainly derived from synthesis in the skin, under the influence of sunlight (specifically shorter wavelength UV radiation), so it remains possible that sunlight-induced molecules in skin, other than vitamin D, may be responsible for, or contribute to, the biological effects observed (eg, nitric oxide, *cis*-urocanic acid).²⁰ To explore this, we investigated the relationship between the measured serum 25(OH)D levels and the erythral UV exposure detected at that time in Perth (32°S, 116°E). For erythral UV exposure, the estimated peak UV level was on December 30, and the low point was June 30 (Fig 1A). For maternal 25(OH)D levels, the estimated peak of the modeled annual distribution was on February 11 and the low point on August 13, that is, 43 days after the estimated peak or nadir in UV level (Fig 1B). We used this time lag to measure the correlation between erythral UV exposures and maternal serum 25(OH)D levels and found a significant association ($r = 0.33$; 95% CI = 0.27–0.39; $P < .0001$; Fig 1C). Serum 25(OH) levels could therefore provide a measure of the production of other molecules produced in skin upon sun exposure. Interestingly, in a previous birth cohort study, measures of erythral UV exposures received by pregnant women during the third trimester of

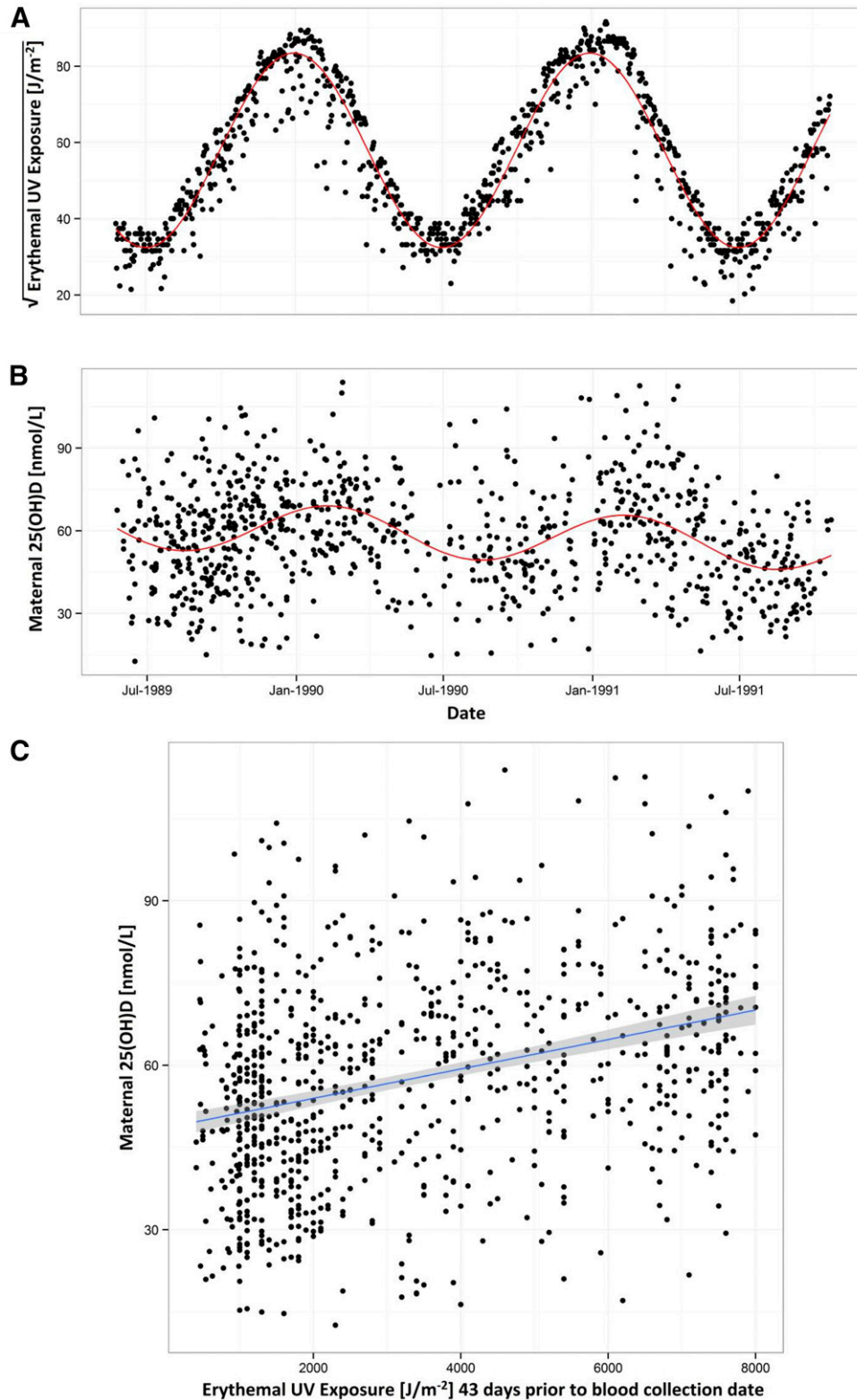


FIGURE 1

Square root of the erythemal UV exposure (A) and serum 25(OH)D levels (B) for 871 pregnant women at 18 weeks' gestation, plotted against the date of blood draw. Erythemal UV radiation in Perth (32° south, 116° east) was estimated from data from the Total Ozone Mapping Spectrometer aboard the Nimbus-7 satellite (<http://iridl.ldeo.colombia.edu/SOURCES/NASA/GSFC/TOMS>). For panels A and B, cosinor models in R 3.0.1 showed significant seasonal components (sine and cosine term P values < 0.025) and are indicated by the solid line. The estimated peak location for erythemal UV exposure was on December 30, which was 43 days before the estimated peak location of serum 25(OH)D levels. In C, erythemal UV exposures 43 days before blood draw significantly correlated with maternal serum 25(OH)D levels ($r = 0.33$; 95% CI 0.27–0.39; $P < 0.001$). The shading is the 95% confidence region of the fitted linear regression line.

pregnancy were positively correlated with measures of bone mineral content, bone area, and area-adjusted bone mineral density in the offspring at 9 to 10 years of age,²¹ whereas maternal serum 25(OH)D levels were not.¹⁴ With respect to development of autoimmune diseases, outcomes attributed to UV-induced vitamin D may in fact reflect the actions of other immunoregulatory molecules produced in skin during exposure to UV irradiation.²⁰

VITAMIN D IN FETAL DEVELOPMENT: AN ACTIVE PLAYER OR APPARENT EFFECTS DUE TO CONFOUNDING?

Our observational studies suggest, but do not prove, that vitamin D plays an active role in fetal lung, brain, and bone development. The possibility remains that the reduced lung, brain, and bone development in the offspring of vitamin D-deficient mothers may not reflect vitamin D deficiency per se but some other health factor in the women that is associated with maternal vitamin D deficiency. To address this, in our analyses, we adjusted for a range of potentially relevant confounders including maternal age, parity, education and smoking, but it was not possible to adjust for every possible confounder. The possibility remains that measures of sufficient serum 25(OH)D during pregnancy reflect a healthy lifestyle with much time spent in sunshine. To our knowledge, there have been no studies to investigate whether outdoor activity during pregnancy, or sun-induced molecules in skin, can complement the regulatory effects of vitamin D in organ development. Although the studies in the experimental animals cannot conclude that vitamin D sufficiency is responsible for optimal organ development during pregnancy, they support vitamin D as a contributor to development processes.

It is possible that the offspring's own vitamin D status may contribute to postnatal development of their lungs,

brain, and bone. This may be most relevant for bone development measured in 20-year-old offspring. Maternal levels of vitamin D reflect a measure at a distinct time of fetal development. In contrast, during childhood and adolescence, vitamin D measures represent a snapshot of only a short time period. Consistent with this, in the Avon Longitudinal Study of Parents and Children study of ~4000 mother-offspring pairs,¹⁴ further inclusion of offspring's current vitamin D status had little influence on associations between maternal vitamin D and bone measures in offspring. In the Raine cohort study, serum 25(OH)D levels in the 6- and 14-year-old offspring were inversely associated with atopy measures.²² However, there was no correlation between maternal serum 25(OH)D measures and atopy of the offspring at 6 years of age.⁶

One may think, in the individual studies reported here, that there may have been confounding by aspects of the mother's health. For example, mothers with impaired lung function may spend less time outdoors and thus have lower 25(OH)D levels and have offspring with impaired lung function. What is striking with the studies reported here is the breadth of health outcomes for which an association is reported; confounding by maternal health status as the explanation for these observed associations is highly unlikely.

SOBERING LESSONS FROM STUDIES IN ADULTS DETERMINING THE REQUIREMENTS FOR VITAMIN D FOR BETTER HEALTH

During the past decade, there have been frequent reports from observational studies of inverse associations between serum 25(OH)D levels and multiple health outcomes. In turn, randomized controlled trials of vitamin D for risk or progression of conditions such as cancer, cardiovascular disease, acute respiratory infections, diabetes, and other autoimmune conditions were

established. Meta-analyses of trials of vitamin D supplementation for various conditions have given equivocal results,^{3,23,24} with a recent meta-analysis suggesting that vitamin D may have, at best, a 15% benefit effect on the risk of myocardial infarction or ischemic heart disease, stroke or cerebrovascular disease, cancer, and total fracture.²⁵ There are several possible explanations for the lack of efficacy of supplementation with vitamin D in clinical trials. These include inadequate vitamin D dosage, recruitment of participants who were not vitamin D deficient (in which case no benefit of supplementation would be expected), insufficient power in the trials to detect a treatment effect, recruitment of individuals whose disease process was too advanced to be reversed, inadequate treatment duration, or that other co-regulators are necessary for vitamin D to work (eg, calcium, serum binding proteins). Alternatively, vitamin D may be a confounder in the observational studies: higher 25(OH)D levels may be simply a surrogate of a generally healthier lifestyle, disease may cause low levels of 25(OH)D through reduced sunlight exposure or altered metabolism (reverse causality),²⁶ or sun exposure may have beneficial health effects that are both vitamin D dependent and independent and that will only be partially replicated by vitamin D supplementation.

Importantly, some negative effects on health have occurred at high levels of serum 25(OH)D, including increased falls and fractures in older people given a large annual dose of 500 000 IU vitamin D.²³ A nonlinear, U-shaped association has been reported between vitamin D levels and acute coronary syndrome and mortality, as well as for other conditions.²⁷

CONCLUSIONS

Despite clear concerns about drawing strong conclusions from observational data that do not confirm that vitamin D is

mechanistically involved, from the analyses of children in our community cohort and the supportive experimental animal studies, pregnancy may be a time of particular sensitivity to vitamin D deficiency. This study of mother-offspring pairs is important because the mothers were not selected for any predisposing condition, and their serum 25(OH)D levels were not skewed to particularly high or low levels as can be contrived in animal studies. Approximately 900 mother-offspring pairs were sufficient to find associations of bone, lung, and brain development with maternal serum 25(OH)D levels. This study was performed in Perth, Western Australia, a city of mild winters. Yet the variations in serum 25(OH)D levels were sufficient to see these associations with organ development and, we propose, predictors of varied health outcomes in later life. Of importance, in this cohort, associations of maternal serum 25(OH)D levels with lung function, indices of neurodevelopment and mental health, and peak bone mass were detected and suggest that sufficient vitamin D is permissive for optimal development of multiple organs, not just bone as would be historically proposed.

INTERPRETATION

Although meta-analyses suggest that vitamin D has relatively minor effects on adult health,^{3,23–25} it remains possible (and indeed likely) that vitamin D may have an important developmental role in the fetus during pregnancy. Confirmation of this will require carefully planned trials of vitamin D supplementation in vitamin D-deficient pregnant women in which outcome measures should include assessment of respiratory, brain, and skeletal development in the offspring. This will not be an easy task and will require significant resources because many of the developmental outcomes will not be

evident for many years and several funding cycles. An unresolved issue is what concentration of maternal serum 25(OH)D is sufficient or indeed optimal in pregnancy. The issue is complicated by the suboptimal performance and lack of harmonization of assays for serum 25(OH)D.²⁸ Reference methods such as liquid chromatography/tandem mass spectrometry are increasingly used but are expensive and labor intensive. Some practitioners advocate high doses of vitamin D of 4000 IU per day during pregnancy, and in a combined analysis of 2 randomized vitamin D supplementation trials in pregnant women, 4000 IU/day was associated with lower risk of hypovitaminosis D and maternal comorbidities of pregnancy than control and 2000 IU/day groups.²⁹ Whatever the supplementation dose, one must ensure that 25(OH)D levels are monitored because excessive levels of serum vitamin D during pregnancy have been associated with increased prevalence of schizophrenia,³⁰ and this U-shaped curve may be relevant for development of other conditions. Despite the uncertainty of the optimal level, our results in children of unselected healthy mothers highlight the impact of sufficient vitamin D on development of lungs, brain, and bone of the fetus. Until we have better data including randomized controlled trials of vitamin D supplementation of pregnant women and comprehensive assessment of the offspring, maintaining a 25(OH)D level of >50 nmol/L in pregnant women must be considered a reasonable target.

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