

Vitamin D status at birth: An important and potentially modifiable determinant of atopic disease in childhood?

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The increasing prevalence of all forms of allergic disease around the world has stimulated an intensive search for environmental factors that might be contributing to this process. Epidemiologic studies have identified parallel increases in the prevalence of vitamin D deficiency and allergic disease, prompting consideration of vitamin D deficiency as a potential explanation for the increase in allergic disease prevalence and severity.¹ Over the past decade, states associated with hypovitaminosis D (eg, low maternal dietary vitamin D intake or confirmed vitamin D deficiency) have often,²⁻⁶ but not uniformly,⁷⁻⁹ been associated with several aspects of allergic disease, including the occurrence, severity, or both of recurrent wheezing, asthma, allergic sensitization, allergic rhinitis, food allergy, and atopic dermatitis.

Vitamin D has long been recognized as a critical determinant of bone health. More recently, its effects on intrauterine and postnatal lung and immune system development and function have been enumerated. A panoply of immune-related activities of vitamin D¹⁰ have been described, including multiple immunologic pathways related to response to infections and modulation of inflammation.¹⁰ Vitamin D, although mostly demonstrated in *in vitro* systems, has been reported to (1) affect the innate immune system through the induction of macrophage production of the antimicrobial peptides cathelicidin and β -defensins, (2) enhance skin barrier function, (3) suppress Toll-like receptor production by monocytes, (4) enhance IL-10 production by mast cells, (5) inhibit dendritic cell activation and function induced by LPS, (6) decrease T_H1 cytokine production, (7) induce regulatory T cells, and (8) inhibit B-lymphocyte function, resulting in diminished IgE secretion.¹⁰

In this issue of the *Journal*, Baiz et al¹¹ report findings from a substudy of the French-based EDEN (Etude des Determinants pre et post natus du developpement et de la sante de l'Enfant)

birth cohort (latitude 46.5°N-48.6°N), examining the relationship between cord blood 25-hydroxy-vitamin D levels and the prevalence of parent-reported physician-diagnosed asthma, allergic rhinitis, wheezing patterns, and atopic dermatitis during the first 5 years of life. The investigators initially enrolled 2002 mother-child pairs in the EDEN cohort in the year 2003, of which only 12% (n = 239) comprise the current analysis set, which required availability of both clinical data through age 5 years and a cord blood sample for 25-hydroxy-vitamin D assay. Although not a study of the effects of postnatal vitamin D supplementation, all children were advised to receive vitamin D supplementation (amount not specified and adherence not monitored) for the first 3 years of life. Clinical outcomes were based on parents' responses to International Study of Asthma and Allergies in Childhood-based questionnaires administered at ages 1, 2, 3, and 5 years without subsequent confirmation of diagnoses through medical record review or study-performed objective assessments. Overall, at least 50% of the study population had cord blood levels of vitamin D in the deficient range (defined as a 25-hydroxy-vitamin D level <20 ng/mL) with a median cord blood 25-hydroxy-vitamin D level of 17.8 ng/mL. As expected, cord blood 25-hydroxy-vitamin D levels varied by season of birth, with the lowest levels occurring in infants born during the winter season. Although cord blood 25-hydroxy-vitamin D levels were not associated with either parent-reported doctor-diagnosed asthma or allergic rhinitis at age 5 years, statistically significant inverse relationships were found relating cord blood 25-hydroxy-vitamin D levels to early transient wheezing (but not late-onset or persistent wheezing) and atopic dermatitis. The importance of these findings is strengthened by the longitudinal nature of the outcome assessments; unfortunately, there were no longitudinal measures of vitamin D levels either prenatally or after delivery. The low proportion of subjects (12% of the original cohort) with complete follow-up and cord blood vitamin D levels raises concern for selection bias and limits the external validity of these findings. Furthermore, the relatively low prevalence of subjects reporting a physician's diagnosis of asthma (8% of 239 subjects) raises concern for possible misclassification of childhood asthma and limits the statistical power for confidently testing for an association between vitamin D status and parent-reported doctor-diagnosed asthma.

These findings are generally, but not entirely, consistent with 2 recent studies examining the associations between cord blood vitamin D levels and allergic and respiratory outcomes in early life.^{12,13} In a New Zealand-based birth cohort (latitude 41°S-43°S), Camargo et al¹² also demonstrated an inverse relationship between cord blood vitamin D levels and the cumulative risk of wheezing by the age of 3 years (as well as 5 years) but no association with asthma by age 5 years. In contrast, Jones et al¹³ studied a cohort of infants born in Perth, Australia (latitude 31.9°S), and found that this cohort, which, on average, had cord blood 25-hydroxy-vitamin D levels that were a bit higher (mean 23.4 ng/mL), demonstrated no

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significant association between cord blood 25-hydroxy-vitamin D levels and recurrent wheezing. Although Camargo et al¹² did not examine whether there was a relationship between vitamin D status and atopic dermatitis, Jones et al¹³ found a very similar inverse association between cord blood 25-hydroxy-vitamin D levels and eczema (for each 4 ng/mL increase in cord blood 25-hydroxy-vitamin D levels, the risk of eczema decreased by 13.3%) as that reported by Baiz et al¹¹ (for each 5 ng/mL increase in cord blood 25-hydroxy-vitamin D levels, the risk of atopic dermatitis decreased by 16%).

Our understanding of the interrelationship between vitamin D status and allergic disease in early life has improved with time, in part because of improved study methodology, with more recent studies examining the direct measurement of cord blood vitamin D levels¹¹⁻¹³ rather than relying on estimates of maternal vitamin D intake.^{2,3} However, a single measure of vitamin D status at the time of delivery is unlikely to provide adequate insight as to vitamin D status throughout pregnancy, and it remains unlikely that the effect of vitamin D status on both lung and immune development is uniform throughout gestation. Future research should include careful consideration of factors related to the determination of vitamin D status (directly measured in serum vs estimated from dietary intake surveys), the time interval and frequency of measurements of vitamin D levels relative to the determination of the outcome of interest, and the specific definitions of the outcomes themselves to meaningfully advance this field of study. The biology of vitamin D homeostasis is complex, and thus appropriate conduct and interpretation of research in this area also requires consideration of factors that influence vitamin D status or confound this relationship, including skin color, altitude, latitude, sun exposure, sunscreen use, season, adiposity, diet (including intake of vitamin D–fortified foods and vitamin D supplements), the presence of chronic disease, and genetic factors. Future prospective studies should consider multiple measurements of vitamin D status over time, both during pregnancy and after delivery, to determine their variability and whether disease development or activity is related to changes in vitamin D status or whether critical windows of time exist during which vitamin D deficiency is most important. In addition, although the findings reported to date have identified associations between vitamin D status and clinical outcomes, there has been much less progress in elucidating the underlying *in vivo* biologic mechanism or mechanisms for this association.

Although studies such as those reported by Baiz et al¹¹ have clearly advanced our understanding of the potential effects of vitamin D status on the development and manifestations of allergic disease, the true clinical interdependence of vitamin D status and disease will only become clear after completion of randomized controlled trials examining the effects of improving vitamin D status on these important clinical outcomes. Recent trials are encouraging in this regard because they have indeed demonstrated that vitamin D supplementation is capable of reducing an important trigger of asthma-related symptoms, namely respiratory tract infections in children. Mongolian schoolchildren with confirmed vitamin D deficiency who received vitamin D supplementation experienced a 50% reduction in the risk of acute respiratory tract infections over a 3-month period.¹⁴ Similarly, vitamin D supplementation in Japanese schoolchildren was associated with a reduced risk of influenza A infection along with a reduction in asthma exacerbations among those with asthma.¹⁵

Given the increasing prevalence of vitamin D deficiency in infancy, the American Academy of Pediatrics recommends that

exclusively and partially breast-fed infants and all non–breast-fed infants receiving less than 32 oz/d vitamin D–fortified milk or formula be supplemented with 400 IU/d vitamin D.¹⁶ These recommendations are consistent with a recent study demonstrating that 2 modifiable dietary intake variables, vitamin D supplementation and cow's milk intake, are the most important determinants of vitamin D status in early childhood, whereas skin pigmentation and season account for substantially smaller degrees of the variation in 25-hydroxy-vitamin D levels.¹⁷

Despite recent findings suggesting improved respiratory outcomes with vitamin D supplementation,^{14,15} it seems premature to recommend vitamin D supplementation above and beyond that recommended by the American Academy of Pediatrics and the Institute of Medicine in an effort to modify atopic disease course. We eagerly await the results of ongoing randomized controlled trials of maternal supplementation of vitamin D during pregnancy, which should provide substantial insight as to the potential causative and thus modifiable effect of vitamin D deficiency in early life on allergic disease outcomes.

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