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Augusto A. Litonjua, MD, MPH, Scott T. Weiss, MD, MS



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JACI Editorial: Vitamin D status through the first 10 years of life: A vital piece of the puzzle in asthma inception

Authors:

Augusto A. Litonjua, MD, MPH (Corresponding Author)

Scott T. Weiss, MD, MS

Affiliation:

Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA

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In the 19th century through the early 20th century, an adequate diet was thought to be composed of proteins, minerals, fat, and carbohydrate. However, experiments in the early 20th century showed that animals fed these purified components alone did not survive. Hence, the search was on for “vital amines” – elements present in foods that were required for health and survival, and later termed vitamins,¹ of which vitamin D was the 4th to be discovered. We now know that humans get vitamin D not only from diet, but also from sun exposure. The investigation of the role of vitamin D as treatment for asthma and allergies dates back to the 1930s, soon after the isolation of vitamin D, where viosterol (activated ergosterol) in large doses (at least 120,000 IU daily) were compared to corn oil, in adults with asthma and hay fever.² Because the mechanism of vitamin D in asthma and allergies could not be determined, this avenue of investigation in humans was largely abandoned. Investigations in animal models continued, showing that exposure to vitamin D by the developing lung in utero led to improved lung maturation and surfactant production, diminished airway inflammation after a viral infection, and lead to decreased airway smooth muscle mass (reviewed in Litonjua³). In addition, studies in immune cells showed that vitamin D is important in the immune response.⁴ Based on our epidemiologic studies and review of the animal experiments of the developing lung, we hypothesized in 2007⁵ that vitamin D deficiency could have a role in the increase in asthma and allergies, and the number of reports in the literature dramatically increased. The observational human studies investigating vitamin D in the development of asthma were understandably mixed, with studies utilizing estimates of maternal intakes of vitamin D generally showing a protective effect of higher vitamin D during pregnancy, and studies utilizing one measure of vitamin D status (25hydroxyvitaminD, 25OHD) generally showing no effects,⁶ likely because the intake estimates were reflective of longer-term intakes while 25OHD level was reflective of shorter term exposures. Clinical trials were supposed to clarify the role of vitamin D in the prevention of asthma and allergies in young children.

The VDAART⁷ and COPSAC₂₀₁₀⁸ trials, both trials of prenatal supplementation of vitamin D to prevent asthma, wheezing, and allergies in young children were recently published. While strict statistical significance were not met in either trial suggesting that power was an issue, there were strikingly identical effects of vitamin D supplementation on asthma and recurrent wheeze in the offspring – about a 20% reduction in the risk for these disorders by 3 years of age. However, it turns out that statistical power was likely not the main problem in the design of these clinical trials. Heaney⁹ recently showed that nutrient trials such as for vitamin D, are different than drug trials in many ways. Primary among these are that unlike drug trials, nutrient trials do not have a real placebo arm due to the fact that all subjects are exposed to some level of the nutrient, and thus, have some circulating level of the nutrient leading to different starting points at the time of supplementation. We have shown this to be the case in our VDAART trial and have shown potentially different effects of supplementation depending on initial level of 25OHD on entry into the trial.¹⁰ Other factors influencing the results of VDAART have been summarized.¹¹

In this issue, Hollams et al¹² add another piece of information to our growing understanding about the effects of vitamin D on asthma occurrence. The investigators followed a birth cohort at high risk for asthma and allergies through the first 10 years of life, with assessment of vitamin D status at birth (cord blood), 6 months, 1, 2, 3, 4, 5, and 10 years. They found that there were consistent inverse associations

of 25OHD level with allergic sensitization in early life, while there were no cross-sectional associations of 25OHD with asthma. However, they also found that over the 10 year period, the number of times a child was found to be deficient in vitamin D (defined as a level of <50 nmol/L, equivalent to <20 ng/ml) was positively associated with the risk for asthma and wheeze at 10 years, suggesting that prevention of vitamin D deficiency throughout childhood was necessary to prevent asthma. These findings are consistent with the results of null cross-sectional reports of the association between vitamin D and asthma and reports where only 1 measurement of vitamin D status was used. These findings also make sense, since the many mechanisms of vitamin D that may prevent asthma (e.g. effect on gene expression, effect on post-viral inflammatory state, balance of TH1 and TH2 responses, and effect on smooth muscle inflammation and remodeling) are dynamic processes responsive to changes in the environment. Thus, maintenance of adequate vitamin D status would logically lead to these beneficial effects.

Other important findings in this study need to be highlighted. First, the authors found that vitamin D status in early life was inversely associated with nasopharyngeal colonization with *Streptococcus* and age of first febrile lower respiratory illness. The authors' findings suggest that vitamin D may be important in helping to establish a beneficial airway microbiome and may have effects on early life respiratory infections. This is consistent with the experimental findings that vitamin D is an important player in the stabilization of the intestinal mucosa¹³ and our group has also found that vitamin D status at birth is a determinant of the early life intestinal microbiome¹⁴. While clinical trials of vitamin D to prevent respiratory infections have been disappointing, this may again be due to the initial levels of 25OHD and the low doses of vitamin D used.¹⁵ A longitudinal observation study suggested that maintenance of 25OHD levels of at least 95 nmol/L (38 ng/ml)¹⁶ was necessary for prevention of viral respiratory illnesses. Second, the authors found that the majority of children could be defined as having vitamin D deficiency at birth, suggesting that pregnant mothers were also likely to be deficient. As suggested by results of recent trials, improving vitamin D status in pregnancy may have provided additional benefits. Third, there was marked variability in 25OHD levels over time (intra-class correlation = 0.31), consistent with previous studies¹⁷ and emphasizing the fact that one measurement is not sufficient as a measure of long-term exposure, and that longitudinal studies with multiple measures of exposure are more informative than cross-sectional studies.

The biology of vitamin D is complex, and we are learning more about it every day. Interpretation of data from this and other studies suggest a dynamic process of asthma and allergy inception that begins in the womb and continues throughout childhood, and likely through adulthood (Figure). Because of the flaws in study design of current human studies that have led to conflicting results or inadequate statistical significance, some have called for tempering the enthusiasm for vitamin D. On the contrary, we feel that there is much more to uncover, such as the dose and timing of supplementation and the level that maximizes protection. While we have surmised that adequate vitamin D status from birth throughout life is necessary, the Hollams article has finally given us a part of the answer, that we at least need to eliminate vitamin D deficiency in childhood to prevent asthma. Rather than tempering the enthusiasm, we need to redouble our efforts to continue to define the role of vitamin D in the inception of asthma.

Only then will we be able to make inroads in solving the asthma puzzle and ultimately achieve the holy grail of preventing the disorder.

Figure legends

Figure 1: Adequate Vitamin D status prenatally and throughout childhood in the prevention of asthma and allergies.

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