

Vitamin D Levels, Asthma, and Lung Function: Time to Act on Deficiency?



Augusto A. Litonjua, MD, MPH *Boston, Mass*

Vitamin D insufficiency (25 hydroxyvitamin D [25OHD] levels of <30 ng/mL) and deficiency (25OHD levels of <20 ng/mL) are prevalent around the world, even in some countries situated near the equator where sun exposure is replete.^{1,2} This is likely due to sun avoidance behaviors in these countries. Deficiency is also prevalent in developed countries such as the United States, despite vitamin D fortification of certain foods,^{1,2} suggesting that the amount of vitamin D from the food supply is insufficient to maintain adequate 25OHD levels in all individuals. An analysis of National Health and Nutrition Examination Survey (NHANES) data in 2009 showed a dramatic decrease in serum 25OHD levels over a roughly 10-year span from 1994 through 2004, with females and non-Hispanic blacks bearing the brunt of the disparities in levels.³ The mean serum 25OHD level was 30 ng/mL (95% CI, 29-30) during NHANESIII and decreased to 24 ng/mL (95% CI, 23-25) during NHANES 2001-2004. As a comparison, 25OHD levels in East African indigenous people living a traditional lifestyle averaged 46 ng/mL,⁴ although admittedly under vastly different circumstances than in Western societies. The recognition that vitamin D deficiency is widespread led to the hypothesis that it contributed to the asthma epidemic.⁵ With regard to asthma, vitamin D has wide-ranging effects, including effects on the developing lung and immune system *in utero* and postnatally,⁶ antimicrobial effects and anti-inflammatory effects after viral infections,⁷ effects on smooth muscle,^{8,9} and more recently, modulating effects on the microbiome in both nasal and intestinal compartments.^{10,11} Many observational studies have been conducted; however, results have been mixed.¹² Several clinical trials on asthma management have also been conducted and a meta-analysis of these trials showed a benefit of vitamin D supplementation on asthma exacerbations.¹³

In this issue of the journal, Han et al¹⁴ present their results, which add to the growing literature of vitamin D in asthma, using data from NHANES for the period 2001 to 2010, comprising more than 10,000 children and more than 24,000 adults, with lung function data on a subset. The main findings of this analysis

showed that vitamin D insufficiency (25OHD < 30 ng/mL) was prevalent in both children (68%) and adults (70%), and was associated with both current asthma and current wheeze in children and current wheeze in adults. In race/ethnicity-stratified analyses, vitamin D insufficiency was associated with current asthma and current wheeze in non-Hispanic white children only and current wheeze in non-Hispanic white and black adults. Lower 25OHD levels were also associated with lower lung function indices. The authors also point out that the prevalence of vitamin D insufficiency declined in the last 2 waves from 2007 through 2010, compared with the earlier waves of the survey from 2001 through 2006, and this coincided with a slight decrease in current asthma prevalence. Although intriguing, this last piece of their results will need further verification in future studies. The main strengths of the study include the following: (1) the large numbers of subjects spanning a decade, although these were not the same subjects followed longitudinally. In essence, these were snapshots of the population over the 10-year span, using the same sampling methodology. The large number of subjects allowed (2) investigation of race/ethnicity-specific analyses, as minority populations were oversampled in NHANES. Most studies to date did not investigate race-specific effects due to power considerations. Finally, (3) the availability of lung function data allowed confirmation of the effects of vitamin D on lung function. Most previous studies have investigated the association of vitamin D with lung function in specific patient subgroups (ie, patients with asthma) rather than a general population sample. The current analysis replicates the finding from an earlier NHANES survey.¹⁵ The main weakness of the study is the cross-sectional nature of the association; thus, no inference on causation can be made. Although vitamin D insufficiency can lead to increased symptoms of asthma and lower lung function, the cross-sectional nature of this analysis cannot exclude the possibility that the reverse is true—that more symptoms and lower lung function led to less outdoor activity and lower vitamin D status. Despite this weakness, this study adds to the accumulating data of an association between vitamin D insufficiency and symptomatic asthma and lower lung function.

The present study also illustrates several important points. First, the current study confirms that vitamin D insufficiency and deficiency are highly prevalent in the US population, with higher prevalence in minority populations. However, this analysis did not find that vitamin D insufficiency was associated with asthma or wheeze in children from minority populations, despite these outcomes being more frequent in these populations. Does this mean that we can conclude that vitamin D does not play a role in asthma symptoms in minority populations? Not quite, in fact, because vitamin D insufficiency is highly prevalent in these minority populations, with 94.4% of the non-Hispanic blacks affected. Thus, the association could not be detected because of the high prevalence of vitamin insufficiency, and highlights a limitation of cross-sectional analyses for highly prevalent

Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass

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Corresponding author: Augusto A. Litonjua, MD, MPH, Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115. E-mail: augusto.litonjua@channing.harvard.edu.

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conditions. Vitamin D may play a role in explaining health disparities between white and black populations, but supplementation studies may better uncover this modulating effect. Next, the study adds to the accumulating evidence that vitamin D plays a role in lung function. Recent studies are elucidating the beneficial role of vitamin D on lung function, and that this effect begins *in utero*. A comparative analysis of mouse and human embryonic lung tissue found that vitamin D-regulated genes were markedly overrepresented in developing lung transcriptomes beginning in early through later lung development.¹⁶ Moreover, 12 of these genes were differentially expressed in immortalized B cell lines from patients with asthma compared with their unaffected siblings, suggesting a link between vitamin D, lung development, and asthma development. Animal studies have shown that *in utero* vitamin D deficiency leads to increased airway smooth muscle mass, altered lung structure, and inflammation.¹⁷⁻¹⁹ Although postnatal vitamin D supplementation can reverse some of these effects,¹⁸ vitamin D supplementation during pregnancy appeared to be more effective in abrogating these effects in the offspring.²⁰ Although results of human studies are mixed, recent studies have shown an effect of vitamin D deficiency at 18 weeks' gestation and impaired lung function in 6-year-old children,²¹ and that vitamin D insufficiency was a determinant of reduced lung growth through early adulthood in a cohort of children with mild to moderate asthma.²²

In conclusion, this large cross-sectional analysis of a subsample of the US population adds to the growing evidence of the link between vitamin D insufficiency and asthma. Although the authors state that vitamin D cannot yet be recommended for the treatment of asthma, a recent Cochrane review found that vitamin D supplementation in patients with mild to moderate asthma reduced the risk of exacerbations requiring systemic corticosteroids and exacerbations requiring emergency department visits or hospitalizations,¹³ primarily in adults, with only 1 study of 22 children contributing information. Although additional supplementation trials are needed for children with asthma, there appears to be sufficient evidence to at least prevent or treat vitamin D deficiency in adults with asthma, and perhaps to get them to a sufficient level. Whether levels higher than 30 ng/mL will be optimal for prevention and treatment of asthma, however, awaits further study.

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