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## Vitamin D deficiency and asthma: Not a strong link—yet

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To the Editor:

We read with interest the article by Drs Litonjua and Weiss<sup>1</sup> on a link between vitamin D deficiency and the incidence of asthma. Indeed, several studies suggest that vitamin D deficiency is an underappreciated public health problem. The prevalence of hypovitaminosis D is dependent on the parameters used to define the need for vitamin D, a steroid hormone that only loosely fits the definition of a vitamin. Low vitamin D, as defined by levels of serum 25-hydroxy vitamin D3 (25D3), is the result of insufficient dietary intake and/or inadequate UV exposure. Theoretically, increasing time spent indoors and the rising use of sunscreen or UV protective clothing have contributed to the growing problem of inadequate vitamin D. However, it is well established that UV is a major risk factor for skin cancer and photodamage. Thus, there is a pressing need to understand optimal vitamin D status to inform recommendations for adequate dietary supplementation but maintain efforts to prevent UV-induced disease.

Recently, several studies have demonstrated that vitamin D is an important regulator of adaptive and innate immune responses in addition to its role in calcium homeostasis and bone health. T cells, monocytes, dendritic cells, and other cells essential to innate immune defense, such as epithelial cells, express the vitamin D receptor.<sup>2</sup> On activation of the vitamin D receptor in these cell types, the expression of an array of target genes is altered. This, in turn, can modify inflammation and immune defense.<sup>3,4</sup> As the authors suggest, it may not be a coincidence that behaviors leading to lower serum vitamin D levels are associated with an increase in immune disorders characterized by a disturbed T<sub>H</sub>1/T<sub>H</sub>2 cytokine balance. Although there is no evidence that these suboptimal levels of vitamin D result in classic disorders associated with hypovitaminosis D such as rickets or osteomalacia, the recent mechanistic connections between vitamin D and the immune system make it tempting to link immunologic disorders prevalent in industrialized societies with lower vitamin D levels.

Although an intriguing suggestion, the link between vitamin D deficiency and the asthma epidemic is premature. In contrast with infectious pulmonary disease, where a clear association has been demonstrated,<sup>5</sup> the data for asthma are less clear.<sup>2</sup> As mentioned by Drs Litonjua and Weiss,<sup>1</sup> comprehensive multidisciplinary studies are necessary to determine the role of vitamin D in asthma pathogenesis. Large trials of infant and maternal supplementation will be required. Appropriate dosing will be key to ensure a benefit and also avoid toxicity. Currently, it is a matter of debate what vitamin D status (as measured by 25D3 serum levels) is sufficient to evaluate appropriate immune function. Serum 25D3 is only one variable in vitamin D regulated systems. Hydroxylation and subsequent activation of 25D3 to 1,25-dihydroxy vitamin D3

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(1,25D3) are crucial for vitamin D3 function. Recent studies demonstrate that this activation step in the extrarenal circulation is more important than previously estimated and that regulation of 1,25D3 at the target tissue will occur independently of serum 25D3 levels.<sup>3,6</sup>

Further experimental and clinical studies are needed to establish a firm link between vitamin D deficiency and asthma. Adverse effects of increased vitamin D intake must be considered. Cells treated with 1,25D3 will increase the expression of cathelicidin, an antimicrobial peptide, and TLR2 and CD14, important microbial recognition molecules.<sup>6</sup> This is beneficial in a setting of infection or injury, where increased innate immunity is essential for protection. However, inappropriate increase in constitutive antimicrobial activity might lead to changes in the resident flora and can be proinflammatory.<sup>7</sup> Furthermore, because the commensal flora is important for effective barrier function at epithelial surfaces and defense against colonisation by pathogens, disturbances in this fragile balance might be disadvantageous.

In summary, the article by Drs Litonjua and Weiss<sup>1</sup> adds to the growing evidence to suggest that vitamin D plays an important role in inflammation. Current dietary recommendations established before knowledge of these events did not consider the need for vitamin D to regulate immune function. Careful oral supplementation might improve some elements of diseases associated with dysregulation of inflammation such as asthma and atopic dermatitis. There is also mounting evidence that vitamin D plays a role in the prevention of breast, colorectal, and prostate cancer. Further prospective clinical trials and additional work to uncover the full range of functions of vitamin D are needed.

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