

TABLE I. Associations between specific IgE antibody titers and total IgE among children living in Sweden

Allergen	Pearson correlation (r)
Cat	0.31 ($P < .001$)
Dust mite	0.22 ($P = .2$)
Grass	0.42 ($P < .001$)
Dog	0.34 ($P < .001$)
Birch	0.21 ($P = .03$)

children ($n = 69$), the prevalence of sensitization to cat, dog, and dust mite was 46.4%, 47.8%, and 11.5%, respectively.³

Further analysis of specific IgE titers and their relationship to total IgE in the 2 areas with similar climates, Siberia and northern Sweden, reveals parallels. In Sweden, high titer of specific IgE antibody (>50 IU/mL) to any allergen was uncommon. In Siberia, high titers of specific IgE to cat and dog were also relatively uncommon. High titers of specific IgE to birch in Siberia appear to be as frequent as lower titers. It is possible that this observation is explained by the time of year that some serum samples were collected (March, April, and May, although not in the same year).⁴ In both regions, only a modest correlation was observed between specific IgE antibody titers to cat, dog, and relevant pollens (birch in Siberia and birch and grass in northern Sweden). The relationship between dust mite and total IgE was not significant in northern Sweden (Table I).

The current analyses of Gusareva et al¹ reinforce our previous suggestion that the relationship between specific and total IgE is directly dependent on the relevant environmental allergen. Allergens that induce high levels of specific IgE antibody can be related to increased total IgE. This concept may seem simple, but it implies that a ranking of antibody responses to specific allergens is possible that predicts total IgE and prevalence of wheezing. We have previously suggested that titers of IgE antibody produced in response to dust mite are higher than titers of IgE to cat in New Zealand.⁵ In turn, higher titers of IgE to dust mite are related to higher total IgE and an increased prevalence of wheezing in New Zealand.³ Combining the results of Gusareva et al¹ with our own, northern Sweden, Siberia, and New Zealand can be ranked according to prevalence of wheezing and increased total IgE on the basis of dust mite exposure.

We agree with Gusareva et al¹ that it would be interesting to look at the relationship between specific IgE antibody and total IgE in other areas. Previously, the overlap in total IgE between allergic and nonallergic persons has complicated large epidemiologic studies. We would argue that examining a single area has been an underlying problem because allergen exposure would be the same throughout the region. By simultaneously studying areas with different allergen exposures, the allergen-specific effects can be observed.

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

To the Editor:

We read with interest the article by Drs Litonjua and Weiss¹ 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.² 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.^{3,4} 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_H1/T_H2 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,⁵ the data for asthma are less clear.² As mentioned by Drs Litonjua and Weiss,¹ 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 (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.^{3,6}

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.⁶ 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.⁷ 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 Weiss¹ 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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Reply

To the Editor:

We thank Drs Schaubert and Gallo¹ for their interest in our recent article, in which we proposed a hypothesis to explain the asthma epidemic, namely that vitamin D deficiency may be partly to blame for the rise in asthma prevalence. We agree with the points that they raise, and although this link is not yet established, we feel that there is sufficient evidence for vitamin D as an immune modulator to propose this hypothesis. Indeed, the main reason for writing this article was to stimulate research into this potential link. We would now like to expound on the main points raised in the letter.

Although we have focused on vitamin D, we are aware that UV light has effects on immune cells via mechanisms that may be independent of the effects of vitamin D.^{2,3} However, because of the known risks of UV light exposure, the best approach to prevention will ultimately be through oral supplementation, if indeed the effects are mediated through the active forms of vitamin D.

As alluded to by Drs Schaubert and Gallo,¹ the appropriate dose and circulating level (as measured by 25-hydroxyvitamin D₃, 25[OH]D) of vitamin D for beneficial immune effects are unknown. This dose is likely to be different from that for bone health and may be different at various stages of the life cycle (ie, prenatal vs postnatal). After acute exposure to sunlight, humans can produce between 10,000 and 20,000 IU vitamin D₃, depending on the intensity of exposure and skin pigmentation.⁴ However, because levels can fluctuate depending on season and behavior,⁵ future epidemiologic research will need to collect information not only on circulating levels of 25(OH)D but also on diet (including supplement use) and on sun exposure behaviors as indices of more chronic exposure. With regard to toxicity, to date, ongoing clinical trials of vitamin D supplementation in pregnant and lactating women have not reported any clinical toxicity with doses as high as 6000 IU/d.⁶ Continued monitoring for potential toxicity in clinical trials will be both prudent and responsible conduct for research. We also agree that extrarenal and tissue-specific activation of vitamin D is important, and studies using animal models and cell systems will be necessary. A corollary is that genetic polymorphisms in the genes encoding the receptor and the enzymes will be important modifiers of the effect of vitamin D, given a particular dose.

Finally, the human microbiota (particularly the gut microbiota)⁷ has important effects on both the innate and adaptive immune system. How vitamin D intersects and interacts with the microbiota is a very important area of future research. We are in agreement with Drs Schaubert and Gallo that well designed multidisciplinary studies are needed to shed light on the role of vitamin D in both asthma pathogenesis and treatment.

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