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Vitamin D, Respiratory Infections, and Obstructive Airway Diseases

*Carlos A. Camargo Jr, Adit A. Ginde,
and Jonathan M. Mansbach*

Abstract Over the past decade, interest has grown in the effects of vitamin D on respiratory infections and obstructive airway diseases (OADs), such as asthma and chronic obstructive pulmonary disease (COPD). Studies suggest that low vitamin D levels increase the risk of acute respiratory infections, which may contribute to incident wheezing illness and cause asthma exacerbations. Although unproven, the increased risk of susceptible hosts to specific respiratory pathogens may contribute to some cases of incident asthma. Likewise, the effect of vitamin D on COPD, while intriguing, is largely unknown. Emerging evidence provides biological plausibility for some of these respiratory findings. For example, vitamin D-mediated innate immunity, particularly through enhanced expression of the human cathelicidin antimicrobial peptide, is important in host defenses against respiratory pathogens. Vitamin D also modulates regulatory T-cell function and interleukin-10 production, which may increase the therapeutic response to corticosteroids in corticosteroid-resistant asthma. Finally, low vitamin D levels may have a role in the pathogenesis of allergies, including anaphylaxis. Further studies, especially randomized controlled trials, are needed to better understand vitamin D's effects on respiratory infections and OADs.

Key Words: Respiratory infections; bronchiolitis; asthma; chronic obstructive pulmonary disease; obstructive airway disease; hCAP-18; interleukin-10; atopic dermatitis; anaphylaxis

1. INTRODUCTION

Research on the effects of vitamin D on the respiratory system could be said to have begun more than a century ago, with work on the beneficial effects of sunlight on tuberculosis (1). This research led to important changes in clinical practice, including the development of health facilities in the mountains to provide tuberculosis patients with better access to sunlight, fresh air, and other putative health benefits. In subsequent years, however, major advances in anti-tuberculosis medications, along with the discovery of vitamin D per se (and its beneficial effects on rickets and overall bone health), led to a dramatically decreased interest in the role of sunlight (or vitamin D) on lung health.

Over the last decade, researchers have again taken interest in the possible antimicrobial effects of vitamin D (2, 3). In addition to studies on the respiratory infection

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risk of nutritionally deficient, often rachitic, children in developing nations (4, 5), more recent studies have examined the vitamin D–respiratory infection association in otherwise well-nourished individuals in developed nations (6, 7). In 1999, emerging data on the immunologic effects of vitamin D led Wjst and Dold to propose that vitamin D supplementation might be the cause of global increases in asthma and allergies (8). Genetic association studies were undertaken to examine this putative harm [e.g., by examining polymorphisms of the vitamin D receptor (VDR) gene] but they provided conflicting results (9–13).

It was in this context that Camargo and colleagues proposed the *opposite* hypothesis at the 2006 meeting of the American Academy of Allergy, Asthma, and Immunology (14) – i.e., widespread vitamin D *insufficiency* (not excess) might explain recent increases in childhood wheezing and asthma. The investigators presented original evidence for this hypothesis from a birth cohort study involving almost 1,200 Boston mother–child pairs. In brief, they found that maternal intake of vitamin D during pregnancy had a striking inverse association with recurrent wheezing in children (Fig. 1). Because most wheezing illness of childhood represents uncomplicated respiratory infection, as opposed to incident asthma (15), the authors cautioned that further research would need to disentangle these two overlapping outcomes (i.e., respiratory infections and asthma).

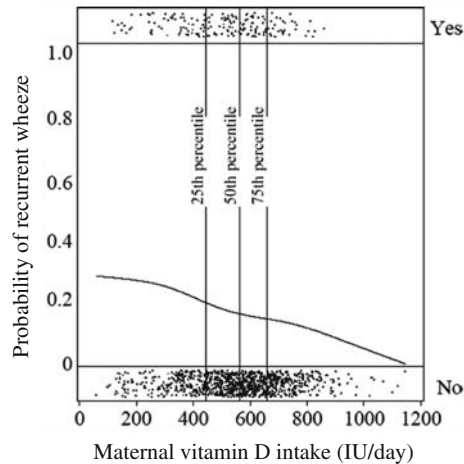


Fig. 1. Association between maternal vitamin D intake during pregnancy and risk of recurrent wheeze in offspring ($n = 1,194$ mother–child pairs in Boston area). The *top band* of dots (Yes) represents children who developed recurrent wheeze, and the *bottom band* of dots (No) represents children who did not. The *vertical lines* represent percentiles of maternal vitamin D intake during pregnancy (adapted from Ref. (56)).

The relation of vitamin D status to respiratory infections and asthma has become a focus of research teams around the world. In this chapter, we will examine these two outcomes, as well as the potential role of vitamin D on chronic obstructive pulmonary disease (COPD). We will also touch briefly on biological mechanisms that may

underlie the complex relationship between vitamin D, respiratory infections, and obstructive airway diseases (OADs).

2. RESPIRATORY INFECTIONS

Respiratory infections are a major cause of morbidity and mortality (16). Although they are often discussed collectively, they are a surprisingly diverse and complex group of infections. In addition to basic issues of disease chronicity (i.e., acute versus chronic infection), respiratory infections are usually categorized by the anatomical areas involved (i.e., upper versus lower tract disease). Acute *upper* respiratory infections include a variety of diagnoses, such as acute nasopharyngitis (e.g., the “common cold”), acute sinusitis, acute pharyngitis, and acute laryngitis and tracheitis (e.g., croup); some researchers also include acute otitis media. By contrast, acute *lower* respiratory infections include many other important and common diagnoses, including bronchiolitis, bronchitis, and pneumonia. Although this may sound quite orderly, it is important to recognize that respiratory infections may (and often do) involve multiple locations.

Another layer of complexity is introduced by the categorization of respiratory infections according to pathogen. For example, acute respiratory infections may be caused by the so-called “cold” viruses [e.g., rhinovirus, adenovirus, respiratory syncytial virus (RSV), parainfluenza] or common bacterial pathogens (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*). The catch-all phrase “respiratory infection” also includes distinctive diseases due to specific pathogens of major public health importance. One example is influenza, the virus responsible for the 1918 flu pandemic that killed more than 50 million people worldwide (17). Another important example is *Mycobacterium tuberculosis*, the cause of tuberculosis.

Bronchiolitis provides an excellent example of the complexity of research on acute respiratory infections (18). Although bronchiolitis is a leading cause of infant hospitalization, with an annual cost of \$543 million in the United States alone (19), it remains a clinical diagnosis with rather vague diagnostic criteria (20–22). For example, in 2006, the American Academy of Pediatrics (AAP) position paper described the typical child with bronchiolitis as being of age <2 years and having “rhinitis, tachypnea, wheezing, cough, crackles, use of accessory muscles, and/or nasal flaring” (23). In other countries, however, we know of strong opinions that bronchiolitis only should be diagnosed among children of age <1 year or that the presence of specific exam findings (e.g., crackles) should be mandatory.

One might think that a better understanding of the microbiologic causes of bronchiolitis would help with disease classification. Indeed, when discussing the clinical course of bronchiolitis, clinicians rely heavily on descriptions of bronchiolitis caused by RSV, the most common cause (24, 25). While almost all children are infected with RSV by age 2 years (26, 27), most children do not present to an acute care setting with clinical bronchiolitis (26, 28). For example, we estimate that <10% of US children infected with RSV will present to the emergency department with bronchiolitis and that only 2–3% are hospitalized (29, 30). Clearly, there is a spectrum of disease severity that extends beyond current understanding. To further complicate matters, many other viruses have been linked to bronchiolitis (Table 1), including rhinovirus (31, 32) and a continually

Table 1
Frequency of Common Viruses Linked to Bronchiolitis in Three Care Settings, As Identified by Polymerase Chain Reaction (Adapted from (18))

	<i>Outpatient (%)^a</i>	<i>Emergency (%)^b</i>	<i>Inpatient (%)^c</i>
Respiratory syncytial virus	11–27	64	69
Parainfluenza	5–13	na	3
Influenza	1–5	4	2
Rhinovirus	46–49	16	21
Metapneumovirus	2	7	5
Combination infections	10–17	14	16

Abbreviation: na denotes not available.

^aBased on upper and lower respiratory infections during infants' first winter (136) and first year (137).

^bBased on children presenting to 14 US emergency departments (138).

^cBased on children hospitalized to 15 US hospitals (Camargo et al., unpublished data).

growing number of new viruses and strains. An unknown percentage of cases may be caused by bacteria such as *Mycoplasma pneumoniae* (33). Thus, increased appreciation of the actual microbiologic cause of bronchiolitis, and its short-term and long-term clinical implications, would further complicate the nosology of this common childhood disease.

Given the complexity and diversity of “respiratory infections,” one might expect that it would be difficult to link an individual factor like vitamin D to risk of developing this composite outcome. To be more specific, vitamin D might have an important association with specific types of respiratory infections, as defined by specific anatomical areas and by specific pathogenic organisms. Vitamin D might also influence disease severity. If these hypotheses were confirmed, the common practice of collapsing all of these diverse infections into one composite outcome would tend to obscure real associations – i.e., one would conclude that there was no association when, in fact, there was one. The scientific literature on vitamin D and respiratory diseases needs to be interpreted with this important caveat in mind.

3. OBSTRUCTIVE AIRWAY DISEASES

3.1. Asthma

Asthma is another common medical condition that is associated with high morbidity and health-care utilization (34, 35). Although the definition of asthma has challenged clinicians for literally centuries, there is fairly widespread acceptance today of the 1987 definition from the American Thoracic Society (36): a chronic lung disease characterized by (1) airway narrowing that is reversible (though not always completely), either spontaneously or with treatment; (2) airway inflammation; and (3) bronchial hyper-responsiveness (BHR) to a variety of stimuli.

Although this definition has proven helpful for some types of researchers, it is very difficult to apply in epidemiologic studies, where subjects may be dispersed over large

geographic areas and where spirometry and hyper-responsiveness testing usually are not feasible. For that reason, asthma epidemiologists have relied on much simpler definitions of asthma, such as an affirmative response to the question: “Do you have doctor-diagnosed asthma?” Although the limitations of this epidemiologic approach are self-evident, this approach actually performs with adequate accuracy (37) to allow epidemiologists to perform asthma surveillance and to begin to examine risk factors of the disease. Similar yes/no questions have led to widespread recognition and concern about the dramatic rise in “asthma” over the past few decades (34).

While respiratory infections occur commonly across the lifespan, and viral infections are common triggers of asthma exacerbations (38, 39), the vast majority of asthma begins in early childhood. Estimates vary but approximately 80–90% of asthma begins before the age of 6 years, with 70% of asthmatic children having asthma symptoms before 3 years of age (40, 41). The etiology of asthma has proven elusive, but we can infer from these clinical observations that the major risk factors must be present in early life. Atopy is one of the strongest risk factors of asthma (42), yet many asthmatic individuals are non-atopic (43). Indeed, there is growing appreciation that the term “asthma” is a syndrome composed of heterogeneous diseases (44).

3.2. Chronic Obstructive Pulmonary Disease

COPD is another common medical condition that is associated with high morbidity and mortality (45). The most widely accepted definition for COPD comes from the Global Initiative for Chronic Obstructive Lung Disease (GOLD): “a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases” (45).

As with asthma, there have been significant disagreements about the definition of COPD over the past few decades. Classical descriptions of COPD have emphasized two major types: “chronic bronchitis” and “emphysema.” Although these COPD types continue to be taught in medical schools, there is now widespread recognition of their considerable overlap. Uncertainty regarding COPD diagnosis has been compounded by the fact that chronic bronchitis was, for many years, a clinical diagnosis (e.g., requiring that the patient has a productive cough for a specified number of months over a specific number of years), while emphysema was an anatomic diagnosis requiring actual parenchymal destruction. The GOLD definition now acknowledges that the chronic airflow limitation characteristic of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), with the relative contributions varying from person to person (45).

4. CHILDHOOD WHEEZING

While experts may differ on the precise definitions of specific respiratory infections, asthma, and COPD, everyone agrees on the heterogeneity of early childhood wheezing. After all, wheezes are just musical sounds caused by the passage of air through

narrowed respiratory tract airways, a condition with many different possible causes. Across the life span, this airway narrowing is most frequently caused by respiratory infections (edema) and/or OADs (mixture of infection, inflammation, and bronchoconstriction). Wheezing can also be caused by many, less common conditions in children (e.g., airway foreign body) and in adults (e.g., decompensated heart failure with the so-called “cardiac wheezing”).

Cohort studies have provided important information about the natural history of childhood wheezing. For example, the landmark studies of Martinez and colleagues clearly demonstrate that many children who wheeze in early childhood have transient episodes during respiratory infections and do not go on to develop asthma (15). Researchers try, with varying levels of success, to divide wheezing children into three different clinical groups: transient early wheezers, non-atopic wheezers, and IgE-associated wheeze/asthma (Fig. 2). The figure nicely demonstrates the clinical adage that “All that wheezes is not asthma.” To further underscore the difference between childhood wheezing and asthma, many young children with asthma often present with recurrent nocturnal cough and no wheezing whatsoever (46). For all of these reasons, one should be cautious about generalizing from findings on even *recurrent* childhood wheezing to actual asthma.

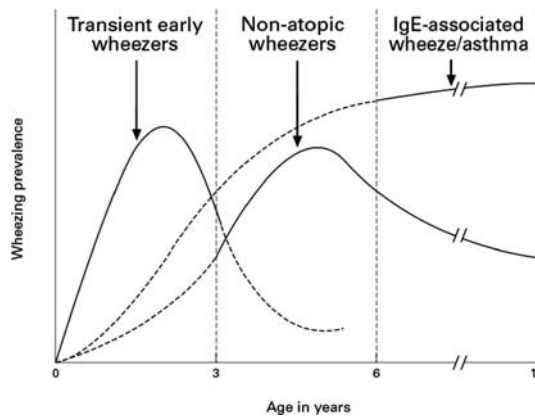


Fig. 2. Hypothetical prevalence of three different wheezing phenotypes in childhood. For each age interval, the overall wheezing prevalence is the sum of the areas under each curve. The *dashed lines* emphasize the possibility of different curve shapes due to many factors, including overlap between the three groups (adapted from Ref. (135)).

5. VITAMIN D AND RESPIRATORY INFECTION

5.1. Tuberculosis

As noted earlier, the first links between vitamin D and respiratory disease stretch back to more than a century. Niels Ryberg Finsen was awarded the 1903 Nobel Prize in Physiology and Medicine (1) in recognition of his innovative work showing that concentrated light radiation could effectively treat lupus vulgaris [skin tuberculosis (TB)]. Although he did not know the mechanism of this therapeutic benefit, it is likely that at least part

of it was due to increased levels of vitamin D. Likewise, for a large part of the twentieth century, sunlight exposure was used as treatment for TB.

In recent years, many investigators have linked vitamin D more directly to TB (47, 48). For example, a hospital-based case-control study in London found that vitamin D deficiency was associated with an odds ratio (OR) of 2.9 [95% confidence interval (CI) 1.3–6.5] for having active TB (49). Susceptibility to TB has also been linked to vitamin D receptor polymorphisms, with the presence of *FokI F* allele protecting against TB infection, and the *TaqI t* allele protecting against active disease but not infection (50). In another recent study, Martineau and colleagues (51) reported that a single dose of 2.5 mg (100,000 IU) of vitamin D (ergocalciferol) enhanced immunity to *M. tuberculosis*. The relationship between vitamin D status and TB is an active area of research.

5.2. Epidemiologic Studies on Respiratory Infections

In addition to TB, vitamin D may have antimicrobial activity against a broad range of respiratory pathogens. Many studies have reported that children with rickets commonly present to hospitals with respiratory infections (52). Although 25-hydroxyvitamin D [25(OH)D] levels of at least 10 ng/ml (25 nmol/l) are known to prevent rickets, the relationship between higher 25(OH)D thresholds and respiratory infection is of greater public health interest, particularly in developed nations. Recent clinical studies have demonstrated a fairly consistent association between lower, but non-rachitic 25(OH)D levels, and increased risk of respiratory infections (6, 7, 53, 54).

For example, a case-control study in India demonstrated that children 2–60-months old with serum 25(OH)D levels <20 ng/ml had 12-fold higher odds of acquiring a severe acute lower respiratory infection (53). Moreover, a Turkish case-control study found that serum 25(OH)D levels were lower in neonatal cases of acute lower respiratory infection (9.1 ng/ml) than in age-matched controls (16.3 ng/ml) (54).

In contrast, a recent Canadian case-control study of children 1–25-months old (55) found no difference in mean serum 25(OH)D levels between patients with acute lower respiratory tract infection (30.8 ng/ml) and hospital controls (30.9 ng/ml). Of note, the average vitamin D status of these children was >30 ng/ml because “virtually all of the infants . . . consumed vitamin D” through fortified infant formula or supplements. We believe that inadequate exposure variation did not allow for proper testing of the study hypothesis.

One of the first cohort studies on this topic was reported in 2007 by Laaksi and colleagues in Finland (6). They reported that young male soldiers with serum 25(OH)D levels <16 ng/ml at baseline had a 63% increased risk of absence from duty due to respiratory infection over the following 6 months, as compared to soldiers with levels of ≥ 16 ng/ml ($P = 0.004$).

Camargo and colleagues established an important relationship between vitamin D status and incident wheezing in two separate birth cohorts at higher latitudes: one in Massachusetts (56) and one in New Zealand (7). In the Massachusetts cohort, Project Viva, the investigators found that lower maternal intake of vitamin D during pregnancy was associated with significantly increased risk of recurrent wheezing (56), as shown in Fig. 1. In these 1,194 mother-child pairs, the mean (SD) total vitamin D intake

during pregnancy was 548 (167) IU/day. By the age of 3 years, 186 children (16%) had recurrent wheeze. Compared with mothers in the lowest quartile of daily intake (median 356 IU), those in the highest quartile (724 IU) had a lower risk of having a child with recurrent wheeze (OR 0.39; 95% CI 0.25–0.62; P for trend <0.001). A 100-IU increase in vitamin D intake was associated with lower risk (OR 0.81; 95% CI 0.74–0.89), regardless of whether vitamin D was from the diet (OR 0.81) or supplements (OR 0.82). Adjustment for 12 potential confounders, including maternal intake of other dietary factors, did not change the results.

This Boston finding was replicated in an independent birth cohort by Devereux and colleagues in Scotland (57). In the 1,212 mother–child pairs, the median (interquartile range) total vitamin D intake during pregnancy was 128 (103–165) IU/day. Compared to mothers in the lowest quintile of daily intake (median 77 IU), those in the highest quintile (275 IU) had lower risk for ever wheeze (OR 0.48; 95% CI 0.25–0.91), wheeze in the previous year (OR 0.35; 95% CI 0.15–0.83), and persistent wheeze (OR 0.33; 95% CI 0.11–0.98) in their 5–year-old children. By contrast, there was no association between maternal vitamin D intake during pregnancy and doctor-diagnosed asthma at the age of 5 years ($P = 0.98$).

In a New Zealand birth cohort, Camargo and colleagues (7) were the first to examine the association between low cord blood levels of 25(OH)D and subsequent risk of respiratory infections and childhood wheezing. In this seemingly healthy cohort of >900 children, 20% of children had a cord blood 25(OH)D level <10 ng/ml, and 73% (cumulative) had a 25(OH)D level <30 ng/ml. Cord blood 25(OH)D level had an inverse association with the risk of wheezing illness at ages of 15 months, 3 years, and 5 years (all $P < 0.05$). Moreover, cord blood 25(OH)D level was inversely associated with the risk of respiratory infection by the age of 3 months: children with 25(OH)D levels <10 ng/ml were at a twofold higher risk than those with levels ≥ 30 ng/ml. These results were independent of season and other potential confounders.

To further explore this issue, we analyzed nationally representative data from Third National Health and Nutrition Examination Survey (NHANES-III) to examine the association between vitamin D status and upper respiratory infection (58). In brief, we found that lower serum 25(OH)D levels were associated with an increased adjusted OR of recent upper respiratory infection (compared with ≥ 30 ng/ml: OR 1.36 for <10 ng/ml and 1.24 for 10–29 ng/ml groups) (58). As shown in Fig. 3, the inverse association was present in all seasons. We also found that the association between serum 25(OH)D <10 ng/ml and upper respiratory infection was stronger among individuals with asthma (OR 5.67) versus those without asthma (OR 1.24; P for interaction = 0.007).

5.3. Preliminary Evidence from Interventional Trials

Although there have been few interventional trials to date, the preliminary data are promising. For example, two interventional cohort studies with 600–700 IU of vitamin D intake daily from cod liver oil/multivitamin supplementation (59) and 60,000 IU weekly from a vitamin D/calcium supplement (60) noted a decrease in respiratory infections in children receiving supplementation. One randomized controlled trial of bone loss in postmenopausal black women found that 7.7% of women randomized to

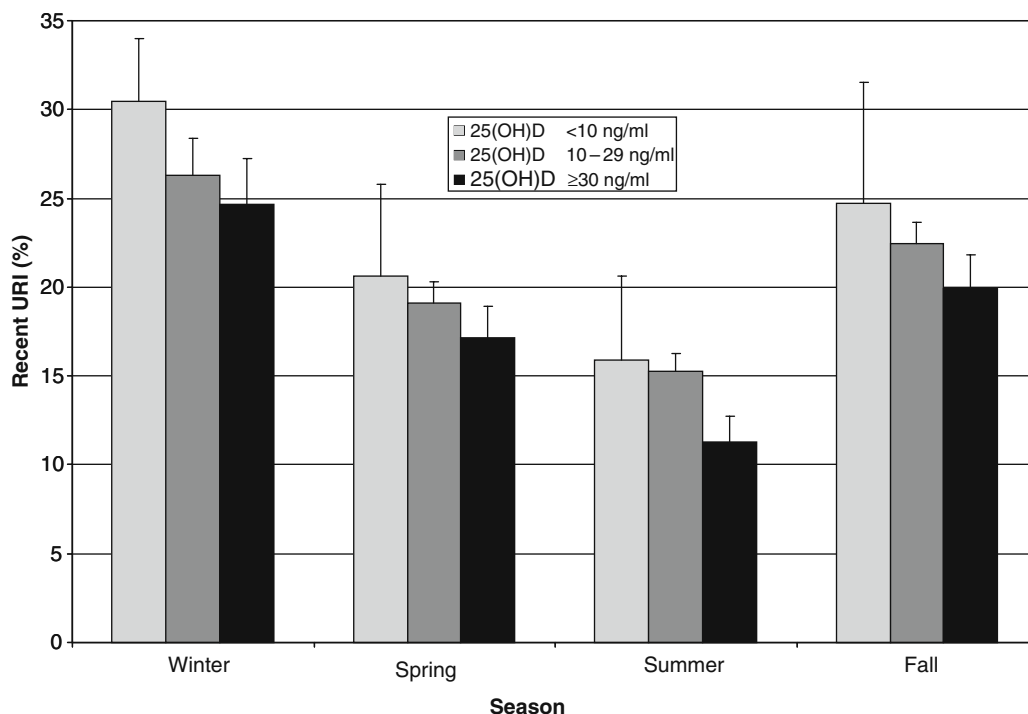


Fig. 3. Association between serum 25-hydroxyvitamin D level and recent upper respiratory infection (URI), by season ($n = 18,883$ participants in Third National Health and Nutrition Examination Survey). Error bars represent standard errors of the estimates (adapted from Ref. (58)).

vitamin D, 800–2,000 IU/day, and reported respiratory symptoms over the 3-year follow-up, compared with 25.0% in the control group (61). Another substudy of a randomized controlled trial for fracture prevention (62) found a possible reduction in wintertime infection in participants randomized to vitamin D, 800 IU/day (adjusted OR 0.90; 95% CI 0.76–1.07), though the result was not statistically significant.

The first interventional study specifically designed to test the vitamin D–respiratory infection hypothesis has been reported in abstract form (63). The investigators randomized 162 adults in New York to vitamin D3 2,000 IU/day versus placebo for 12 weeks between December and March. The mean 25(OH)D level at baseline was similar between the two groups (vitamin D 25.6 ng/ml versus control 25.2 ng/ml) and increased to 35.5 ng/ml in the vitamin D group while staying “virtually constant” among controls. Despite this increase, the investigators found no benefit on incidence or severity of viral upper respiratory tract infections in this relatively small and healthy sample of adults.

Taken together, the interventional studies provide support for an inverse association between vitamin D supplementation and respiratory infection – despite some recent null studies. The positive studies were not designed to test the study hypothesis, and they were limited by the relatively low dose of vitamin D supplementation used; the impact

of elevating 25(OH)D levels to >30 ng/ml (or even >40 ng/ml) merits investigation. Such trials would be particularly attractive in high-risk populations, such as children in day-care centers, residents of nursing homes, hospital personnel, or individuals with OAD.

6. VITAMIN D AND ASTHMA

6.1. *Asthma Pathogenesis*

The exact role of vitamin D in the pathogenesis of asthma remains unclear. Given the early age of asthma onset (64, 65), and growing evidence on the developmental origins of health and disease (66), the role of maternal diet on the risk of asthma in offspring is a particularly intriguing topic. Although investigators have debated the potential role of nutrient intake on asthma risk for more than a decade, multiple reviews of diet and asthma have said nothing about vitamin D as a potential risk factor for asthma (67–70).

As discussed by Camargo and colleagues (56), considerable epidemiologic data suggest a possible association between vitamin D insufficiency and the asthma epidemic. The prevalence of both conditions is higher in racial/ethnic minorities, obese individuals, and westernized populations (34, 71). Furthermore, large cross-sectional studies of adolescents and adults have found that vitamin D insufficiency is correlated with lower pulmonary function, including forced expiratory volume in 1 s and forced vital capacity (72, 73). Of course, the causal nature of these cross-sectional associations is uncertain. Although it is possible that low levels of vitamin D cause asthma, it is also possible that individuals with asthma exercise outdoors less often and that simple lifestyle differences could create vitamin D insufficiency. Likewise, some children with asthma historically have avoided milk intake (an important dietary source of vitamin D in US children) (56), and this food avoidance could also create a spurious inverse association between vitamin D intake and asthma. Prospective studies (especially randomized trials) could help investigators to address these important methodological concerns.

As noted earlier, the hypothesis that low vitamin D may cause asthma – and that sunlight exposure and supplements may prevent asthma – is disputed by Wjst, who has described vitamin D supplementation as an important cause of asthma (8, 74). The strongest support for this putative harm comes from a birth cohort in northern Finland (75). In this study, Hypponen, Wjst, and colleagues reported that regular vitamin D supplementation ($\geq 2,000$ IU/day) in the first year of life increased the risks of developing atopy, allergic rhinitis, and asthma by the age of 31 years. However, this finding may be related to the very high dose of vitamin D supplementation (i.e., a dose-specific effect). The Finnish study was also limited by the absence of data on maternal intake of vitamin D and the inability to control for major confounders. Furthermore, recall bias may have affected the ascertainment of early life asthma and allergies. Another recent study from the United Kingdom also raised the possibility that higher levels of vitamin D might cause atopy and asthma (76). This study also has important methodological limitations (e.g., small sample and only 30% follow-up at the age of 9 years). Nevertheless, these two European studies raise possible concerns.

Other evidence, however, suggests that vitamin D has no apparent association with incident asthma or may even have a modest protective effect. For example, preliminary evidence from two family-based studies demonstrated that gene polymorphisms on the

vitamin D receptor were associated with childhood and adult asthma (9, 10), but these results were not confirmed (11, 13). Also, as described in Section 5, birth cohorts in Boston (56) and Scotland (57) found an inverse association between maternal intake of vitamin D during pregnancy and risk of childhood wheezing. The Scottish investigators reported that lower maternal vitamin D intake was associated with a borderline significant decrease in bronchodilator response ($P = 0.04$), but there was no association with doctor-diagnosed asthma or other asthma-related outcomes, such as spirometry or exhaled nitric oxide concentration (57). Both findings were limited, however, by the measurement of vitamin D status from diet and supplements alone. Thus, the unique contribution of the New Zealand birth cohort is the concurrent demonstration that low serum 25(OH)D levels in cord blood were associated with increased risk of respiratory infections and childhood wheezing but had no association with the risk of current asthma at the age of 5 years (7). The null finding applied to both atopic asthma and non-atopic asthma, with atopy defined by skin-prick testing for common allergens at the age of 15 months.

Taken together, it seems unlikely that vitamin D status in pregnancy is a major contributor to the current asthma epidemic. We hypothesize that if a modest association exists between vitamin D insufficiency and incident asthma, then it would be mediated through increased risk of respiratory infection in early life. In a recent study from the Childhood Origins of Asthma (COAST) birth cohort in Wisconsin, Jackson and colleagues (77) found that wheezing rhinovirus illness during infancy predicted development of asthma at 6 years of age. Linking these rhinovirus data and the aforementioned birth cohort data, it is possible that vitamin D insufficiency may contribute to the seasonal nature of the infectious bronchiolitis in infants (78). Early viral respiratory infections in a genetically susceptible host may induce subsequent asthma development, and if vitamin D mediates some part of this pathway, there might be a new strategy for preventing some cases of asthma. Likewise, chronic infection with atypical bacteria may participate in asthma pathogenesis for a subset of patients, in addition to playing a role in lung inflammation and corticosteroid resistance in asthma (79). For these susceptible individuals, correction of vitamin D deficiency not only would provide overall health benefits (71) but might contribute to asthma prevention.

6.2. Asthma Control

Most people with asthma respond well to inhaled corticosteroids, the “preferred” long-term control medication for asthma according to the 2007 NIH asthma guidelines (80). Nevertheless, asthma control on even “optimal” controller therapy leaves room for improvement (81). This is particularly true in a subset of asthmatic patients with known corticosteroid resistance (82). Xystrakis and colleagues in London recently studied the effect of vitamin D in this relatively small asthma subgroup (83). They administered vitamin D to a small group of healthy individuals and steroid-resistant asthmatic patients and found that the intervention enhanced subsequent responsiveness to dexamethasone due to induction of interleukin (IL)-10. The authors concluded that vitamin D could potentially increase the therapeutic response to corticosteroids in steroid-resistant asthma patients. These experimental results await replication. Moreover, the

implications of this finding to the larger population of asthmatic patients with suboptimal control (despite the use of inhaled corticosteroids) are not known.

6.3. Asthma Exacerbation

Viral respiratory infections, particularly rhinovirus, are associated with 50–85% of asthma exacerbations (38, 39). Most adults experience 2–4 upper respiratory infections per year, while children experience 6–10 (84). Individuals with asthma may be more susceptible to respiratory infection and have increased frequency of lower respiratory tract symptoms of higher severity and duration (85). The emerging role of vitamin D in innate immune responses may explain predisposition to infection and asthma exacerbation in certain populations.

As presented earlier in this review, there is growing evidence of a “protective” association between vitamin D and respiratory infection in the general population (6, 7, 53, 54, 59, 61). However, there are only sparse data on the association in asthmatic individuals. In our analysis of the NHANES-III data (58), we found that the association between serum 25(OH)D levels <10 ng/ml and upper respiratory infection was stronger among individuals with asthma (OR 5.67) compared with those without asthma (OR 1.24; *P* for interaction = 0.007). Moreover, Litonjua and colleagues (86) recently examined the association between serum 25(OH)D levels and risk of severe asthma exacerbations (defined as an asthma-related emergency department visit or hospitalization). In 1,022 asthmatic children in the Childhood Asthma Management Program (CAMP), they found that children with low baseline 25(OH)D levels (<30 ng/ml) were more likely to have a severe asthma exacerbation over a 4-month period (OR 1.50; 95% CI 1.13–1.98).

7. VITAMIN D AND COPD

7.1. COPD Pathogenesis

Although vitamin D insufficiency may also play a role in COPD pathogenesis, data are sparse. Indirect evidence for an association comes from numerous studies reporting an increased association between osteoporosis and COPD (87–92), usually independent of corticosteroid use. Although serum 25(OH)D levels have not been directly linked to COPD, Black and Scragg (72) reported a strong dose–response correlation in NHANES between serum 25(OH)D levels and pulmonary function, including forced expiratory volume in the first second (FEV₁), which is a key marker for increased susceptibility and diagnosis of COPD. They found that the adjusted FEV₁ was 126 ml lower in the lowest 25(OH)D quintile compared to the highest quartile. Moreover, this difference appeared higher in participants with doctor diagnosis of chronic bronchitis (248 ml) or emphysema (344 ml), although the test for interaction was underpowered and not statistically significant. Proposed mechanisms were explored in the accompanying editorial (93) and include the role of 1,25(OH)D in modulating the formation of matrix metalloproteinases, fibroblast proliferation, and collagen synthesis (94, 95). Additionally, vitamin D-mediated immunomodulation could affect airway inflammation, a central process in the pathogenesis of COPD (96).

Genetic studies have also suggested a possible association between vitamin D and COPD pathogenesis (12, 97–99). Specifically, the vitamin D-binding protein [also known as the group-specific component of serum globulin (Gc-globulin)] is the major carrier protein of 25(OH)D in blood. In a Japanese population, Ito and colleagues found a strong association between Gc-globulin polymorphism and increased susceptibility to COPD (99). While these data appear promising, the association between vitamin D-binding protein and COPD progression, as measured by the rate of decline in pulmonary function, has yielded mixed results (99, 100). Large prospective studies are needed to address the potential role of vitamin D in COPD pathogenesis.

7.2. Acute Exacerbations of COPD

Similar to asthma, many acute exacerbations of COPD (AECOPD) are caused by common respiratory viral pathogens, such as rhinovirus, influenza, parainfluenza, and respiratory syncytial virus. While no direct data link vitamin D and AECOPD, vitamin D-mediated immune mechanisms may play a role in the prevention of respiratory infection and associated AECOPD. In our analysis of the NHANES-III data (58), we found that the association between serum 25(OH)D levels <10 ng/ml and upper respiratory infection might be stronger among individuals with COPD (OR 2.26) compared with those without COPD (OR 1.27); statistical power was limited, however, and the difference was not statistically significant (P for interaction = 0.30). Further studies of the role of vitamin D in AECOPD are warranted.

8. POTENTIAL MECHANISMS

8.1. Vitamin D and Innate Immunity

Emerging evidence indicates that vitamin D has an important role in the innate immune system, which helps to prevent infection without the need for immunologic memory from previous exposure to the pathogen (52). Innate immunity includes the production of antimicrobial peptides that are important in host defenses against respiratory pathogens, such as viruses, bacteria, and fungi (101–105). These peptides include β -defensins and cathelicidins (e.g., hCAP-18 or LL-37), and are produced on epithelial surfaces and within circulating leukocytes (52).

The only human cathelicidin antimicrobial peptide (hCAP-18) provides a particularly attractive explanation for the apparent inverse association between serum 25(OH)D levels and risk of respiratory infection. hCAP-18 enhances microbial killing in phagocytic vacuoles, acts as a chemoattractant for neutrophils and monocytes, and has a defined vitamin D-dependent mechanism (105). In a landmark study, Liu and colleagues (102) reported that in *M. tuberculosis*-infected macrophages, there was a 30-fold increased cathelicidin expression in 1,25(OH)₂D-treated cells compared with controls, which corresponded to a 50% reduction in *M. tuberculosis* viability at 3 days. The individuals with serum 25(OH)D levels less than approximately 10 ng/ml had the least efficient cathelicidin expression, and those with serum 25(OH)D levels above approximately 30 ng/ml had the highest induction of cathelicidin mRNA. Furthermore, black individuals, known to have increased susceptibility to TB infection, had low serum 25(OH)D levels and

inefficient cathelicidin mRNA induction, but supplementation of 25(OH)D to normal range enhanced cathelicidin induction fivefold, to similar levels as the white patients.

Liu and colleagues extended these findings to provide further evidence that cathelicidin is the mechanism that enhances vitamin D-mediated antimicrobial activity against *M. tuberculosis* (103). In these experiments, a short, interfering RNA was used specifically to block cathelicidin mRNA and protein expression, which eliminated vitamin D-mediated enhanced intracellular killing of *M. tuberculosis* that was observed in controls.

Thus, vitamin D-mediated increases in cathelicidin provide an excellent explanation for the extensively described link between sun exposure, vitamin D, and TB (47, 48) – and presumably other respiratory infections. In brief, pathogenic antigens interact with Toll-like receptors on macrophages to upregulate the expression of genes that code for the vitamin D receptor and for the 1α -hydroxylase enzyme that converts 25(OH)D into the biologically active 1,25-(OH)₂D (102). In turn, 1,25-(OH)₂D interacts with the promoter on the cathelicidin gene and enhances hCAP-18 production in myeloid cells (101), bronchial epithelial cells (104), and keratinocytes (106). Furthermore, Weber and colleagues found that 25(OH)D could induce intracellular hCAP-18 through the autocrine induction of the 1α -hydroxylase enzyme (106). These diverse pathways would be of particular importance for neonates (107), a group with a significant correlation ($r = 0.23$; $P = 0.002$) between cord blood levels of 25(OH)D and hCAP-18 (Camargo et al., unpublished data).

8.2. Vitamin D and Adaptive Immunity

Another proposed mechanism for vitamin D-mediated effects on respiratory infections and OADs includes modulation of antigen-presenting cells such as macrophages (108, 109). Vitamin D also affects the generation of regulatory T cells (Treg) (110, 111) that express potentially inhibitory cytokines (IL-10 and TGF β) and the ability to potently inhibit antigen-specific T-cell activation (112). A murine model of pulmonary eosinophilic inflammation demonstrated that vitamin D supplementation of adult mice led to changes in cytokines, IgE levels, and airway eosinophilia during allergen sensitization (113).

Although many laboratory studies suggest that vitamin D induces a shift in the balance between Th1- and Th2-type cytokines toward Th2 dominance (52, 114), Pichler and colleagues (115) found that in CD4⁺ and CD8⁺ human cord blood cells, vitamin D not only inhibits IL-12-generated interferon-gamma production (Th1 type) but also suppresses IL-4 and IL-4-induced expression of IL-13 (Th2 type). In theory, this balanced Th1–Th2 regulation may modulate asthma and other allergic diseases. The role of regulatory T cells and IL-10 in the balance of the T-helper type 1 (Th1)-type and Th2-type cytokines and asthma phenotype was recently reviewed (116). Thus, the differences between the studies on the Th1–Th2 dominance may lie in the timing of exposure of the cells to vitamin D (i.e., prenatal versus postnatal); the response of naïve T cells to vitamin D exposure may differ from that of mature cells when exposed to vitamin D (117). Another possibility is that the association depends on the vitamin D status of the individual. In other words, lower vitamin D intakes (e.g., to correct a deficiency state)

may have different consequences than relatively high-dose supplementation, where an excess of vitamin D may indeed have adverse effects. These hypotheses merit further investigation.

8.3. Vitamin D, Atopy, and Allergies

Although this chapter focuses on the respiratory system, the allergic foundations of asthma support a brief discussion of how vitamin D may affect atopy and allergy risk. *Atopy* is defined as IgE sensitization to a variety of allergens, such as different foods (e.g., peanut) and insect venoms. Atopy is different from an actual *allergic reaction*, which requires actual clinical manifestations (e.g., atopic dermatitis, allergic rhinitis, and allergic asthma). Finally, *anaphylaxis* is the most severe form of an acute allergic reaction and requires involvement of multiple organ systems (118). The biological mechanisms of how vitamin D might influence atopy and allergies are presented briefly above (section 8.2) and discussed in more detail elsewhere (52, 108, 114). Although the clinical and epidemiological data are limited, there are a few studies of potential relevance to the present discussion that we will briefly summarize here.

An allergic condition of particular interest in the study of asthma is *atopic dermatitis*, an early step in the classic “allergic march” (119). The nosology of this and related conditions (e.g., eczema) is controversial but we consider eczema, the more inclusive skin condition, of which atopic eczema (atopic dermatitis) is one example. Based on vitamin D-mediated effects on innate immunity, and the anticipated reductions in bacterial colonization of the skin, we hypothesize that vitamin D might have beneficial effects on both the incidence and the severity of atopic dermatitis. Recent evidence that vitamin D supplementation increases skin production of cathelicidin in patients with atopic dermatitis (120) supports this hypothesis. Indeed, ecologic studies suggest higher prevalence of eczema at higher latitudes (121, 122). Moreover, a recent case-control study demonstrated that atopic dermatitis was more common among obese individuals with low 25(OH)D levels (<10 ng/ml), as compared to obese individuals with 25(OH)D levels of ≥ 30 ng/ml (123). Another epidemiologic study, however, suggested a potential *increase* in eczema risk (76), and two birth cohorts with crude outcome data found no association at all (56, 57). In terms of disease modification, investigators in Boston performed the first randomized, double-blind, placebo-controlled trial in a small sample of children with winter-related atopic dermatitis and found evidence of skin improvement with vitamin D supplementation (124). Larger clinical trials are underway.

There are sparse data on the relation of vitamin D with allergic rhinitis. The Finnish study by Hyponen and colleagues suggested that supplementation of infants with high daily doses ($\geq 2,000$ IU/day) increased risk (75). A cross-sectional study by Wjst and Hyponen also reported a positive association between serum 25(OH)D levels and prevalence of allergic rhinitis (125), consistent with their hypothesis that higher levels of vitamin D cause allergic disease. Although the authors acknowledge that these results could be due to confounding, we believe that a more likely explanation is reverse causality (e.g., individuals with allergic rhinitis are less likely to go outside and, consequently, have lower levels of 25(OH)D). Prospective cohort studies are needed to better

define the relation of vitamin D with allergic rhinitis, which is a strong risk factor for childhood asthma (42).

More evidence for a link between vitamin D and allergic conditions comes from recent ecologic studies of EpiPen prescribing (126–128), a surrogate marker for anaphylaxis (129). Camargo and colleagues (126) observed a strong north–south gradient for the prescription of EpiPens in the United States, with the highest rates found in New England (Fig. 4). Population-adjusted rates were positively associated with several factors (e.g., number of health-care providers); however, a multivariate analysis controlling for all of these factors suggested that they did not mediate the strong north–south gradient. The investigators hypothesized that vitamin D may play a role in the etiology of anaphylaxis (126). They recently confirmed this north–south gradient using a similar study design but restricted to urban areas in order to better control for this important determinant of health-care utilization (127). In a third ecologic analysis, Mullin and Camargo recently demonstrated a south–north gradient for prescription of self-injectable epinephrine in Australia (128), consistent with the distribution of UVB in the Southern hemisphere.

Although the atopic dermatitis findings can be explained by vitamin D-mediated benefits on innate immunity (130), the anaphylaxis findings (126–128) present a conundrum: How is it that vitamin D lowers the risk of childhood wheezing (respiratory

EpiPen Prescriptions per 1,000 State Residents

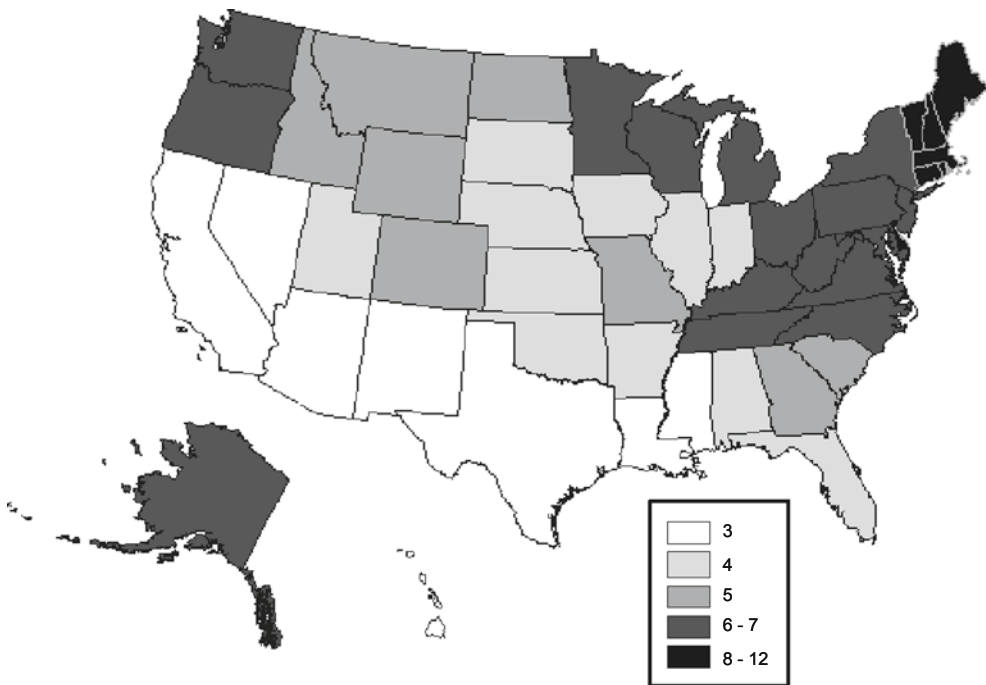


Fig. 4. Regional differences in EpiPen prescriptions (per 1,000 persons), a surrogate measure of anaphylaxis prevalence (adapted from Ref. (126)).

infections) and possibly anaphylaxis but does not lower the risk of actual asthma? The answer undoubtedly involves a number of host and environmental factors, as well the heterogeneity of the respiratory/allergy outcomes.

9. FUTURE RESEARCH ON VITAMIN D, RESPIRATORY INFECTIONS, AND OADs

Although the preliminary data in this chapter are promising, many scientific gaps remain. Figure 5 provides a summary of what is known in early 2009. Low levels of vitamin D appear to increase the risk of infections, with an unproven (but probably small) role on incident asthma. By contrast, it seems likely that increased risk of respiratory infections among asthmatic individuals would worsen asthma severity and control. There are sparse data on the effect of vitamin D on the two major components of asthma (inflammation and BHR) but vitamin D status in early life has no apparent association with incident childhood asthma. Finally, the relation of low vitamin D status to atopy and allergic conditions is uncertain, with theoretical reasons suggesting why allergy risk should be higher with supplementation but ecologic studies suggesting the opposite (i.e., areas of highest UVB exposure have the lowest rates of EpiPen prescribing).

Low vitamin D levels

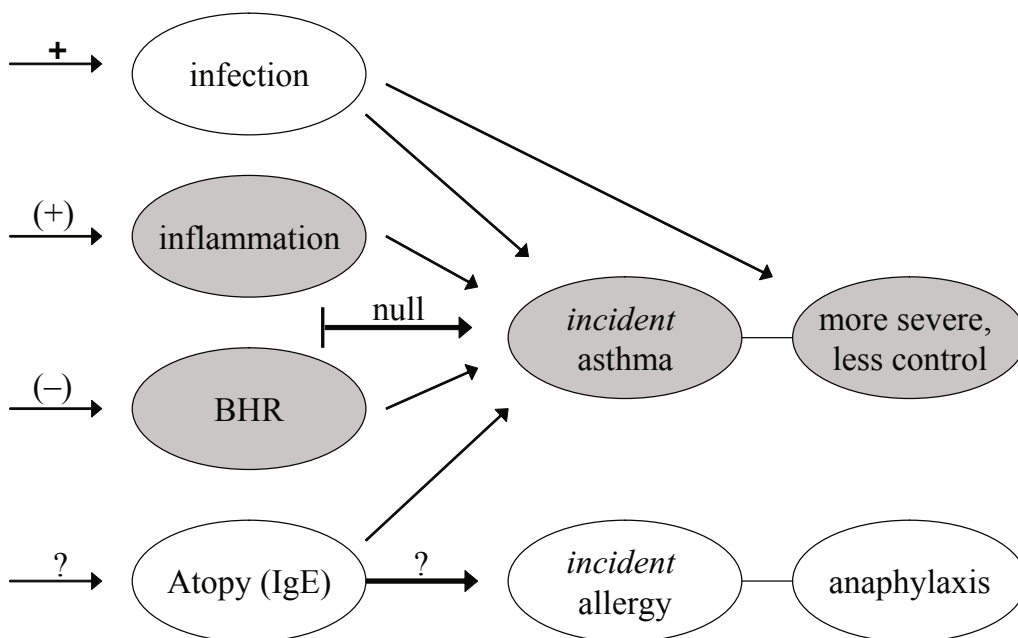


Fig. 5. Summary of current understanding of the associations between low vitamin D status and major respiratory/allergic conditions. BHR denotes bronchial hyper-responsiveness. Associations are summarized as follows: + denotes positive; (+), maybe positive; null, no apparent association; (-), maybe negative; and ?, mixed results or unknown.

Although there are many possible “next steps,” an initial one would be to examine the association between vitamin D status at birth (e.g., using cord blood 25(OH)D levels) with respiratory infections in early childhood. It is important for other groups to confirm the New Zealand birth cohort findings (7) in diverse populations of children. Another important step would be to further describe the association between vitamin D and respiratory infection as it relates to the development of asthma, chronic asthma control, and risk for asthma exacerbations. These issues also are critically important for COPD, a field that remains almost entirely unexplored.

In all of these epidemiologic studies, the issue of reverse causation should be carefully addressed, particularly in cross-sectional studies. Because prevalent OAD, decreased OAD control, and increased OAD exacerbations probably contribute to decreased time outdoors (and, therefore, decreased sunlight exposure), the presence of vitamin D insufficiency may actually follow, rather than cause, the outcomes measured. The use of longitudinal cohort designs will help to address this very important methodological issue. Future epidemiologic studies also will need to carefully account for the likelihood of confounding from the many health-related factors associated with frequent sun exposure, such as outdoor physical activity (131).

Additionally, measurement of immune markers, including hCAP-18, regulatory T cells, IL-10, and other markers of the Th1–Th2 balance, may help to elucidate the mechanisms of the observed associations and provide additional face validity. Animal models in which these relevant pathways can be manipulated or knocked out will provide additional support and rationale for the associations between vitamin D and OAD. However, animal models should be selected with care. For example, it appears that only primates have the vitamin D response element on the promoter of the cathelicidin gene. Accordingly, mouse, rat, and dog cell lines do not appear to require vitamin D for cathelicidin expression and thus have been unsuccessful in evaluating this vitamin D-mediated pathway (101). Thus, many animal models may be of limited utility in testing the hypothesized association between vitamin D and respiratory infections.

Ultimately, large randomized controlled trials of vitamin D supplementation will be needed to confirm the ability to reverse the suboptimal outcomes associated with vitamin D insufficiency. In these studies, higher doses of supplementation (at least 1,000–2,000 IU/day and probably more in high-risk populations during winter months) may be required to maximize potential benefit. Current IOM recommendations for vitamin D supplementation (e.g., 200–600 IU/day, depending on age) are unlikely to achieve the serum 25(OH)D levels (i.e., at least 30–40 ng/ml) that appear necessary for good general health, including prevention of infections. Many experts already argue that current recommended doses of vitamin D supplementation are woefully inadequate to meet the need for higher serum 25(OH)D levels (71, 132). For example, raising serum 25(OH)D levels from 20 to 32 ng/ml requires an additional 1,700 IU of vitamin D per day (133).

Consideration to adequate dosage in future trials and measurement of pre- and post-supplementation serum 25(OH)D levels will help to optimize trial conditions. Additionally, as the relative importance of vitamin D in different age and racial/ethnic groups is unknown, diverse study participants or multiple studies of different demographic subgroups will help us to understand this potential interaction.

Progress in these endeavors will undoubtedly suggest new research avenues. For example, there is a growing research on the importance of vitamin D supplementation in *cystic fibrosis* patients (134). Confirmation of a vitamin D benefit for respiratory infections and OADs suggests that vitamin D may be of particular importance for diseases such as *bronchiectasis*, which represents a combination of recurrent infections and obstructive airway disease. One could present a similar argument for *chronic sinusitis* and other conditions that we have not directly addressed in this review. The demonstration of a vitamin D-related benefit would add to the relatively few effective treatment options available for these conditions today.

10. CONCLUSIONS

Over the past decade, interest has grown in the effects of vitamin D on respiratory infections and obstructive airway diseases (OADs), such as asthma and chronic obstructive pulmonary disease (COPD). Observational studies suggest that low vitamin D levels increase the risk of acute respiratory infections from diverse respiratory pathogens in both lower and upper airways. Post-hoc analyses of randomized trials on vitamin D and bone health support this possibility. This increased risk of infection may contribute to incident wheezing illness in children and adults and cause asthma exacerbations. Although unproven, the increased risk of susceptible hosts to specific respiratory pathogens may contribute to some cases of incident asthma. Likewise, the effect of vitamin D on COPD, while intriguing, is largely unknown. Emerging evidence provides biological plausibility for some of these respiratory findings. For example, vitamin D-mediated innate immunity, particularly through enhanced expression of the human cathelicidin antimicrobial peptide (hCAP-18), is important in host defenses against respiratory pathogens. Vitamin D also modulates regulatory T-cell function and interleukin-10 production, which may increase the therapeutic response to corticosteroids in corticosteroid-resistant asthma. Finally, low vitamin D levels may have a role in the pathogenesis of allergies, including anaphylaxis. Further studies are needed to better understand vitamin D's effects on respiratory infections and OADs. Randomized controlled trials of higher dose vitamin D supplementation (e.g., at least 1,000 IU/day), particularly in the winter season at higher latitudes, will help clarify if vitamin D can prevent or reduce the severity of respiratory infections. In turn, these insights may prove helpful in preventing OAD exacerbations and the achievement of disease control.

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REFERENCES

1. Lawrence G (1784) Tools of the trade: the Finsen Light. *Lancet* 2002:359
2. Cannell JJ, Vieth R, Umhau JC et al (2006) Epidemic influenza and vitamin D. *Epidemiol Infect* 134:1129–1140
3. Zasloff M (2006) Fighting infections with vitamin D. *Nat Med* 12:388–390
4. Muhe L, Lulseged S, Mason KE, Simoes EA (1997) Case–control study of the role of nutritional rickets in the risk of developing pneumonia in Ethiopian children. *Lancet* 349:1801–1804
5. Najada AS, Habashneh MS, Khader M (2004) The frequency of nutritional rickets among hospitalized infants and its relation to respiratory diseases. *J Trop Pediatr* 50:364–368
6. Laaksi I, Ruohola JP, Tuohimaa P et al (2007) An association of serum vitamin D concentrations <40 nmol/l with acute respiratory tract infection in young Finnish men. *Am J Clin Nutr* 86: 714–717
7. Camargo CA Jr, Ingham T, Wickens K et al (2008) Cord blood 25-hydroxyvitamin D levels and risk of childhood wheeze in New Zealand [abstract]. *Am J Respir Crit Care Med* 177(suppl):A993
8. Wjst M, Dold S (1999) Genes, factor X, and allergens: what causes allergic diseases? *Allergy* 54: 757–759
9. Poon AH, Laprise C, Lemire M et al (2004) Association of vitamin D receptor genetic variants with susceptibility to asthma and atopy. *Am J Respir Crit Care Med* 170:967–973
10. Raby BA, Lazarus R, Silverman EK et al (2004) Association of vitamin D receptor gene polymorphisms with childhood and adult asthma. *Am J Respir Crit Care Med* 170:1057–1065
11. Vollmert C, Illig T, Altmüller J et al (2004) Single nucleotide polymorphism screening and association analysis – exclusion of integrin beta 7 and vitamin D receptor (chromosome 12q) as candidate genes for asthma. *Clin Exp Allergy* 34:1841–1850
12. Laufs J, Andrason H, Sigvaldason A et al (2004) Association of vitamin D binding protein variants with chronic mucus hypersecretion in Iceland. *Am J Pharmacogenomics* 4:63–68
13. Wjst M (2005) Variants in the vitamin D receptor gene and asthma. *BMC Genet* 6:2
14. Camargo CA Jr, Rifas-Shiman SL, Litonjua AA et al (2006) Prospective study of maternal intake of vitamin D during pregnancy and risk of wheezing illnesses in children at age 2 years [abstract]. *J Allergy Clin Immunol* 117:721–722
15. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ (1995) Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 332: 133–138
16. Graham NM (1990) The epidemiology of acute respiratory infections in children and adults: a global perspective. *Epidemiol Rev* 12:149–178
17. Taubenberger JK, Morens DM (1918) Influenza: the mother of all pandemics. *Emerg Infect Dis* 2006(12):15–22
18. Mansbach JM, Camargo CA Jr (2009) Update on bronchiolitis. *Emerg Med Crit Care Rev* 29(4): 741–755
19. Pelletier AJ, Mansbach JM, Camargo CA Jr (2006) Direct medical costs of bronchiolitis hospitalizations in the United States. *Pediatrics* 118:2418–2423
20. Fleisher GR (2000) Infectious disease emergencies. In: Fleisher GR, Ludwig S (eds) *Textbook of pediatric emergency medicine*, 4th edn. Philadelphia, Lippincott William & Wilkins, pp. 754–755
21. Hanson IC, Shearer WT (1999) Bronchiolitis. In: McMillan JA, DeAngelis CD, Feigin RD, Warshaw JB (eds) *Oski's pediatrics: principles and practice*, 3rd edn. Lippincott Williams & Wilkins, Philadelphia, pp. 1214–1216
22. Welliver R (2004) Bronchiolitis and infectious asthma. In: Feigin R, Cherry J, Demmler G, Kaplan S (eds) *Textbook of pediatric infectious diseases*, 5th edn. Philadelphia, Saunders, pp. 273–285
23. American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis (2006) Diagnosis and management of bronchiolitis. *Pediatrics* 118:1774–1793.
24. Glezen WP, Loda FA, Clyde WA Jr et al (1971) Epidemiologic patterns of acute lower respiratory disease of children in a pediatric group practice. *J Pediatr* 78:397–406

25. Hall CB, Walsh EE, Schnabel KC et al (1990) Occurrence of groups A and B of respiratory syncytial virus over 15 years: associated epidemiologic and clinical characteristics in hospitalized and ambulatory children. *J Infect Dis* 162:1283–1290
26. Glezen WP, Taber LH, Frank AL, Kasel JA (1986) Risk of primary infection and reinfection with respiratory syncytial virus. *Am J Dis Child* 140:543–546
27. Ukkonen P, Hovi T, von Bonsdorff CH, Saikku P, Penttinen K (1984) Age-specific prevalence of complement-fixing antibodies to sixteen viral antigens: a computer analysis of 58,500 patients covering a period of eight years. *J Med Virol* 13:131–148
28. Levine DA, Platt SL, Dayan PS et al (2004) Risk of serious bacterial infection in young febrile infants with respiratory syncytial virus infections. *Pediatrics* 113:1728–1734
29. Mansbach JM, Emond JA, Camargo CA Jr (2005) Bronchiolitis in US emergency departments 1992–2000: epidemiology and practice variation. *Pediatr Emerg Care* 21:242–247
30. Mansbach JM, Clark S, Christopher NC et al (2008) Prospective multicenter study of bronchiolitis: predicting safe discharges from the emergency department. *Pediatrics* 121:680–688
31. Papadopoulos NG, Bates PJ, Bardin PG et al (2000) Rhinoviruses infect the lower airways. *J Infect Dis* 181:1875–1884
32. Korppi M, Kotaniemi-Syrjanen A, Waris M, Vainionpaa R, Reijonen TM (2004) Rhinovirus-associated wheezing in infancy: comparison with respiratory syncytial virus bronchiolitis. *Pediatr Infect Dis J* 23:995–999
33. Henderson FW, Clyde WA Jr, Collier AM et al (1979) The etiologic and epidemiologic spectrum of bronchiolitis in pediatric practice. *J Pediatr* 95:183–190
34. Moorman JE, Rudd RA, Johnson CA et al (2007) National surveillance for asthma – United States, 1980–2004. *MMWR Surveill Summ* 56:1–54
35. Ginde AA, Espinola JA, Camargo CA Jr (2008) Improved overall trends but persistent racial disparities in emergency department visits for acute asthma, 1993–2005. *J Allergy Clin Immunol* 122:313–318
36. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma (1987). This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, November 1986. *Am Rev Respir Dis* 136:225–244.
37. Toren K, Brisman J, Jarvholm B (1993) Asthma and asthma-like symptoms in adults assessed by questionnaires. A literature review. *Chest* 104:600–608
38. Nicholson KG, Kent J, Ireland DC (1993) Respiratory viruses and exacerbations of asthma in adults. *BMJ* 307:982–986
39. Johnston SL, Pattemore PK, Sanderson G et al (1995) Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *BMJ* 310:1225–1229
40. Yunginger JW, Reed CE, O’Connell EJ, Melton LJ 3rd, O’Fallon WM, Silverstein MD (1992) A community-based study of the epidemiology of asthma. Incidence rates, 1964–1983. *Am Rev Respir Dis* 146:888–894
41. Wainwright C, Isles AF, Francis PW (1997) Asthma in children. *Med J Aust* 167:218–223
42. Guilbert TW, Morgan WJ, Zeiger RS et al (2004) Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. *J Allergy Clin Immunol* 114:1282–1287
43. Arbes SJ Jr, Gergen PJ, Vaughn B, Zeldin DC (2007) Asthma cases attributable to atopy: results from the Third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol* 120:1139–1145
44. Borish L, Culp JA (2008) Asthma: a syndrome composed of heterogeneous diseases. *Ann Allergy Asthma Immunol* 101:1–8; quiz 8–11, 50
45. Global strategy for the diagnosis, management, and prevention of COPD. Available from: www.goldcopd.org . Last accessed 1 Dec 2008 (Accessed 1 Dec 2008, at www.goldcopd.org .)
46. Abouzgheib W, Pratter MR, Bartter T (2007) Cough and asthma. *Curr Opin Pulm Med* 13:44–48
47. Nnoaham KE, Clarke A (2008) Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. *Int J Epidemiol* 37:113–119
48. Martineau AR, Honecker FU, Wilkinson RJ, Griffiths CJ (2007) Vitamin D in the treatment of pulmonary tuberculosis. *J Steroid Biochem Mol Biol* 103:793–798

49. Wilkinson RJ, Llewelyn M, Toossi Z et al (2000) Influence of vitamin D deficiency and vitamin D receptor polymorphisms on tuberculosis among Gujarati Asians in west London: a case-control study. *Lancet* 355:618–621
50. Wilbur AK, Kubatko LS, Hurtado AM, Hill KR, Stone AC (2007) Vitamin D receptor gene polymorphisms and susceptibility to tuberculosis in native Paraguayans. *Tuberculosis (Edinb)* 87:329–337
51. Martineau AR, Wilkinson RJ, Wilkinson KA et al (2007) A single dose of vitamin D enhances immunity to mycobacteria. *Am J Respir Crit Care Med* 176:208–213
52. Adams JS, Hewison M (2008) Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity. *Nat Clin Pract Endocrinol Metab* 4:80–90
53. Wayse V, Yousafzai A, Mogale K, Filteau S (2004) Association of subclinical vitamin D deficiency with severe acute lower respiratory infection in Indian children under 5 years. *Eur J Clin Nutr* 58:563–567
54. Karatekin G, Kaya A, Salihoğlu O, Balci H, Nuhoglu A (2009) Association of subclinical vitamin D deficiency in newborns with acute lower respiratory infection and their mothers. *Eur J Clin Nutr* 63:473–477
55. Roth DE, Jones AB, Prosser C, Robinson JL, Vohra S (2009) Vitamin D status is not associated with the risk of hospitalization for acute bronchiolitis in early childhood. *Eur J Clin Nutr* 63:297–299
56. Camargo CA Jr, Rifas-Shiman SL, Litonjua AA et al (2007) Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 years of age. *Am J Clin Nutr* 85:788–795
57. Devereux G, Litonjua AA, Turner SW et al (2007) Maternal vitamin D intake during pregnancy and early childhood wheezing. *Am J Clin Nutr* 85:853–859
58. Ginde AA, Mansbach JM, Camargo CA Jr (2009) Association between serum 25-hydroxyvitamin D level and upper respiratory tract infections in the Third National Health and Nutrition Examination Survey. *Arch Intern Med* 169:384–390
59. Linday LA, Shindledecker RD, Tapia-Mendoza J, Dolitsky JN (2004) Effect of daily cod liver oil and a multivitamin-mineral supplement with selenium on upper respiratory tract pediatric visits by young, inner-city, Latino children: randomized pediatric sites. *Ann Otol Rhinol Laryngol* 113:891–901
60. Rehman PK (1994) Sub-clinical rickets and recurrent infection. *J Trop Pediatr* 40:58
61. Aloia JF, Li-Ng M (2007) Re: epidemic influenza and vitamin D. *Epidemiol Infect* 135:1095–1096; author reply 7–8
62. Avenell A, Cook JA, MacLennan GS, Macpherson GC (2007) Vitamin D supplementation to prevent infections: a sub-study of a randomised placebo-controlled trial in older people (RECORD trial, ISRCTN 51647438). *Age Ageing* 36:574–577
63. Mikhail M, Aloia JF, Pollack S et al (2008) A randomized controlled trial of vitamin D3 supplementation for the prevention of viral upper respiratory tract infections [abstract]. In: 30th American Society for Bone and Mineral Research Annual Meeting, Montreal, Canada
64. Gern JE, Lemanske RF Jr, Busse WW (1999) Early life origins of asthma. *J Clin Invest* 104:837–843
65. Warner JA, Jones CA, Jones AC, Warner JO (2000) Prenatal origins of allergic disease. *J Allergy Clin Immunol* 105:S493–S498
66. Gillman MW (2005) Developmental origins of health and disease. *N Engl J Med* 353:1848–1850
67. Weiss ST (1997) Diet as a risk factor for asthma. *Ciba Found Symp* 206:244–257; discussion 53–57
68. Romieu I, Trenga C (2001) Diet and obstructive lung diseases. *Epidemiol Rev* 23:268–287
69. Spector SL, Surette ME (2003) Diet and asthma: has the role of dietary lipids been overlooked in the management of asthma? *Ann Allergy Asthma Immunol* 90:371–377; quiz 7–8, 421
70. Devereux G, Seaton A (2005) Diet as a risk factor for atopy and asthma. *J Allergy Clin Immunol* 115:1109–1117; quiz 18
71. Holick MF, Vitamin D (2007) Deficiency. *N Engl J Med* 357:266–281
72. Black PN, Scragg R (2005) Relationship between serum 25-hydroxyvitamin D and pulmonary function in the third national health and nutrition examination survey. *Chest* 128:3792–3798
73. Burns JS, Dockery DW, Neas LM et al (2007) Low dietary nutrient intakes and respiratory health in adolescents. *Chest* 132:238–245
74. Wjst M (2006) The vitamin D slant on allergy. *Pediatr Allergy Immunol* 17:477–483

75. Hypponen E, Sovio U, Wjst M et al (2004) Infant vitamin d supplementation and allergic conditions in adulthood: northern Finland birth cohort 1966. *Ann NY Acad Sci* 1037:84–95
76. Gale CR, Robinson SM, Harvey NC et al (2008) Maternal vitamin D status during pregnancy and child outcomes. *Eur J Clin Nutr* 62:68–77
77. Jackson DJ, Gangnon RE, Evans MD et al (2008) Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 178:667–672
78. Mansbach JM, Camargo CA Jr (2008) Bronchiolitis: lingering questions about its definition and the potential role of vitamin D. *Pediatrics* 122:177–179
79. Sutherland ER, Martin RJ (2007) Asthma and atypical bacterial infection. *Chest* 132:1962–1966
80. National Asthma Education and Prevention Program (2007) Expert Panel report 3: guidelines for the diagnosis and management of asthma: full report. In. Washington DC: US Government Printing Office; 2007:417 pp. NIH Publication No. 07–4051.
81. Bateman ED, Boushey HA, Bousquet J et al (2004) Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med* 170:836–844
82. Ito K, Chung KF, Adcock IM (2006) Update on glucocorticoid action and resistance. *J Allergy Clin Immunol* 117:522–543
83. Xystrakis E, Kusumakar S, Boswell S et al (2006) Reversing the defective induction of IL-10-secreting regulatory T cells in glucocorticoid-resistant asthma patients. *J Clin Invest* 116:146–155
84. Heikkinen T, Jarvinen A (2003) The common cold. *Lancet* 361:51–59
85. van Elden LJ, Sachs AP, van Loon AM et al (2008) Enhanced severity of virus associated lower respiratory tract disease in asthma patients may not be associated with delayed viral clearance and increased viral load in the upper respiratory tract. *J Clin Virol* 41:116–121
86. Litonjua AA, Hollis BW, Schuemann B et al (2008) Low serum vitamin D levels are associated with greater risks for severe exacerbations in childhood asthmatics [abstract]. *Am J Respir Crit Care Med* 177(suppl):A993
87. Leech JA, Dulberg C, Kellie S, Pattee L, Gay J (1990) Relationship of lung function to severity of osteoporosis in women. *Am Rev Respir Dis* 141:68–71
88. Biskobing DM (2002) COPD and osteoporosis. *Chest* 121:609–620
89. Katsura H, Kida K (2002) A comparison of bone mineral density in elderly female patients with COPD and bronchial asthma. *Chest* 122:1949–1955
90. Jorgensen NR, Schwarz P, Holme I, Henriksen BM, Petersen LJ, Backer V (2007) The prevalence of osteoporosis in patients with chronic obstructive pulmonary disease: a cross sectional study. *Respir Med* 101:177–185
91. Kjensli A, Mowinckel P, Ryg MS, Falch JA (2007) Low bone mineral density is related to severity of chronic obstructive pulmonary disease. *Bone* 40:493–497
92. Ohara T, Hirai T, Muro S et al (2008) Relationship between pulmonary emphysema and osteoporosis assessed by CT in patients with COPD. *Chest* 134:1244–1249
93. Wright RJ (2005) Make no bones about it: increasing epidemiologic evidence links vitamin D to pulmonary function and COPD. *Chest* 128:3781–3783
94. Dobak J, Grzybowski J, Liu FT, Landon B, Dobke M (1994) 1,25-Dihydroxyvitamin D3 increases collagen production in dermal fibroblasts. *J Dermatol Sci* 8:18–24
95. Koli K, Keski-Oja J (2000) 1alpha,25-dihydroxyvitamin D3 and its analogues down-regulate cell invasion-associated proteases in cultured malignant cells. *Cell Growth Differ* 11:221–229
96. Spurzem JR, Rennard SI (2005) Pathogenesis of COPD. *Semin Respir Crit Care Med* 26:142–153
97. Schellenberg D, Pare PD, Weir TD, Spinelli JJ, Walker BA, Sandford AJ (1998) Vitamin D binding protein variants and the risk of COPD. *Am J Respir Crit Care Med* 157:957–961
98. Ishii T, Keicho N, Teramoto S et al (2001) Association of Gc-globulin variation with susceptibility to COPD and diffuse panbronchiolitis. *Eur Respir J* 18:753–757
99. Ito I, Nagai S, Hoshino Y et al (2004) Risk and severity of COPD is associated with the group-specific component of serum globulin 1F allele. *Chest* 125:63–70
100. Sandford AJ, Chagani T, Weir TD, Connett JE, Anthonisen NR, Pare PD (2001) Susceptibility genes for rapid decline of lung function in the lung health study. *Am J Respir Crit Care Med* 163:469–473

101. Gombart AF, Borregaard N, Koeffler HP (2005) Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D₃. *FASEB J* 19:1067–1077
102. Liu PT, Stenger S, Li H et al (2006) Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 311:1770–1773
103. Liu PT, Stenger S, Tang DH, Modlin RL (2007) Cutting edge: vitamin D-mediated human antimicrobial activity against *Mycobacterium tuberculosis* is dependent on the induction of cathelicidin. *J Immunol* 179:2060–2063
104. Yim S, Dhawan P, Raganath C, Christakos S, Diamond G (2007) Induction of cathelicidin in normal and CF bronchial epithelial cells by 1,25-dihydroxyvitamin D(3). *J Cyst Fibros* 6:403–410
105. Hiemstra PS (2007) The role of epithelial beta-defensins and cathelicidins in host defense of the lung. *Exp Lung Res* 33:537–542
106. Weber G, Heilborn JD, Chamorro Jimenez CI, Hammarsjo A, Torma H, Stahle M (2005) Vitamin D induces the antimicrobial protein hCAP18 in human skin. *J Invest Dermatol* 124:1080–1082
107. Levy O (2007) Innate immunity of the newborn: basic mechanisms and clinical correlates. *Nat Rev Immunol* 7:379–390
108. Griffin MD, Xing N, Kumar R (2003) Vitamin D and its analogs as regulators of immune activation and antigen presentation. *Annu Rev Nutr* 23:117–145
109. Lin R, White JH (2004) The pleiotropic actions of vitamin D. *Bioessays* 26:21–28
110. Gregori S, Giarratana N, Smiroldo S, Uskokovic M, Adorini LA (2002) 1alpha,25-dihydroxyvitamin D(3) analog enhances regulatory T-cells and arrests autoimmune diabetes in NOD mice. *Diabetes* 51:1367–1374
111. Meehan MA, Kerman RH, Lemire JM (1992) 1,25-Dihydroxyvitamin D₃ enhances the generation of nonspecific suppressor cells while inhibiting the induction of cytotoxic cells in a human MLR. *Cell Immunol* 140:400–409
112. Schwartz RH (2005) Natural regulatory T cells and self-tolerance. *Nat Immunol* 6:327–330
113. Matheu V, Back O, Mondoc E, Issazadeh-Navikas S (2003) Dual effects of vitamin D-induced alteration of TH1/TH2 cytokine expression: enhancing IgE production and decreasing airway eosinophilia in murine allergic airway disease. *J Allergy Clin Immunol* 112:585–592
114. Cantorna MT, Zhu Y, Froicu M, Wittke A (2004) Vitamin D status, 1,25-dihydroxyvitamin D₃, and the immune system. *Am J Clin Nutr* 80:1717S–1720S
115. Pichler J, Gerstmayr M, Szepefalusi Z, Urbanek R, Peterlik M, Willheim M (2002) 1 alpha,25(OH)₂D₃ inhibits not only Th1 but also Th2 differentiation in human cord blood T cells. *Pediatr Res* 52:12–18
116. Xystrakis E, Urry Z, Hawrylowicz CM (2007) Regulatory T cell therapy as individualized medicine for asthma and allergy. *Curr Opin Allergy Clin Immunol* 7:535–541
117. Annesi-Maesano I (2002) Perinatal events, vitamin D, and the development of allergy. *Pediatr Res* 52:3–5
118. Sampson HA, Munoz-Furlong A, Campbell RL et al (2006) Second symposium on the definition and management of anaphylaxis: summary report – second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *Ann Emerg Med* 47:373–380
119. Hahn EL, Bacharier LB (2005) The atopic march: the pattern of allergic disease development in childhood. *Immunol Allergy Clin North Am* 25:231–246
120. Hata TR, Kotol P, Jackson M et al (2008) Administration of oral vitamin D induces cathelicidin production in atopic individuals. *J Allergy Clin Immunol* 122:829–831
121. Weiland SK, Husing A, Strachan DP, Rzehak P, Pearce N (2004) Climate and the prevalence of symptoms of asthma, allergic rhinitis, and atopic eczema in children. *Occup Environ Med* 61:609–615
122. Staples JA, Ponsonby AL, Lim LL, McMichael AJ (2003) Ecologic analysis of some immune-related disorders, including type 1 diabetes, in Australia: latitude, regional ultraviolet radiation, and disease prevalence. *Environ Health Perspect* 111:518–523
123. Oren E, Banerji A, Camargo CA Jr (2008) Vitamin D and atopic disorders in an obese population screened for vitamin D deficiency. *J Allergy Clin Immunol* 121:533–534

124. Sidbury R, Sullivan AF, Thadhani RI, Camargo CA Jr (2008) Randomized controlled trial of vitamin D supplementation for winter-related atopic dermatitis in Boston: a pilot study. *Br J Dermatol* 159:245–247
125. Wjst M, Hypponen E (2007) Vitamin D serum levels and allergic rhinitis. *Allergy* 62:1085–1086
126. Camargo CA Jr, Clark S, Kaplan MS, Lieberman P, Wood RA (2007) Regional differences in EpiPen prescriptions in the United States: the potential role of vitamin D. *J Allergy Clin Immunol* 120:131–136
127. Camargo CA Jr, Clark S, Pearson JF, Kaplan MS, Lieberman P, Wood RA (2009) Latitude, UVB exposure, and EpiPen prescriptions in 38 urban areas [abstract]. *J Allergy Clin Immunol* 123(suppl):S109
128. Mullins RJ, Camargo CA Jr (2008) Childhood anaphylaxis in Australia: geographic and socioeconomic influences [abstract]. *Intern Med J* 38(suppl 6):A161.
129. Simons FE, Peterson S, Black CD (2002) Epinephrine dispensing patterns for an out-of-hospital population: a novel approach to studying the epidemiology of anaphylaxis. *J Allergy Clin Immunol* 110:647–651
130. Schaubert J, Gallo RL (2008) Antimicrobial peptides and the skin immune defense system. *J Allergy Clin Immunol* 122:261–266
131. Scragg R, Camargo CA Jr (2008) Frequency of leisure-time physical activity and serum 25-hydroxyvitamin D levels in the US population: results from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol* 168:577–586; discussion 87–91
132. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B (2006) Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr* 84:18–28
133. Barger-Lux MJ, Heaney RP, Dowell S, Chen TC, Holick MF (1998) Vitamin D and its major metabolites: serum levels after graded oral dosing in healthy men. *Osteoporos Int* 8:222–230
134. Green D, Carson K, Leonard A et al (2008) Current treatment recommendations for correcting vitamin D deficiency in pediatric patients with cystic fibrosis are inadequate. *J Pediatr* 153:554–559
135. Stein RT, Holberg CJ, Morgan WJ et al (1997) Peak flow variability, methacholine responsiveness and atopy as markers for detecting different wheezing phenotypes in childhood. *Thorax* 52:946–952
136. Legg JP, Warner JA, Johnston SL, Warner JO (2005) Frequency of detection of picornaviruses and seven other respiratory pathogens in infants. *Pediatr Infect Dis J* 24:611–616
137. Kusel MM, de Klerk NH, Kebadze T et al (2007) Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. *J Allergy Clin Immunol* 119:1105–1110
138. Mansbach JM, McAdam AJ, Clark S et al (2008) Prospective multicenter study of the viral etiology of bronchiolitis in the emergency department. *Acad Emerg Med* 15:111–118