Vitamin D and Asthma

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Vitamin D deficiency and asthma are common conditions that share risk factors such as African American ethnicity, inner-city residence, and obesity. This review provides a critical examination of current experimental and epidemiologic evidence of a causal association between vitamin D status and asthma or asthma morbidity, including potential protective mechanisms such as antiviral effects and enhanced steroid responsiveness. Because most published epidemiologic studies of vitamin D and asthma or asthma morbidity are observational, a recommendation for or against vitamin D supplementation as preventive or secondary treatment for asthma is not advisable and must await results of ongoing clinical trials. Should these trials confirm a beneficial effect of vitamin D, others will be needed to assess the role of vitamin D supplementation to prevent or treat asthma in different groups such as infants, children of school age, and ethnic minorities.

Keywords: vitamin D; asthma; asthma morbidity

Asthma is a major public health problem in the United States (1) and worldwide (2). For unclear reasons, the prevalence of asthma increased from a period likely preceding the 1960s to at least the 1990s. Although there is recent evidence of no or modest further increase in asthma rates in countries with high disease prevalence (1–3), the causes of the "asthma epidemic" are incompletely understood.

Vitamin D is an essential nutrient with significant immunomodulatory effects (4, 5). The observation that vitamin D deficiency and asthma share risk factors such as urban residence (6, 7), obesity (8, 9), and African American ethnicity (10, 11) has generated interest in exploring a link between these two conditions. In this review, we discuss recent findings from experimental and human studies of vitamin D and asthma, critically assess current evidence for potential protective mechanisms of vitamin D against asthma and asthma morbidity, and provide general recommendations for future studies in this field.

VITAMIN D METABOLISM AND PHYSIOLOGY

Sun exposure is the main source of vitamin D in humans. Solar UVB radiation photolyzes 7-dehydro-cholesterol in the skin to previtamin D_3, which is then converted to vitamin D_3 (cholecalciferol) (12). Cholecalciferol from the skin and diet is hydroxylated in the liver to 25-hydroxyvitamin D_3 (25[OH]D) and stored. Parathyroid hormone controls calcium-phosphate homeostasis by regulating hydroxylation of 25(OH)D to its biologically active form ($1,25[OH]_2D_3$) in the kidney.

Vitamin D signaling predominantly occurs through binding of $1,25(OH)_2D_3$ to the vitamin D receptor (VDR), formation of a heterodimer with retinoid X receptor, and subsequent regulation of gene expression by binding of this heterodimer to genomic sequences known as vitamin D response elements (VDREs). Hydroxylation of 25(OH)D in extrarenal sites (13) and differential expression of genes relevant to immune response and cancer in response to vitamin level suggest pleiotropic effects of vitamin D in humans (14). Adequacy of vitamin D level is assessed by measuring serum or plasma level of 25(OH)D, which is the major circulating form and is correlated with secondary hyperparathyroidism and skeletal diseases such as rickets (12).

EPIDEMIOLOGY OF VITAMIN D DEFICIENCY

Vitamin D skin metabolism is influenced by melanin content of the skin, age, factors affecting sun exposure (latitude, season, time outdoors, and clothing), body fat, and sunscreen use (15). Dietary intake (mostly from oily fish, fortified grains, and dairy products) and supplements are a secondary source of vitamin D. On the basis of skeletal effects, vitamin D inadequacy (deficiency) was recently defined as a serum 25(OH)D < 20 ng/ml by a panel from the Institute of Medicine of the National Academy of Sciences (16). Vitamin D insufficiency has been previously defined as a serum 25(OH)D of 20 to 29 ng/ml (17), but the Institute of Medicine panel found inconclusive evidence for this threshold. This newly proposed definition of vitamin D sufficiency (i.e., $\geqslant$20 ng/ml) has generated great controversy (18, 19) largely because of its significant impact on the epidemiologic and clinical assessment of vitamin D insufficiency. Thus, there is no consensus on optimal vitamin D levels for nonmusculoskeletal health.

Regardless of the threshold used, vitamin D deficiency or insufficiency has likely increased in the United States over the last decades due to changes in behavior (e.g., less time outdoors) (20) and diet. In a recent study of 9,757 United States subjects 1 to 21 years of age, approximately 9% and approximately 61% of participants had vitamin D deficiency (defined by the authors as serum 25[OH]D < 15 ng/ml) and insufficiency (defined by the authors as serum 25[OH]D $= 15$–29 ng/ml), respectively (21). Predictors of vitamin D deficiency included older age, female gender, African- or Mexican-American ethnicity, obesity, the use of electronic devices, and reduced dairy intake (21). Reduced vitamin D levels have been found in populations living near the Equator (e.g., in Saudi Arabia, Israel, India, and Costa Rica) and in the southeastern United States (15, 22), suggesting that lifestyle can have major effects on vitamin D status regardless of latitude. Mounting evidence exists for a role of vitamin D in nonskeletal diseases (e.g., infectious illnesses, cancer, and

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T helper (Th)1-related autoimmune diseases, such as type I diabetes) (15, 17).

VITAMIN D AND THE IMMUNE SYSTEM

Vitamin D has significant yet incompletely understood effects on innate and adaptive immunity (4, 15). The immune-modulatory role of vitamin D is supported by the presence of VDRs and the hydroxylation of 25(OH)D in relevant cell types, including macrophages and dendritic cells (23–26).

In experimental studies, vitamin D has been shown to inhibit proliferation of CD4+ T cells (27) and to reduce the production of Th1 cytokines (24, 27–30) and IL-17 (31, 32). Studies of vitamin D and Th2 cytokines have yielded inconsistent results (perhaps due to differences in target cell types and the timing and dose of vitamin administration) (15, 33). For example, vitamin D has been shown to enhance (34) and inhibit (35) IL-4 synthesis by cultured naive T cells. In mouse models of allergic airway inflammation (AAI), vitamin D (36) or UVB radiation (37) has been shown to inhibit AAI and to reduce IL-4 levels in bronchoalveolar lavage fluid. Consistent with potentially complex effects of vitamin D on asthma, VDR knock-out mice have elevated serum levels of IL-13 and IgE but do not develop AAI, supporting a key role for VDR lung expression in airway inflammation (38).

One way that vitamin D may influence asthma pathogenesis is through modulation of T regulatory cells (Tregs) (39). Vitamin D (alone or with glucocorticoids) has been reported to promote differentiation of naive T cells into IL-10–secreting Tregs (40, 41). Vitamin D has also been shown to increase serum levels of the immune-modulatory cytokines TGF-β and IL-10 in humans (40, 42) and to enhance the benefits of allergen immunotherapy in murine AAI by IL-10– and TGF-β–dependent mechanisms (43). In human T cells, vitamin D down-regulates dendritic cell Ox40L, which is required for Th2 priming, and up-regulates TGF-β. This leads to increased TGF-β–positive Tregs and lower Th2 cytokine levels (44).

VITAMIN D AND ASTHMA

Results of experimental studies (*see above*) and genetic association studies of the VDR (45, 46) have motivated observational studies of vitamin D and asthma in humans. These studies (summarized in Table 1) have differed in study design, sample size, and assessment of vitamin D status, which may explain their seemingly conflicting findings.

A cross-sectional study of Finnish adults found that vitamin D supplementation (assessed in infancy) was associated with increased risk of asthma (47). However, this study lacked vitamin D measures and had inadequate follow-up data on study participants (47). Case-control studies of serum vitamin D and asthma in British adults (48) and African American children and young adults (49) yielded conflicting findings (no association between vitamin D and asthma in the British study vs. a strong positive association between vitamin D insufficiency or deficiency and asthma in African Americans). Both studies were limited by lack of data on vitamin D status in early life and potential selection bias.

Birth cohort studies allow us to prospectively assess the relation between an exposure and an outcome of interest. Although a birth cohort study of British children reported a strong association between serum vitamin D levels in late pregnancy and asthma at 9 years of age, it had inadequate follow-up of participating children (50). Birth cohort studies in Boston, Scotland, Japan, and Finland (each including $\geqslant$750 mother–child pairs) have shown that maternal dietary intake of vitamin D (assessed by food frequency questionnaires) during pregnancy is inversely associated with wheeze and recurrent wheeze (51–53) or asthma (54) in early childhood. All studies were limited by relatively short duration (from 1.3 to 5 yr, making a diagnosis of asthma challenging), significant loss to follow-up, and lack of serum vitamin D measures during pregnancy or in infancy. An additional birth cohort study of children in New Zealand found that vitamin D level in cord blood was inversely associated with wheeze but not with incident asthma by 5 years of age (55). Although a birth cohort study of Australian children found an association between vitamin D level at 6 years of age and asthma in boys at 14 years of age, it lacked vitamin D measures in early life and had substantial loss to follow–up, and the analyses were unadjusted for potential confounders (56).

In summary, there is insufficient evidence of a causal association between vitamin D status and asthma *per se*. The inverse association between maternal intake of vitamin D during pregnancy or cord blood level of vitamin D and childhood wheeze, reported in the best available observational (birth cohort) studies (51–53, 55), merits further assessment in ongoing clinical trials.

VITAMIN D, ASTHMA MORBIDITY, AND ASTHMA EXACERBATIONS

In addition to a potential role in the primary prevention of asthma, there is considerable interest in assessing whether vitamin D protects against or reduces asthma morbidity. Table 2 summarizes the main results of studies of vitamin D and asthma morbidity or asthma control.

Vitamin D insufficiency or deficiency (defined as a 25[OH]D level $<$ 30 ng/ml) was present in 175 (28%) of 616 children with asthma in Costa Rica (22), in whom serum vitamin D level was inversely associated with total IgE, eosinophil count, hospitalizations for asthma, use of anti-inflammatory medications, and airway hyperresponsiveness (22). A temporal and causal relation between vitamin D and asthma morbidity cannot be established from that cross-sectional study. To follow up on those results, Brehm and colleagues conducted a longitudinal study of serum vitamin D and severe asthma exacerbations (defined as at least one hospitalization or visit to the Emergency Department) in 1,024 North American children with mild to moderate persistent asthma (57). In that study, vitamin D insufficiency or deficiency (a 25[OH]D level $<$ 30 ng/ml) at baseline was associated with increased risk of severe asthma exacerbations during 4 years of follow-up. The magnitude of the observed association was greater in children who did not receive inhaled corticosteroids (ICS) and who had vitamin D insufficiency than in children who received ICS but had vitamin D insufficiency or in those who did not receive ICS but had sufficient levels of vitamin D. This finding and others (*see below*) suggest that vitamin D enhances steroid responsiveness.

Further evidence that vitamin D may protect against asthma exacerbations is provided by a recent 6-month clinical trial of vitamin D_3 supplementation (500 IU/d) as adjuvant therapy to ICS to reduce asthma morbidity in 48 Polish children (58). In that study, there was no difference in serum vitamin D level between treatment groups, likely due to an insufficient dose of vitamin D. However, children in the intervention group were less likely to have a vitamin D level that decreased during the trial, and there were significantly fewer children with an asthma exacerbation ($n = 4$ or 16.7%) in the vitamin D group than in the placebo group ($n = 11$ or 45.8%). Findings from this small clinical trial must be interpreted with caution due to nonstandardized assessment of asthma exacerbations

TABLE 1. OBSERVATIONAL STUDIES OF VITAMIN D AND ASTHMA

Reference	Study Design	Main Findings	Study Limitations
Hypponen *et al.* (47)	Cross-sectional study of 7,648 Finnish adults at 31 yr of age	Vitamin D supplementation in the first year of life was associated with increased risk of asthma (OR, 1.33; 95% CI, 0.97–1.82)	29.3% of subjects with data on vitamin D supplementation in infancy were lost to follow-up No study visits between 4 and 31 yr of age Lack of serum vitamin D measures in infancy
Devereux *et al.* (48)	Case-control study of 160 adults in the United Kingdom	No significant association between serum vitamin D level and asthma	Small sample size, cross-sectional design Low vitamin D level common in all participants Inability to exclude vitamin D effects in early life
Freishtat *et al.* (49)	Case-control study of 106 African American subjects 6 to 20 yr of age	Vitamin D insufficiency or deficiency (<30 ng/ml) was associated with asthma (OR, 42; 95% CI, 4.4–399)	Small sample size/cross-sectional design Inability to exclude selection bias (imbalanced numbers and characteristics for cases and controls)
Gale *et al.* (50)	Birth cohort study of 596 British mother-child pairs; 178 children assessed at 9 yr of age	Maternal serum vitamin D > 75 nmol/L during pregnancy was associated with 5.4-fold increased risk of childhood asthma (95% CI for OR, 1.1–26.7) at 9 yr of age	70% of subjects lost to follow-up No study visits between 9 mo and 9 yr of age
Devereux *et al.* (51)	Birth cohort study of 2,000 mother-child pairs; 1,212 children assessed at 5 yr of age	Compared with the lowest quintile, the highest quintile of maternal intake of vitamin D during pregnancy was associated with reduced risks of ever, current, and persistent (OR, 0.33; 95% CI, 0.11–0.98) wheeze	39.4% of children not followed up to 5 yr of age Lack of serum vitamin D levels during pregnancy
Camargo *et al.* (52)	Birth cohort study of 2,128 children in Massachusetts, of whom 1,194 were assessed at 3 yr of age	Each 100-IU increment in vitamin D intake during pregnancy was associated with reduced risk of recurrent wheeze (OR, 0.81; 95% CI, 0.74–0.89)	43.8% of children not followed up to 3 yr of age Short duration of follow-up, uncertain diagnosis of asthma Lack of serum vitamin D levels during pregnancy
Miyake *et al.* (53)	Birth cohort study of 1,002 Japanese mother–child pairs; 763 children assessed at 16–24 mo of age	Maternal intake of vitamin D above the first quartile (⩾172 IU/d) during pregnancy was associated with reduced risk of wheeze (OR, 0.64; 95% CI, 0.43–0.97)	23.9% of children lost to follow-up No serum vitamin D measures during pregnancy Short duration of follow-up, uncertain diagnosis of asthma
Erkkola *et al.* (54)	Birth cohort study of 3,565 children with HLA-DQB1–conferred susceptibility to type I diabetes; 1,669 children assessed at 5 yr of age	Compared with the bottom three quartiles, the highest quartile of total intake of vitamin D during pregnancy was associated with reduced risk of asthma (HR, 0.76; 95% CI, 0.59–0.99)	53.2% of subjects not included in the analysis because of loss to follow-up or incomplete data Lack of serum vitamin D measures during pregnancy Highly selected cohort
Camargo *et al.* (55)	Birth cohort study of 1,105 children in New Zealand, of whom 823 (83.4%) were followed up to 5 yr of age	Cord blood levels of vitamin D were inversely associated with wheeze at all time points but not with incident asthma by 5 yr of age	25.5% of children lost to follow-up at 5 yr of age Relatively short duration of follow-up, uncertain diagnosis of asthma
Hollams *et al.* (56)	Birth cohort study of 2,834 mother–child pairs; 989 assessed at 6 yr of age and 1,380 children assessed at 14 yr of age (693 children seen at 6 and 14 yr of age)	No significant cross-sectional association between serum vitamin D and current asthma at 6 or 14 yr of age; vitamin D level at 6 yr of age was associated with asthma in boys at 14 yr of age	Analysis of vitamin D level at 6 yr of age and asthma at 14 yr of age was unadjusted Substantial loss of follow-up

Definition of abbreviations: CI = confidence interval; HR = hazard ratio; OR = odds ratio.

and lack of significant improvement in lung function or symptom score.

Two small cross-sectional studies have found that vitamin D level is positively correlated with asthma control (59) and inversely correlated with exercise-induced bronchoconstriction (60) in Italian children with asthma. However, reverse causation and confounding cannot be excluded as alternative explanations for these findings.

In brief, promising and consistent evidence from observational studies and a small clinical trial suggest that vitamin D protects against asthma exacerbations.

ONGOING CLINICAL TRIALS

Given the suggestive evidence of protective effects of vitamin D from observational studies, several ongoing clinical trials are testing whether vitamin D supplementation prevents asthma or reduces asthma morbidity. Table 3 summarizes the main characteristics of the ongoing trials that are attempting to enroll at least 250 subjects and that are registered in http://clinicaltrials.gov. Two of these trials are testing whether vitamin D supplementation during pregnancy prevents asthma by 3 years of age (NCT00920621 and NCT00856947) and will be completed in 2014; continued follow-up of participants will be needed to adequately assess asthma. Three additional trials (to be completed in 2013 and 2014) are testing whether vitamin D supplementation prevents moderate asthma exacerbations in adults when added to low-dose ICS in adults with asthma and persistent symptoms (NCT01248065), reduces the incidence of upper respiratory infections (URIs) and asthma exacerbations in children (1–5 yr of age) with and without asthma (NCT01419262), or delays the time to a first URI or a severe disease exacerbation in adolescents and adults with asthma (NCT00978315). In addition to treatment efficacy, ongoing trials should yield valuable additional information about dosing, monitoring toxicity, and the safety of vitamin D supplementation in different age groups.

TABLE 2. STUDIES OF VITAMIN D AND ASTHMA MORBIDITY, ASTHMA CONTROL, OR STEROID RESPONSIVENESS

Reference	Study Design	Main Findings	Study Limitations
Brehm *et al.* (22)	Cross-sectional study of 616 children with asthma in Costa Rica	Serum vitamin D level was inversely associated with indicators of asthma morbidity or severity, including hospitalizations, use of antiinflammatory medications (OR, 0.18; 95% CI, 0.05–0.67), and airway hyperresponsiveness	Inability to fully exclude "reverse causation" (e.g., reduced vitamin D levels due to reduced sun exposure in children with severe asthma)
Chinellato *et al.* (59)	Cross-sectional study of 75 Italian children with asthma	Vitamin D level was positively correlated with the Childhood Asthma Control Test ($r = 0.28$; $P = 0.01$) and was higher in children with controlled asthma than in those without ($P = 0.02$ for trend)	Inability to exclude reverse causation Lack of adjustment for confounders Small sample size
Chinellato *et al.* (60)	Cross-sectional study of 45 Italian children with mild intermittent asthma	Serum vitamin D level was lower in children with exercise-induced bronchoconstriction than in those without	Small sample size Lack of adjustment for confounders Inability to exclude reverse causation
Searing *et al.* (78)	Cross-sectional study of 100 children with asthma in Denver, Colorado	Serum vitamin D was positively correlated with lung function and enhanced glucocorticoid action in peripheral blood mononuclear cells; vitamin D was inversely correlated with total IgE, degree of atopy, and use of inhaled or oral steroids	Lack of adjustment for potential confounders Inability to exclude reverse causation
Sutherland *et al.* (79)	Cross-sectional study of 54 adults with persistent asthma in Denver, Colorado	Serum vitamin D was positively correlated with FEV_1 and glucocorticoid response; vitamin D insufficiency or deficiency (< 30 ng/ml) was associated with airway hyperresponsiveness	Small sample size Inability to exclude reverse causation Lack of adjustment for potential confounders other than age, sex, and body mass index
Brehm *et al.* (57)	Longitudinal study of 1,024 North American children with mild to moderate persistent asthma	Vitamin D insufficiency or deficiency (25[OH]D $\leqslant$ 30 ng/ml) at baseline was associated with increased risk of severe asthma exacerbations ($\geqslant$1 hospitalization or Emergency Department visit) over 4 yr of follow-up (OR, 1.5; 95% CI, 1.1–1.9)	Lack of repeated measures of serum vitamin D over time No information about vitamin D supplementation
Majak *et al.* (58)	6-mo trial of vitamin D_3 (500 IU/d) as adjuvant therapy to ICS to reduce asthma morbidity in 48 Polish children	Children who received vitamin D supplementation and ICS had a lower frequency of asthma exacerbations (4 or 16.7%) than those who received ICS and placebo (11 or 45.8%)	No difference in vitamin D level between treatment groups, likely due to the low dose used Asthma exacerbation not defined according to current standards No objective markers of viral infection

Definition of abbreviations: CI = confidence interval; ICS = inhaled corticosteroid; OR = odds ratio.

HOW COULD VITAMIN D PROTECT AGAINST ASTHMA MORBIDITY?

Antiviral Properties

Airway epithelial cells can hydroxylate 25(OH)D to its active form ($1,25(OH)_2D_3$) (61), leading to increased differentiation and recruitment of macrophages (28), enhanced production of cathelicidin and CD14, and potentiation of host defenses against *Mycobacterium tuberculosis* and other bacteria, fungi, and viruses (62–65).

Vitamin D deficiency and influenza epidemics follow similar seasonal patterns (66–68), and vitamin D level has been inversely associated with the risk of respiratory illnesses in observational studies of children and adults (69–73). A U.S. cross-sectional study of approximately 19,000 subjects 12 years of age or older showed that reduced serum vitamin D was associated with an increased risk of self-reported upper respiratory infections, particularly in subjects with chronic obstructive pulmonary disease or asthma (69). Two clinical trials of vitamin D to prevent (74) or reduce the severity of (71, 74) respiratory infections in adults showed no (74) or modest (71) effects. Limitations of those trials include short follow-up or low vitamin D dose and nonmicrobiologic assessment of respiratory illnesses (74, 71). A recent trial showed that vitamin D_3 supplementation (1,200 IU/d) during winter reduced the incidence of influenza A (diagnosed by antigen testing in nasopharyngeal swabs) but not influenza B in 167 Japanese schoolchildren (relative risk [RR], 0.58; 95% confidence interval [CI], 0.34–0.99) (75). A subgroup (exploratory) analysis showed that vitamin D supplementation reduced the risk of disease exacerbations in children with asthma (RR, 0.17; 95% CI, 0.04–0.73). The antiviral properties of vitamin D are further supported by a recent observational study of 284 Finnish infants hospitalized with a wheezing illness, in whom vitamin D level was inversely associated with coinfection with respiratory syncytial virus or rhinovirus (OR, 0.92; 95% CI, 0.84–0.99) (76).

Enhanced Steroid Responsiveness

Xystrakis and colleagues showed that adding vitamin D to cell cultures increases glucocorticoid-induced secretion of IL-10 by Tregs, with similar effects *ex vivo* in patients with steroid-resistant asthma (77). Consistent with a role of vitamin D on enhancing steroid responsiveness, cross-sectional studies of children (78) and adults (79) (Table 2) have shown that a low vitamin D level is associated with impaired lung function (78, 79) and increased steroid use (78) or decreased *in vitro* steroid response (albeit by a seemingly IL-10–independent mechanism) (79).

Down-regulation of Atopy

Experimental findings suggest complex and incompletely understood effects of vitamin D on innate and adaptive immune responses (*see above*). A large cross-sectional United States

TABLE 3. ONGOING CLINICAL TRIALS OF VITAMIN D SUPPLEMENTATION TO PREVENT ASTHMA OR REDUCE ASTHMA MORBIDITY

Title; ID no.*	Target Date for Completion	Type/ Design	Study population	Study Hypothesis/Primary Outcome(s)	Treatment Arms	Secondary Outcomes	Limitations
Maternal Vitamin D Supplementation to Prevent Childhood Asthma (VDAART); NCT00920621	June, 2014	Multicenter (US), randomized, double-blind, placebo-controlled	870 pregnant women (18–39 yr of age) and their offspring Participating women must report a history of asthma or allergies in themselves or the child's father	Adequate vitamin D supplementation in the pregnant mother is associated with reduced incidence of asthma in the child during the first 3 yr of life	Vitamin D_3 (4,000 IU/d) plus prenatal multivitamins vs. placebo plus prenatal multivitamins	Eczema, allergic sensitization, and LRIs Vitamin D status in mother and child Prematurity and other perinatal complications	High-risk cohort Short duration of follow-up Nonassessment of postnatal vitamin D supplementation
Vitamin D Supplementation During Pregnancy for Prevention of Asthma in Childhood (ABCvitaminD); NCT00856947	March, 2014	Single site (Denmark), randomized, double-blind, placebo-controlled	600 pregnant women older than 17 yr and their children	Vitamin D supplementation during pregnancy and 1 wk after delivery will prevent asthma symptoms (recurrent wheeze) in the first 3 yr of life	Vitamin D (2,400 IU/d) vs. placebo Treatment arms stratified by a second (fish oil) intervention	Eczema, allergy, and LRIs/URIs Vitamin D status in mother and child Growth	Length of follow-up not sufficient to assess an effect on asthma *per se* Statistical power may be inadequate Nonassessment of postnatal vitamin D supplementation
Study of the Effect of Vitamin D as an Add-on Therapy to Corticosteroids in Asthma (VIDA); NCT01248065	December, 2012	Multicenter (US), randomized, double-blind, placebo-controlled	400 subjects, 18 yr old with serum 25(OH)D $<$ 30 ng/ml who have asthma with persistent symptoms despite low-dose ICS	Adding vitamin D supplementation to a controller medication (ICS) helps prevent worsening of asthma symptoms and asthma attacks (treatment failure/ moderate exacerbation) over a 28-wk period	Vitamin D_3 (100,000 IU loading dose followed by 4,000 IU/d) plus low-dose ICS (cyclesonide, 160 μg bid) vs. placebo plus low-dose ICS	Lung function changes from baseline	Non assessment of viral infections
DO IT Trial: Vitamin D Outcomes and Interventions In Toddlers; NCT01419262	May, 2013	Multicenter (Canada), randomized, double-blind, controlled	400 children 1 to 5 yr of age who do and do not have asthma	Preschoolers receiving "high-dose" vitamin D supplementation during the wintertime will be less likely to have (laboratory-confirmed) URIs	Vitamin D_3 (2,000 IU/d) vs. vitamin D_3 (400 IU/d)	URIs by parental report Asthma exacerbations Vitamin D status	No-assessment of atopy Potential misclassification of asthma
Trial of Vitamin D Supplementation in Asthma (ViDiAs); NCT00978315	August, 2013	Multicenter (UK), randomized, double-blind, placebo-controlled	250 subjects $>$15 to $<$81 yr of age who have physician-diagnosed asthma	Vitamin D supplementation will influence time to URIs and time to severe asthma exacerbation in adult and adolescent patients over 1 yr of follow-up	Vitamin D_3 (as 2-monthly oral doses of Vigantol oil) vs. 2-monthly oral doses of Miglyol oil (placebo)	Asthma Control Test score Time to healthcare use for URI or severe asthma exacerbation	Potential misclassification of asthma and URIs

Definition of abbreviations: ICS = inhaled corticosteroids; URI = upper respiratory infections; LRI = lower respiratory infections.
* Clinicaltrials.gov identifier.

study reported that serum vitamin D level was positively associated with an increased risk of physician-diagnosed allergic rhinitis (but not allergic sensitization) in non-Hispanic whites and African Americans younger than 20 years of age (80). A cross-sectional study of Finnish adults reported that vitamin D supplementation during infancy was associated with increased risks of allergic sensitization and allergic rhinitis at 31 years of age (47). That study had inadequate follow-up of participants. In contrast, a birth cohort study of Finnish children at risk for type I diabetes mellitus found an inverse association between maternal intake of vitamin D during pregnancy and allergic rhinitis (diagnosed by questionnaire: HR, 0.85; 95% CI, 0.75–0.97) (54) and sensitization to food allergens (81) at 5 years of age.

Similar to the conflicting findings reported for allergic sensitization or allergic rhinitis, cross-sectional studies of children and adults have shown a U-shaped relation between serum vitamin D and total IgE at 45 years of age (82), an inverse association between serum vitamin D and total IgE at school age (22), or no association at school age (57).

There is insufficient and weak evidence for an association between vitamin D status and atopy or atopic diseases other than asthma. Interpretation of the available studies of vitamin D and atopy is limited by the inability to exclude confounding or selection bias (due to differential loss of follow-up) as alternative explanations for the observed results and by a lack of adequate assessment of vitamin D status or allergic sensitization.

Other Potential Mechanisms

The relation between vitamin D status and obesity is complex and bidirectional. In obese individuals, serum vitamin D level is inversely correlated with total body fat, which is partly explained by increased storage of vitamin D in adipose tissue. On the other hand, vitamin D may influence lipofibroblast differentiation and adipogenesis *in utero* (83, 84), and factors correlated with reduced vitamin D levels in mothers (obesity) and their neonates (birth during winter) have been associated with increased birth weight and subsequent obesity in childhood (85, 86). A recent study of Colombian schoolchildren found that reduced vitamin D level at baseline was associated with an increased risk of developing greater adiposity over 2 years of follow-up (87). Given that being overweight or obesity has been associated with asthma and increased asthma severity in children and adults (8), it is reasonable but highly speculative to postulate that vitamin D supplementation reduces asthma morbidity through beneficial effects on weight control.

Vitamin D has been positively correlated with lung function measures, as shown in a cross-sectional study of 14,000 U.S. adults (88). In a murine model, the offspring of two groups of female BALB/c mice (one group was fed a vitamin D–sufficient diet, and the other was fed a vitamin D–insufficient diet) and vitamin D–sufficient male mice were compared regarding lung volume and function, as assessed by plethysmography and the forced oscillation technique (89). In that model, mice born to mothers with vitamin D deficiency were shown to have decreased lung function (primarily by reduced lung volume) without changes in somatic growth. Although there was suggestive evidence of altered lung structure, the nature of the observed structural difference was not conclusive. These data are consistent with an earlier study that showed decreased lung compliance in pups born to vitamin D–deficient rats (90). Indeed, polymorphisms in the VDR gene (*VDR*) have been linked to increased airway resistance in mice (91). Vitamin D has also been shown to stimulate alveolar type II cell DNA synthesis (92) and surfactant production (93, 94) and may regulate alveolarization (95, 96). Thus, vitamin D deficiency may predispose to asthma or increase asthma morbidity by altering lung development in early life.

Finally, vitamin D may influence asthma by regulating the expression of disease-susceptibility genes. Recent studies have demonstrated *in vitro* binding of VDR in approximately 2,500 to 3,500 genes in lymphoblastoid and preosteoblastic cell lines; a fraction (~200–1,000) of these genes are differentially expressed after calcitriol stimulation, and some are in autoimmune pathways (14, 97). Expression of one of these genes (IL receptor B [*IL17RB*]) has been positively correlated with total IgE in children with asthma (98), and a second gene (tumor necrosis factor ligand superfamily, member 4 [*TNFS4*]) has been implicated in mediation of allergic responses in conjunction with thymic stromal lymphopoietin (*TSLP*) (99, 100).

SUMMARY AND FUTURE DIRECTIONS

Findings from experimental and human studies suggest beneficial effects of vitamin D on asthma and asthma morbidity (Figure 1). Given the known limitations of observational studies, however, a recommendation for or against vitamin D supplementation as preventive or adjuvant therapy for asthma cannot be made until ongoing and future clinical trials are completed. Should these clinical trials yield positive results, others studies will be needed to assess the optimal delivery, dosing, and safety of vitamin D supplementation to prevent and treat asthma.

If a beneficial effect of vitamin D on asthma is confirmed, protective mechanisms should be explored. Current evidence most consistently favors a beneficial effect of vitamin D on asthma morbidity by prevention of viral infections and enhanced steroid responsiveness, which can, alone or together, explain the observed inverse associations between vitamin D status and severe asthma exacerbations in childhood. Although down-regulation of Th2 immune responses may ultimately explain a primary preventive effect of vitamin D against asthma, there is weak and inconsistent evidence for a link between vitamin D and atopic responses. For example, antiviral properties may explain the observed inverse association between maternal vitamin D intake or status during pregnancy and wheeze before 5 years of age. Much work needs to be done to confirm or refute the beneficial effects of vitamin D on asthma through promoting normal lung development or prevention of obesity.

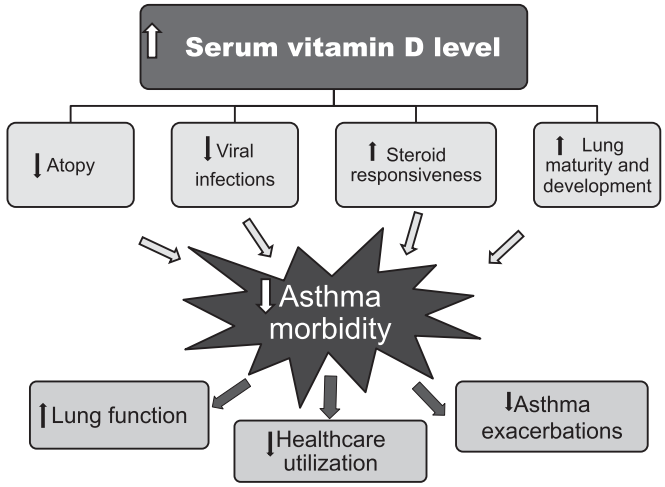

Figure 1. Potential protective effects of vitamin D against asthma morbidity.

A question often asked by clinicians is whether patients with asthma should be screened for vitamin D deficiency or insufficiency. There is no evidence to support such screening for the purpose of asthma management. However, it would be advisable to measure a serum vitamin D level in children and adults who belong to groups at high risk for vitamin D deficiency, namely African Americans, Mexican Americans, and individuals who are obese or have limited sun exposure (e.g., those who are institutionalized) (101). Vitamin D supplementation is only recommended for patients who have a serum vitamin D (25[OH] D) level less than 20 ng/ml because this could compromise their musculoskeletal health.

Ongoing clinical trials (Table 3) should yield valuable insights into the role of vitamin D supplementation in preventing the development of childhood asthma and reducing asthma morbidity. Questions to be addressed in future clinical trials include (*1*) whether vitamin D supplementation protects against viral illnesses or prevents childhood asthma when given in infancy (with or without supplementation during pregnancy), (*2*) whether vitamin D reduces severe asthma exacerbations or improves asthma control (as adjuvant to ICS) in children of school age, and (*3*) whether vitamin D is more effective in members of ethnic minority groups at risk for vitamin D deficiency.

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