Published in final edited form as:
Curr Allergy Asthma Rep. 2014 September ; 14(9): 461. doi:10.1007/s11882-014-0461-5.

Vitamin D and Asthma – Life After VIDA?

John M. Brehm, MD, MPH
Children's Hospital of Pittsburgh of UPMC, and the University of Pittsburgh 4401 Penn Avenue, Pittsburgh, PA 15224 Phone 412-692-9597 john.brehm@chp.edu

Abstract

The vitamin D hypothesis postulates that lower vitamin D levels are causally associated with increased asthma risk and asthma severity. Multiple epidemiological studies have shown an inverse relationship between circulating vitamin D levels (in the form of 25-hydroxy-vitamin D) and asthma severity and control, and lung function. However, in the recently published VIDA study, vitamin D supplementation failed to show an improvement in asthma control in adults. This article reviews the current epidemiological and trial evidence for vitamin D and asthma, and explores some of the possible alternative explanations for previous findings (including "reverse causation" and the importance of studying children and adults). We also address some of the unique challenges of conducting vitamin D trials, and potential ways to address them. Finally, I will argue for further clinical trials of vitamin D in asthma, especially in children, using knowledge gained from the VIDA trial.

Keywords

Vitamin D; Asthma; Epidemiology; Clinical Trials; Treatment; Prevention

Introduction

Asthma is one of the most common chronic diseases of childhood in the United States, and a major source of healthcare expenditures worldwide.[1] The prevalence of asthma has increased since the 1960's, and in the US this trend appears to be continuing.[2] Several hypotheses have been proposed to explain this rise in disease prevalence, including increased exposure to air pollution, tobacco smoke, and allergens.[3] Vitamin D deficiency shares risk factors with several other socio-demographic risk factors for asthma, such as African American or Puerto Rican ethnicity[4], obesity[5], and inner city residence[6]. In addition to this, children have been spending more time indoors during the day due to school, video games, and television.[7] This has led to the hypothesis that vitamin D deficiency may play a role in asthma pathogenesis.

Compliance with Ethics Guidelines

Conflict of Interest John M. Brehm declares that he receives support from the National Institutes of Health (K08 HL111201).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

While this review will primarily focus on the epidemiological studies and clinical trials of vitamin D and asthma, data from animal and *in vitro* models have provided compelling supporting evidence and potential mechanisms for how vitamin D may influence the development of asthma (reviewed recently in reference [8]). This review will examine the potential alternative explanations for the observed associations between vitamin D deficiency and asthma severity (such as "reverse causation"). Next, this review will argue for more clinical trials of vitamin D supplementation, despite the negative findings of the VIDA study.[9] Finally, I will address some of the unique challenges in designing and interpreting clinical trials of vitamin D.

Vitamin D metabolism and deficiency

Vitamin D is a generic term for the two major forms of vitamin D; ergocalciferol (vitamin D2) is derived from plants and only available as a supplement. Cholecalciferol (vitamin D3) is created by exposure of the skin to UV-B radiation, and is also available through supplements, supplemented foods, and naturally through a few foods (such as cod liver oil). Both of these forms of vitamin D are hydroxylated in the liver to form 25-hydroxyvitamin D2 or D3 (25-OH-vitamin D), which are the main circulating forms of vitamin D, and used by most investigators as the primary markers of vitamin D sufficiency.[10] Parathyroid hormone varies inversely with 25-OH-vitamin D levels, and is sometimes used as a confirmatory measure. 25-OH-vitamin D is hydroxylated primarily in the kidney, but also by immune cells throughout the body, to form 1,25-dihydroxy-vitamin D (also known as calcitriol). Although this is the active form, 1,25-dihydroxyvitamin D production is tightly regulated by the kidney, and does not rise predictably in response to supplementation.[10]

A recent study cast doubt on the use of 25-OH-vitamin D without accounting for levels of vitamin D binding protein (to which most serum vitamin D is bound).[11] Using data from black and white Americans, these investigators found that blacks had lower levels of vitamin D binding protein than whites, resulting in similar levels of bioavailable 25-OH-vitamin D despite blacks having lower overall 25-OH-vitamin D levels. These findings may be explained by genetic polymorphisms that help protect against acquired vitamin D insufficiency secondary to darker skin pigmentation.[12] This study's clinical outcome was bone mineral density, and it remains unclear whether the results are applicable to non-skeletal related health outcomes such as asthma.

Lifestyle and skin pigmentation play an important role in determining vitamin D sufficiency. Light-skinned individuals exposing ~25% of body surface area at noon in northern latitudes during a sunny day in summer generate 1,000 IU of vitamin D in ~7 minutes,[13] enough to surpass Institute of Medicine recommendations for daily intake.[14] Increased time spent indoors, however, may be resulting in lower endogenous production of vitamin D in human populations.[7] This is underscored by the fact that individuals with vitamin D insufficiency can be found throughout the world, including in tropical locations (e.g. Puerto Rico, Hawaii, Saudi Arabia, and India[15,16]).

Asthma risk and severity

Although the origins of the vitamin D hypothesis are rooted in shared risk factors asthma, the most compelling evidence suggests that vitamin D may play an important role in modifying asthma severity. Our group was the first to show that lower serum 25-OH-vitamin D levels were associated with markers of increased disease severity in a cross-sectional study of 616 Costa Rican children with asthma, including increased hospitalizations, anti-inflammatory medication use, and airway hyperresponsiveness.[17] We found similar results in a prospective study of North American children who were part of the Childhood Asthma Management Program trial of inhaled corticosteroids (ICS) in mild to moderate persistent asthmatics.[18] We also showed that baseline vitamin D sufficiency and ICS use were synergistically associated with fewer asthma exacerbations over the course of the study. Finally, we showed that in Puerto Rican children with asthma, vitamin D insufficiency was associated with increased risk of severe asthma exacerbations, independent of racial ancestry (estimated from genome-wide genetic data), time spent outdoors, and dietary intake of vitamin D.[15] These results have been replicated multiple times, with other groups having shown inverse associations between vitamin D levels and markers of asthma severity and asthma control.[19-25]

There is also growing evidence showing that adults and children with asthma have lower vitamin D levels than unaffected individuals.[20,26-30] This data is somewhat mixed though, with at least one study showing increased asthma risk[31], and several others showing no association with asthma risk.[32-38] It is difficult to interpret these types of cross-sectional studies because current vitamin D level may not reflect the vitamin D level at the time of asthma incidence.

A separate set of studies has examined *prospectively* whether vitamin D is associated with asthma risk. Studies of maternal vitamin D or cord-blood at the time of delivery have also been mixed, with some finding an inverse association with asthma risk in offspring[3940], others finding no association,[4142] and at least one showing increased risk of asthma in the offspring of mothers with the highest levels of vitamin D.[43] In a study of vitamin D levels in children, lower vitamin D levels at age 6 was associated with increased asthma risk at age 14.[44]

Alternatives to the vitamin D hypothesis

Although most epidemiological studies show an association between lower vitamin D levels and increase asthma severity, there are alternative explanations for these findings. First, reverse causation is a potential concern in correlation studies. The vitamin D hypothesis states that lower vitamin D levels are *causally* associated with increased asthma severity. It is possible that the association is causal, but in the opposite direction from the vitamin D hypothesis. For example, since vitamin D is synthesized in the skin by exposure to UV-B radiation, it is possible that children who are sicker due to their asthma may spend more time indoors, and therefore have lower vitamin D levels. To help test this, we looked at the association between vitamin D levels and asthma exacerbations using a multivariate model, adjusting for time spent outdoors, racial ancestry as estimated from genetic data, and atopy.[15] All of these are potential confounders of the relationship between vitamin D and

asthma. We found that even after adjusting for these exposures, there was still a strong relationship between vitamin D insufficiency and asthma exacerbations.

Another potential issue is that vitamin D may be a negative acute phase reactant. Several studies have reported an acute drop in serum 25-hydroxy-vitamin D levels with elective knee or hip arthroplasty, implying that the changes in vitamin D levels are simply a marker of inflammation.[45,46] While this is one possible explanation, there is no clear biological mechanism for how this would occur as an unrelated phenomenon. Another explanation, consistent with the vitamin D hypothesis, is that serum 25-hydroxy-vitamin D is converted to active 1,25-dihydroxy vitamin D as an appropriate response to acute inflammation, acutely depleting the serum supply of 25-hydroxy-vitamin D.[47]

Finally, as others have pointed out,[48] most studies have looked at the association between 25-OH-vitamin D levels and asthma or asthma outcomes. The research question in these types of study is very different than the most important research question: “does vitamin D supplementation reduce the risk of asthma, or asthma severity?” To answer this question, we need well-designed randomized clinical trials of vitamin D supplementation.

Supplementation trials

There are very few randomized trials of vitamin D for respiratory outcomes such as asthma. The most important is the recently published VIDA trial,[9] which randomized 408 adults with poorly controlled asthma to high-dose cholecalciferol or placebo. There were no significant differences in the primary outcomes of this study, including treatment failure or time to first exacerbation. In an exploratory analysis of subjects who responded to vitamin D therapy with a rise in serum 25-OH-vitamin D level to >30 ng/ml, actively treated subjects had an overall lower rate of treatment failure and exacerbations compared to placebo. These results are intriguing because they suggest that supplementation is only beneficial if the level is successfully raised. Another interpretation though, based on the concept of serum vitamin D levels being a surrogate of inflammation discussed earlier, is that the study subjects with less severe asthma were more likely to respond to supplementation. Since this subgroup analysis was not pre-specified in the clinicaltrials.gov registration, these results must be interpreted with caution. However, the findings are important because they suggest that a vitamin D dosing regimen based on a targeted serum 25-hydroxy-vitamin D level may be better than a fixed-dosing regimen. Another important point about this study is that it was conducted in adults, while the strongest evidence for vitamin D and asthma is in pediatric cohorts.

Several small studies have included children in trials of vitamin D and asthma. One notable study from Japan randomized 430 school children to 1200 IU of vitamin D3 or placebo and found that children randomized to active treatment had an 8% absolute risk reduction in influenza A infection compared to the placebo group (10.8% vs 18.6% respectively, P = .04).[49] About one quarter of these children had asthma, and those who were randomized to cholecalciferol had fewer asthma exacerbations during the study period than children without asthma who were assigned to placebo (P = .006).

Another study examined acute respiratory infections in 247 children in Mongolia who were part of the larger Blue Sky Study[50] of vitamin D supplementation in a high-risk group.[51] These children had profoundly low vitamin D levels at baseline (median 7 ng/ml), and the intervention group received milk fortified with only 300 IU of vitamin D3 vs. unfortified milk. Although the original Blue Sky Study showed that this intervention did not raise vitamin D levels to a level > 20 ng/ml,[50] the children in this treatment arm had half the risk of developing an acute respiratory infection during the course of the study. Upper respiratory tract infections are an important cause of asthma exacerbations, so these two studies provide further evidence for studying asthma exacerbations as a primary outcome of a clinical trial of vitamin D in asthma.

In a small study from Poland randomized children with mild asthma to budesonide + 500 IU of cholecalciferol or budesonide alone,[52] vitamin D appeared to result in a small but transient improvement in asthma symptoms over the 6 months of the study, with no difference in the two groups by the end of the study. No children had severe asthma exacerbations during the course of the study (as defined by an increase in anti-inflammatory medication use). Notably, the mean vitamin D levels in both groups were ~35 ng/ml, which is higher than the cutoff of 30 ng/ml that is commonly used to define insufficiency, and much higher than the cutoff for deficiency (20 ng/ml).[10] Based on our previous work, we would expect that children with vitamin D levels lower than 30 ng/ml would be more likely to benefit from supplementation.[15,18]

Challenges for clinical trials of vitamin D and asthma

The two most important research questions to be answered by clinical trials are: 1) does vitamin D supplementation reduce the risk of developing asthma, and 2) does vitamin D supplementation improve asthma severity (e.g. does it reduce asthma exacerbations or improve asthma control)? The epidemiological data for the first question suggests that if vitamin D plays a role in the future development of atopy, it may occur as early as prenatally. Two studies of vitamin D intake as measured by food frequency questionnaire found that mothers with the highest levels of vitamin D intake had children with lower risk of wheeze.[53,54] Based on these preliminary data, a trial known as the Vitamin D Antenatal Asthma Reduction Trial (VDAART) is currently recruiting pregnant women and randomizing them to either high dose (4,400 IU) or low dose (400 IU) cholecalciferol to determine whether the children born to women in the high dose group have a lower risk of asthma.[55] This type of study is challenging to conduct, since children may not develop asthma during the time frame of the study (3 years of child follow-up after birth). Also, some children who are diagnosed with asthma before age 3 will actually have transient wheeze of childhood, and will not have asthma or impaired lung function at a later age.[56,57] So while the results of this trial will be informative, it is also imperative that these children be followed up to confirm the initial findings on the study.

In contrast, studies of children or adults with established asthma should not require such prolonged follow-up to establish a treatment effect, but this depends on the population being studied. Most of our own research has focused on children with mild to moderate persistent asthma, so this is a study population with strong *a priori* evidence for a treatment effect.

Additionally, children with mild to moderate persistent asthma have a higher risk of the outcomes relevant to a clinical trial of asthma (e.g. exacerbations and poor control), which reduces the sample size needed to detect a clinically relevant effect.

In contrast, much of the available data in severe asthma provides important mechanistic insights, but does not show associations with clinically relevant outcomes. For example, T lymphocytes, cultured from steroid-resistant asthmatics, restore their ability to secrete the anti-inflammatory interleukin 10 in response to dexamethasone when co-treated with calcitriol.[58] Without data showing a clinically relevant response, there is insufficient epidemiological evidence to justify a large clinical trial in this population.

Vitamin D trials will need to be designed with several challenges in mind (**Table 1)**. For example, a challenge unique to vitamin D is that humans can synthesize large amounts of vitamin D through cutaneous exposure to sunlight. Therefore the exogenous vitamin D provided in the trial will almost certainly not be the only contributor to serum 25-OH-vitamin D levels. If cutaneous production of vitamin D is equally distributed between treatment arms, it should not bias the results, but instead would result in a reduction in statistical power to detect a difference between the treatment groups. Ideally a study of vitamin D will be recruited within a single season, or more practically, follow all study subjects for an entire year, to reduce the effects of the solar cycle on participant vitamin D levels.

A more concerning source of bias may occur, however, if one study arm systematically receives more vitamin D than another arm. Because study subjects are aware of the purpose of the study, sicker subjects may choose to take larger amounts of vitamin D, or spend more time outside, which would mask a true beneficial effect of vitamin D supplementation. To guard against this, study participants need to be blinded to their assignment, but also advised that extra supplement use could put them above the recommended daily allowance as set by the Institute of Medicine.[59] Despite these concerns, the data from randomized trials should be analyzed in as “intention to treat” for the primary analysis. This will help minimize bias that could occur in an analysis of serum 25-OH-vitamin D levels. However, based on the results from the VIDA trial, a reasonable strategy would be to use a flexible vitamin D dosing to target a serum 25-hydroxy-vitamin D level > 30 ng/ml.[9]

An issue that is unique to supplement studies performed in the United States is that the FDA regulates dietary supplements differently than drugs. According to a draft guidance released in 2010, and finalized in 2013, the FDA requires an Investigational New Drug application (IND) for a supplement that is intended to for a therapeutic function.[60] Since many supplement manufacturers do not supply the FDA with the necessary information to be marketed as a therapeutic drug, the investigator is then required to conduct time-consuming and expensive testing of dietary supplements, costs that are prohibitive for many academic researchers. [61] Perhaps in part due to the concern expressed by researchers and supplement manufacturers regarding this potentially chilling effect on supplement research, the FDA re-opened the comment period for a second round (which closed on April 7th, 2014).

While the expenses of a full IND application may be prohibitive, it does ensure tighter stringency of the drug product than might be found in the non-FDA regulated supplement market. Of particular relevance for trials using vitamin D supplements is a study in which investigators tested the potency of 12 common brands of over the counter cholecalciferol.[62] They found that only one manufacturer had potency that was within tolerable limits (90 to 120% of stated dose) for every pill within and across different drug lots. However, when averaging 5 pills from a single bottle, the variability was decreased, and two thirds of bottles were within tolerable limits. For the purposes of a vitamin D study, the average dose over a multiple week period is probably more important than the dose on any single day. Even if the study is IND exempt, researchers would be prudent to test their drug product for potency to ensure that the treatment doses are accurate.

Conclusions

In summary, multiple epidemiological studies have found an association between lower serum 25-OH-vitamin D levels and increased asthma severity, reduced lung function, and poor asthma control. Higher maternal intake of vitamin D (but not maternal vitamin D levels) have been associated with reduced risk of wheezing and asthma in their children. Small trials suggest a possible role for vitamin D supplementation in children, but the first multicenter trial of supplementation in adults with asthma was negative for the primary outcomes. Based on these findings, I believe that well-designed clinical trials are needed to determine whether vitamin D supplementation improves asthma related outcomes in children.

References and Recommended Reading

Papers of particular interest, published recently have been highlighted as:

• Of importance

•• Of major importance

1. Akinbami LJ, Moorman JE, Bailey C, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. NCHS data brief. 2012(94):1–8.
2. Moorman JE, Akinbami LJ, Bailey CM, et al. National surveillance of asthma: United States, 2001-2010. Vital & health statistics. Series 3, Analytical and epidemiological studies / [U.S. Dept. of Health and Human Services, Public Health Service, National Center for Health Statistics]. 2012(35):1–67.
3. Eder W, Ege MJ, von Mutius E. The asthma epidemic. N Engl J Med. 2006; 355(21):2226–2235. [PubMed: 17124020]
4. Celedon JC, Sredl D, Weiss ST, Pisarski M, Wakefield D, Cloutier M. Ethnicity and skin test reactivity to aeroallergens among asthmatic children in Connecticut. Chest. 2004; 125(1):85–92. [PubMed: 14718425]
5. Dixon AE, Holguin F, Sood A, et al. An official American Thoracic Society Workshop report: obesity and asthma. Proceedings of the American Thoracic Society. 2010; 7(5):325–335. [PubMed: 20844291]
6. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy. 2004; 59(5):469–478. [PubMed: 15080825]

7. Dollman J, Norton K, Norton L. Evidence for secular trends in children's physical activity behaviour. British journal of sports medicine. 2005; 39(12):892–897. discussion 897. [PubMed: 16306494]

8. Mann EH, Chambers ES, Pfeffer PE, Hawrylowicz CM. Immunoregulatory mechanisms of vitamin D relevant to respiratory health and asthma. Ann N Y Acad Sci. 2014

9**. Castro M, King TS, Kunselman SJ, et al. Effect of Vitamin D3 on Asthma Treatment Failures in Adults With Symptomatic Asthma and Lower Vitamin D Levels: The VIDA Randomized Clinical Trial. JAMA : the journal of the American Medical Association. 2014 [Recently published multicenter AsthmaNet trial showing no beneficial effect of vitamin D supplementation in adults with asthma for the pre-specified outcomes. Exploratory analyses suggest a beneficial role in treated responders.]

10**. Holick MF. Vitamin D deficiency. N Engl J Med. 2007; 357(3):266–281. [PubMed: 17634462] [Excellent review of the role of vitamin D in skeletal and non-skeletal health.]

11. Powe CE, Evans MK, Wenger J, et al. Vitamin D-binding protein and vitamin D status of black Americans and white Americans. N Engl J Med. 2013; 369(21):1991–2000. [PubMed: 24256378]

12. Holick MF. Bioavailability of vitamin D and its metabolites in black and white adults. N Engl J Med. 2013; 369(21):2047–2048. [PubMed: 24256384]

13. Terushkin V, Bender A, Psaty EL, Engelsen O, Wang SQ, Halpern AC. Estimated equivalency of vitamin D production from natural sun exposure versus oral vitamin D supplementation across seasons at two US latitudes. Journal of the American Academy of Dermatology. 2010; 62(6):929, e921–929. [PubMed: 20363523]

14. Ross AC, Manson JE, Abrams SA, et al. IOM 2011 Dietary Reference Intakes for Calcium and Vitamin D. 2011

15. Brehm JM, Acosta-Perez E, Klei L, et al. Vitamin D Insufficiency and Severe Asthma Exacerbations in Puerto Rican Children. Am J Respir Crit Care Med. 2012

16. Lange NE, Litonjua A, Hawrylowicz CM, Weiss S. Vitamin D, the immune system and asthma. Expert Rev Clin Immunol. 2009; 5(6):693–702. [PubMed: 20161622]

17**. Brehm JM, Celedon JC, Soto-Quiros ME, et al. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. Am J Respir Crit Care Med. 2009; 179(9):765–771. [PubMed: 19179486] [First epidemiological study to show an association between reduced serum vitamin D levels and increased asthma severity.]

18. Brehm JM, Schuemann B, Fuhlbrigge AL, et al. Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study. J Allergy Clin Immunol. 2010; 126(1):52–58. e55. [PubMed: 20538327]

19. Chinellato I, Piazza M, Sandri M, Peroni D, Piacentini G, Boner AL. Vitamin D serum levels and markers of asthma control in Italian children. The Journal of pediatrics. 2011; 158(3):437–441. [PubMed: 20870246]

20. Gupta A, Sjoukes A, Richards D, et al. Relationship between serum vitamin D, disease severity, and airway remodeling in children with asthma. Am J Respir Crit Care Med. 2011; 184(12):1342–1349. [PubMed: 21908411]

21. Korn S, Hubner M, Jung M, Blettner M, Buhl R. Severe and uncontrolled adult asthma is associated with vitamin D insufficiency and deficiency. Respir Res. 2013; 14(1):25. [PubMed: 23432854]

22. Samrah S, Khatib I, Omari M, et al. Vitamin D deficiency and level of asthma control in women from North of Jordan: a case-control study. J Asthma. 2014

23. Searing DA, Zhang Y, Murphy JR, Hauk PJ, Goleva E, Leung DY. Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use. J Allergy Clin Immunol. 2010; 125(5):995–1000. [PubMed: 20381849]

24. Sutherland ER, Goleva E, Jackson LP, Stevens AD, Leung DYM. Vitamin D Levels, Lung Function, and Steroid Response in Adult Asthma. American Journal of Respiratory and Critical Care Medicine. 2010; 181(7):699–704. [PubMed: 20075384]

25. Wu AC, Tantisira K, Li L, et al. Effect of vitamin D and inhaled corticosteroid treatment on lung function in children. Am J Respir Crit Care Med. 2012; 186(6):508–513. [PubMed: 22798322]

26. Freishtat RJ, Iqbal SF, Pillai DK, et al. High prevalence of vitamin D deficiency among inner-city African American youth with asthma in Washington, DC. The Journal of pediatrics. 2010; 156(6): 948–952. [PubMed: 20236657]
27. Alyasin S, Momen T, Kashef S, Alipour A, Amin R. The relationship between serum 25 hydroxy vitamin d levels and asthma in children. Allergy, asthma & immunology research. 2011; 3(4):251–255.
28. Bener A, Ehlayel MS, Tulic MK, Hamid Q. Vitamin D deficiency as a strong predictor of asthma in children. International archives of allergy and immunology. 2012; 157(2):168–175. [PubMed: 21986034]
29. Maalmi H, Berraies A, Tangour E, et al. The impact of vitamin D deficiency on immune T cells in asthmatic children: a case-control study. Journal of asthma and allergy. 2012; 5:11–19. [PubMed: 22690128]
30. Checkley W, Robinson CL, Baumann LM, et al. 25-hydroxy vitamin D levels are associated with childhood asthma in a population-based study in Peru. Clin Exp Allergy. 2014
31. Goleva E, Searing DA, Jackson LP, Richers BN, Leung DY. Steroid requirements and immune associations with vitamin D are stronger in children than adults with asthma. J Allergy Clin Immunol. 2012
32. Tolppanen AM, Sayers A, Granell R, Fraser WD, Henderson J, Lawlor DA. Prospective association of 25-hydroxyvitamin d3 and d2 with childhood lung function, asthma, wheezing, and flexural dermatitis. Epidemiology. 2013; 24(2):310–319. [PubMed: 23377091]
33. Devereux G, Wilson A, Avenell A, McNeill G, Fraser WD. A case-control study of vitamin D status and asthma in adults. Allergy. 2010; 65(5):666–667. [PubMed: 19845573]
34. Hughes AM, Lucas RM, Ponsonby AL, et al. The role of latitude, ultraviolet radiation exposure and vitamin D in childhood asthma and hayfever: an Australian multicenter study. Pediatr Allergy Immunol. 2010
35. Menon J, Maranda L, Nwosu BU. Serum 25-hydroxyvitamin D levels do not correlate with asthma severity in a case-controlled study of children and adolescents. Journal of pediatric endocrinology & metabolism : JPEM. 2012; 25(7-8):673–679. [PubMed: 23155692]
36. Mai XM, Langhammer A, Camargo CA Jr. Chen Y. Serum 25-hydroxyvitamin D levels and incident asthma in adults: the HUNT Study. Am J Epidemiol. 2012; 176(12):1169–1176. [PubMed: 23204497]
37. Gergen PJ, Teach SJ, Mitchell HE, et al. Lack of a relation between serum 25-hydroxyvitamin D concentrations and asthma in adolescents. Am J Clin Nutr. 2013; 97(6):1228–1234. [PubMed: 23595876]
38. Ozaydin E, Butun MF, Cakir BC, Kose G. The association between vitamin d status and recurrent wheezing. Indian journal of pediatrics. 2013; 80(11):907–910. [PubMed: 23539249]
39. Camargo CA Jr. Ingham T, Wickens K, et al. Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. Pediatrics. 2011; 127(1):e180–187. [PubMed: 21187313]
40. Zosky GR, Hart PH, Whitehouse AJ, et al. Vitamin D Deficiency at 16-20 Weeks Gestation Is Associated with Impaired Lung Function and Asthma at 6 Years of Age. Annals of the American Thoracic Society. 2014
41. Morales E, Romieu I, Guerra S, et al. Maternal vitamin D status in pregnancy and risk of lower respiratory tract infections, wheezing, and asthma in offspring. Epidemiology. 2012; 23(1):64–71. [PubMed: 22082994]
42. Pike KC, Inskip HM, Robinson S, et al. Maternal late-pregnancy serum 25-hydroxyvitamin D in relation to childhood wheeze and atopic outcomes. Thorax. 2012; 67(11):950–956. [PubMed: 22707522]
43. Gale CR, Robinson SM, Harvey NC, et al. Maternal vitamin D status during pregnancy and child outcomes. Eur J Clin Nutr. 2008; 62(1):68–77. [PubMed: 17311057]
44. Hollams EM, Hart PH, Holt BJ, et al. Vitamin D and atopy and asthma phenotypes in children: a longitudinal cohort study. Eur Respir J. 2011; 38(6):1320–1327. [PubMed: 21565922]
45. Waldron JL, Ashby HL, Cornes MP, et al. Vitamin D: a negative acute phase reactant. Journal of clinical pathology. 2013; 66(7):620–622. [PubMed: 23454726]

46. Reid D, Toole BJ, Knox S, et al. The relation between acute changes in the systemic inflammatory response and plasma 25-hydroxyvitamin D concentrations after elective knee arthroplasty. Am J Clin Nutr. 2011; 93(5):1006–1011. [PubMed: 21411617]
47. Heaney RP. Serum 25-hydroxyvitamin D is a reliable indicator of vitamin D status. Am J Clin Nutr. 2011; 94(2):619–620. author reply 620. [PubMed: 21775574]
48. Wjst M. Is vitamin D supplementation responsible for the allergy pandemic? Curr Opin Allergy Clin Immunol. 2012; 12(3):257–262. [PubMed: 22517291]
49*. Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. Am J Clin Nutr. 2010; 91(5): 1255–1260. [PubMed: 20219962] [Important trial showing a reduced risk of asthma exacerbations in a subset of asthmatic children in a vitamin D supplementation trial.]
50. Rich-Edwards JW, Ganmaa D, Kleinman K, et al. Randomized trial of fortified milk and supplements to raise 25-hydroxyvitamin D concentrations in schoolchildren in Mongolia. Am J Clin Nutr. 2011; 94(2):578–584. [PubMed: 21697075]
51. Camargo CA Jr. Ganmaa D, Frazier AL, et al. Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia. Pediatrics. 2012; 130(3):e561–567. [PubMed: 22908115]
52. Majak P, Olszowiec-Chlebna M, Smejda K, Stelmach I. Vitamin D supplementation in children may prevent asthma exacerbation triggered by acute respiratory infection. J Allergy Clin Immunol. 2011; 127(5):1294–1296. [PubMed: 21315433]
53. Camargo CA Jr. Rifas-Shiman SL, Litonjua AA, et al. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. Am J Clin Nutr. 2007; 85(3): 788–795. [PubMed: 17344501]
54. Devereux G, Litonjua AA, Turner SW, et al. Maternal vitamin D intake during pregnancy and early childhood wheezing. Am J Clin Nutr. 2007; 85(3):853–859. [PubMed: 17344509]
55. Litonjua AA, Lange NE, Carey VJ, et al. The Vitamin D Antenatal Asthma Reduction Trial (VDAART): Rationale, design, and methods of a randomized, controlled trial of vitamin D supplementation in pregnancy for the primary prevention of asthma and allergies in children. Contemporary clinical trials. 2014; 38(1):37–50. [PubMed: 24614387]
56. Lodge CJ, Lowe AJ, Allen KJ, et al. Childhood wheeze phenotypes show less than expected growth in FEV1 across adolescence. Am J Respir Crit Care Med. 2014
57. Lau S, Illi S, Sommerfeld C, et al. Transient early wheeze is not associated with impaired lung function in 7-yr-old children. Eur Respir J. 2003; 21(5):834–841. [PubMed: 12765430]
58*. Xystrakis E, Kusumakar S, Boswell S, et al. Reversing the defective induction of IL-10-secreting regulatory T cells in glucocorticoid-resistant asthma patients. J Clin Invest. 2006; 116(1):146–155. 58. [PubMed: 16341266] [Landmark paper describing a potential protective mechanism for vitamin D in severe asthma.]
59. Ross AC, Manson JE, Abrams SA, et al. The 2011 Report on Dietary Reference Intakes for Calcium and Vitamin D from the Institute of Medicine: What Clinicians Need to Know. J Clin Endocrinol Metab. 2010
60. FDA. [May 7th, 2014] 2013. http://www.fda.gov/downloads/Drugs/Guidances/UCM229175.pdf.
61. Klein M, Sanders ME, Duong T, Young HA. Probiotics: from bench to market. Ann N Y Acad Sci. 2010; 1212(Suppl 1):E1–14. [PubMed: 21105878]
62. LeBlanc ES, Perrin N, Johnson JD Jr. Ballatore A, Hillier T. Over-the-counter and compounded vitamin D: is potency what we expect? JAMA internal medicine. 2013; 173(7):585–586. [PubMed: 23400578]

Table 1

Unique challenges for clinical trials of vitamin D supplementation, and potential solutions

Challenges	Potential solutions
Variability in sun exposure during the trial	• Subject follow-up for a single season (e.g. winter only) • Subject follow-up for an entire calendar year (one solar cycle)
High variability in drug potency	• Measure the single pill and average pill variability in drug potency • Restrict study medications to a single production lot, if possible • If not possible, ensure that drugs from different lots are equally distributed across treatment arms
Off-protocol vitamin D consumption/UV-B exposure	• Allocation concealment combined with education about maximum recommended daily allowances • Analysis should be performed as “intention to treat” rather than based on serum 25-OH-vitamin D levels • Conservative sample size calculations during trial design to account for a loss of power
Fixed dosing protocol may not achieve vitamin D sufficiency	• An alternative is to add once monthly “as needed” high-dose cholecalciferol for subjects with serum 25-hydroxy-vitamin D levels < 30 ng/ml. Subjects with sufficient levels would need to receive a placebo to preserve blinding.