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Vitamin D as an Adjunctive Therapy in Asthma. Part 2: A Review of Human Studies

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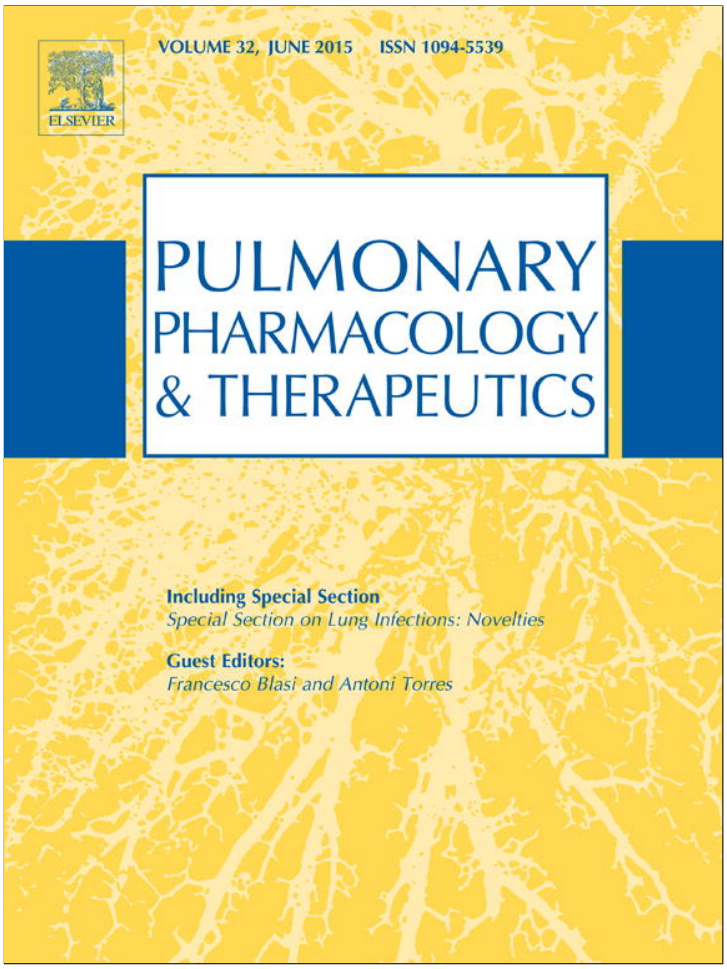

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Vitamin D as an adjunctive therapy in asthma. Part 2: A review of human studies

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ABSTRACT

Vitamin D deficiency (VDD) is highly prevalent worldwide, with adverse effects on bone health but also potentially other unfavorable consequences. VDD and asthma-incidence/severity share many common risk factors, including winter season, industrialization, poor diet, obesity, dark skin pigmentation, and high latitude. Multiple anatomical areas relevant to asthma contain both the enzyme responsible for producing activated vitamin D and the vitamin D receptor suggesting that activated vitamin D (1,25-dihydroxyvitamin D) may have important local effects at these sites.

Emerging evidence suggests that VDD is associated with increased airway hyperresponsiveness, decreased pulmonary function, worse asthma control, and possibly decreased response to standard anti-asthma therapy. However the effect is inconsistent with preliminary evidence from different studies suggesting vitamin D is both beneficial and detrimental to asthma genesis and severity.

Current evidence suggests that supplementation with moderate doses of vitamin D may be appropriate for maintenance of bone health in asthmatics, particularly steroid users. However emerging data from an increasing number of randomized, controlled, intervention studies of vitamin D supplementation in pediatric and adult asthma are becoming available and should help determine the importance, if any of vitamin D for asthma pathogenesis.

The purpose of this second of a two-part review is to review the current human literature on vitamin D and asthma, discussing the possible consequences of VDD for asthma and the potential for vitamin D repletion as adjunct therapy.

1. Introduction

Much human research on vitamin D and asthmatic disease is now available. This second part of a two-part review will briefly introduce vitamin D and its sources. However, the main focus will be human evidence linking vitamin D to human asthma, including epidemiological, case-control, cross-sectional, prospective and intervention studies. We will discuss the merits and limitations of each study design regarding asthma and vitamin D. However, unanswered questions remain. We have reviewed mechanisms by which vitamin D may influence asthmatic disease in part one of this two-part review [92]. Therefore, we will conclude this review with some recommendations for future research in the area.

There are two major forms of fat-soluble vitamin D: vitamin D_2 (ergocalciferol) available from plant sources such as ultraviolet-B (UV-B) irradiated mushrooms and vitamin D_3 (cholecalciferol) available from animal sources such as oily fish and produced in human skin upon exposure to ultraviolet B radiation (UV-B). Although both forms of vitamin D are bioactive and available as a dietary supplement, it is recognized that vitamin D_3 is more potent [159].

Systemic vitamin D status is reliably indicated by the serum level of 25-hydroxyvitamin D (25(OH)D) [70,75,78], which reflects cutaneous photosynthesis and oral intake from both diet and supplements. Currently, there is no consensus on optimal levels of 25(OH)D. The 2010 Institute of Medicines (IOM) recommended that vitamin D deficiency (VDD) be defined as a 25(OH)D level <50 nmol/L, with a level >50 nmol/L representing vitamin D

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Abbreviations list

% predicated FEV_1	percent predicated based on normative values for healthy age and BMI matched subjects.
1,25D	1,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D
AAR	allergic rhinitis + allergic asthma
ACQ	asthma control questionnaire
ACT	asthma control test
AD	atopic dermatitis
AR	allergic rhinitis
ASM	airway smooth muscle
ATAQ	asthma therapy assessment questionnaire
BALF	bronchoalveolar lavage fluid
BMI	body mass index
d	day
DB	double-blind
DBRCT	double-blind, randomized, placebo controlled trial
ED	emergency department
eNO	exhaled nitric oxide
FeNO	fraction of exhaled nitric oxide
FEV_1	forced expiratory volume in 1 s
FIV_1	forced inspiratory volume in 1 s
FoxP3	forkhead box P3
FVC	forced vital capacity
GCS	glucocorticoids
GINA	global initiative for asthma
hs-CRP	high sensitivity C reactive protein
ICS	inhaled corticosteroid
IFN γ	interferon gamma
IgE	immunoglobulin E
IL	interleukin
IM	intramuscularly
IOM	Institute of Medicines
ISAAC	International Study of Asthma and Allergies in Childhood
IU	international unit
LABA	long-acting β-agonist
LL-37	the protein precursor to hCAP-18 which undergoes extracellular cleavage to generate a 37-residue active cationic peptide
NHANES	National Health and Nutrition examination survey
OCS	oral corticosteroid
OGG-1	8-Oxoguanine-DNA glycosylase;
OR	odds ratio
PC_{20}-FEV_1	provocation dose of methacholine require to induce a 20% drop in FEV_1
PEFR	peak expiratory flow rate
RCT	randomized controlled trial
ROS	reactive oxygen species
RTI	respiratory tract infection
RXRα	retinoid X receptor-α
SCIT	subcutaneous immunotherapy
SIT	specific immunotherapy
SOD	superoxide dismutases – enzymes which catalyze the dismutation of the superoxide radical
SR	steroid resistant
T-reg cells	regulatory T cells
TGF	transforming growth factor
Th	t helper
UV-B	ultraviolet-B radiation
VDBP	vitamin D binding protein
VDD	vitamin D deficiency
VDI	vitamin D insufficiency
VDR	vitamin D receptor
VDRE	vitamin D response element
VDS	vitamin D sufficiency
VDT	vitamin D toxicity

sufficiency (VDS) [139]. However, these guidelines have been criticized as being overly conservative by being based almost solely on studies of bone health [69,167]. Higher 25(OH)D levels (e.g. >100 nmol/L) have been suggested to be necessary for optimal immune function and respiratory outcomes [17,76,78,79,166].

For the purposes of this review we will use the most up to date recommendations from the Endocrine Society [76] – see Table 1. Despite advances about the importance of vitamin D, VDD is widespread worldwide with recent estimates suggesting 1 billion people are affected worldwide [74].

Although some foods contain vitamin D (mainly oily fish and fortified products), the major source for most humans is cutaneous photosynthesis under the influence of UV-B radiation from sunshine [74]. Therefore, VDD – like asthma – is more common in polluted, industrialized regions [115], at high latitude [87] and in winter season [49]. Similar to asthma, body size and adiposity [51], as well as darker skin pigmentation [38], exposure to cigarette smoke [10,73,123,153], pollution [9,89] and physical inactivity [73,145,163] are associated with decreased vitamin D status. Other determinants of vitamin D status include clothing and sunblock use [116], inadequate diet and supplement usage as well as genetic variation [179].

Table 1
Definitions of vitamin D status based on serum 25(OH)D level [76].

Definition	Abbreviation	Serum 25(OH)D level
Vitamin D deficiency	VDD	50 nmol/L
Vitamin D insufficiency	VDI	50–75 nmol/L
Vitamin D sufficiency	VDS	75–250 nmol/L
Vitamin D toxicity	VDT	>375 nmol/L

It is notable that the environmental changes attributable to the increase in asthma incidence and severity also cause VDD. The recent emergence of widespread VDD appears related to sun avoidance and seems to parallel the increased incidence of multiple diseases, including asthma.

2. Methods

References were identified by searches of MEDLINE, CINAHL, EMBASE and online Cochrane databases through January 2015. Keywords used included vitamin D and asthma, wheezing, airway inflammation, airway smooth muscle, and respiratory infection. Only manuscripts published in English are included. Articles were chosen according to their relevance for this review and their bibliographies were also searched for further references.

3. Results and discussion

3.1. Evidence linking vitamin D to asthma

There are two opposing theories regarding the effect of increasing 25(OH)D status in asthma. We will consider both

theories and present existing cross sectional and interventional evidence.

3.1.1. Is vitamin D detrimental in asthma?

Wjst and Dold first hypothesized that the introduction of vitamin D fortified foods was related to the asthma and allergy epidemic, suggesting that if protective antigen-reactive Th1 memory cells fail to develop, the subsequent predominance of Th2 cells can trigger allergic reactions [180]. This initial hypothesis was based on the observation that the introduction of vitamin D food fortification and specific vitamin D supplementation strategies seems to mirror the emergence of an asthma epidemic [175–178]. However, there is little evidence that 25(OH)D levels increased during this period and it is likely that several factors may even decreased 25(OH)D levels, including increased indoor time (i.e. indoor occupations and recreation) and increased sunscreen use. However, some animal work has seemingly supported the view that vitamin D is detrimental in asthma. VDR knockout mice do not develop airway inflammation or experimental asthma [174]. The same group went on to demonstrate that VDR expression is mandatory for the induction of lung inflammation [173]. Together these animal reports suggest that vitamin D and the VDR are important regulators of lung inflammation.

This initial hypothesis and animal model evidence was supported by limited human evidence. The first human report of potentially increased risk of atopy with vitamin D supplementation came in 1993. Peanut oil used for the pharmacological preparation of vitamin D to prevent peanut sensitization was associated with a markedly increased risk of allergen sensitization (OR = 9.0; $p < 0{:}003$) compared to the supplement without allergen [44]. Later trials of supplementation with peanut oil or water with dissolved vitamin D alone or in combination with vitamin A demonstrated increased adverse allergic outcomes, including asthma [45,97,98]. The preparations used contained a combination of peanut oil as well as vitamins A and D, and therefore it is difficult to speculate on the individual contribution of each component. These early reports are supported by several prospective studies suggesting that early vitamin D supplementation may increase the risk of allergic disease among healthy infants [8,59,82,130,164] and that vitamin D may have detrimental effects on childhood lung function [42] and atopic disease [71,181].

However, the effect of vitamin D on immune and inflammatory signals may outweigh any potential shifting of Th1–Th2 balance and the majority of existing mechanistic [92] as well as observational data suggest that vitamin D repletion may be therapeutic in asthma. In fact, some authors have suggested that VDD may be responsible for the increase in allergic diseases and asthma prevalence worldwide [171,107,106]. However, interventional data has proved inconsistent (see below).

3.1.2. Epidemiologic data

There is decreased opportunity for vitamin D skin photosynthesis at higher latitude [74]. Therefore if vitamin D is truly important in asthmatic disease we can expect higher asthma incidence at higher latitude. Indeed, several reports have suggested that latitude is positively correlated to asthma [2,56,87,95] and allergy [80]. However, not all ecological studies demonstrate this effect, with some studies noting no interaction [81,114], and others still an increased risk at lower latitude [131,151,170,176,187]. It should be noted that geographical latitude can only ever serve as a proxy for vitamin D status. Many factors affect asthma prevalence and may also vary by region, including healthcare resources, local population, genetics and pollution. Additionally, many factors affect the prevalence of VDD and may also vary by region and latitude, including diet and supplement use, religious clothing and sun habits. Indeed, VDD has been reported to common in low latitude countries with abundant sunshine [124,52].

Ethnic groups with darker skin have higher prevalence and severity of asthma when compared to those with lighter skin pigmentation residing in similar locations [57,62,65,119]. Although, many factors could contribute to this observation (e.g. dietary habits, healthcare access), it is noteworthy that those with darker skin pigmentation have the same capacity but significantly decreased efficiency of cutaneous vitamin D photosynthesis upon exposure to UV-B [38]. Therefore, heavily pigmented individuals will typically have lower 25(OH)D status compared to lighter pigmented individuals residing at similar latitudes [68,72].

Nevertheless, a randomized trial of Norwegian children with atopic eczema demonstrated significant improvements after 4 weeks in a sunny climate [26]. Further, an observational study in 2007 of Spanish asthmatic children revealed that health related quality of life was highest in summer and lowest in autumn [60]. Indeed, sunny hours have been inversely associated with asthma prevalence [5]. Additionally, a subsequent longitudinal cohort study of 415 Australian children followed from birth to age 16, demonstrated that reported summer sun exposure was associated with reduced eczema and rhinitis but not inhalant allergen sensitization or asthma risk [90]. However, other studies note an increased risk of asthma and allergic disease with higher UV-B exposure [131]. These discrepancies can potentially be explained by recent trends in lifestyle e.g. sunscreen use and increased time spent indoors, which would decrease vitamin D photosynthesis. Considering that UV-B radiation is the major source of vitamin D for most populations, these observations appear to support a role for vitamin D in asthma.

Epidemiologic data demonstrate a positive association between 25(OH)D level and pulmonary function in healthy children [184,185], adults [19,37,158], elderly males but not females [165], asthmatics [154], smokers [101] and those with COPD [86]. A detailed retrospective analysis from the UK demonstrated a linear association between 25(OH)D and lung function including both forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC), which was consistent through the seasons and not fully explained by infections, adiposity or other lifestyle or socioeconomic measures [16]. A 20 year, Danish, prospective study with 18,507 subjects demonstrated that lower plasma 25(OH)D levels were associated with both lower lung function and faster decline in lung function (both FVC & FEV_1) [1]. Additionally, a cross-sectional analysis of 650 mainly black, smokers revealed that there was no relationship between 25(OH)D and cathelicidin levels, but that lung function decrements were associated with low cathelicidin and were greatest among individuals with lower 25(OH)D levels [99].

Supporting the idea that vitamin D is important in asthmatic and atopic disease, inverse associations between 25(OH)D and allergy [58,83,148] as well as asthma [107,58,88] have also been reported. However, other reports suggest that dietary vitamin D [127] and serum 25(OH)D concentrations [147] were not related to FEV_1 and that risk for atopic disease, including allergic rhinitis [181] and eczema [71] was higher with increased 25(OH)D. Taken together, most but not all existing epidemiological reports suggest that 25(OH)D may be an important and modifiable variable in the maintenance of lung health.

3.1.3. Case-control studies of vitamin D status and asthma

25 case control studies totaling 2568 asthmatic cases and 4376 controls have examined vitamin D intake, status as well as correlations with respiratory/atopic parameters in asthma cases compared to controls (see Table 2).

The case-control study by Carraro et al. deserves attention. The authors conducted a comprehensive observational study

Table 2
Case control studies of vitamin D status and asthma.

Population	Age (years)	Location	Latitude	Main findings	Reference
80 adult asthmatics & 80 age & sex-matched controls.	18–50	Aberdeen, Scotland & Norfolk England	52–57°N	No significant differences in energy-adjusted vitamin D intake or 25(OH)D between cases & controls. All subjects were VDD.	[48]
85 African-American, childhood asthmatics & 21 healthy controls.	6–20	Washington DC, USA	39° N	VDD & VDI significantly greater in cases than controls.	[57]
50 childhood asthmatics & 50 healthy controls.	6–18	Shiraz, Iran	30° N	25(OH)D was significantly lower in cases than controls and positively correlated with FEV_1 and FEV_1/FVC. No correlation with eosinophil counts, asthma duration, number of hospitalization or unscheduled visits in the previous year.	[3]
45 asthmatic children & 59 healthy controls.	9–11	Verona, Italy	45° N	No significant difference in 25(OH)D between cases and controls. 25(OH)D positively correlated with FVC and FEV_1 but negatively with exercise induced bronchoconstriction.	[35,36]
483 asthmatic children & 483 age, gender & ethnicity matched controls.	<15	Doha, Qatar	25° N	25(OH)D levels were significantly lower and IgE significantly higher in cases than controls with a negative correlation evident. Cases had less exposure to sunshine and lower exercise. VDD was the strongest predictor of asthma in this population.	[53] and [15]
36 children with SR asthma, 26 with moderate asthma, and 24 healthy controls.	6–16	London, England	52° N	25(OH)D levels were significantly lower in SR asthma than either mild asthmatics or controls and inversely correlated with ASM mass, bronchodilator response and IgE but positively correlated with asthma control, FEV_1 and FVC. Further low 25(OH)D was correlated with asthma exacerbation and medication usage.	[66]
287 asthmatic children & 273 healthy children.	6–14	San Juan, Puerto Rico	18° N	No significant difference in 25(OH)D between cases and controls. Lower 25(OH)D correlated with severe asthma exacerbation, atopy, and a lower FEV_1/FVC in cases.	[22]
103 asthmatics & 102 healthy control subjects.	8.5–46	Denver, Colorado	39° N	VDD was evident in 47.6% of patients and 56.8% of controls. In multivariate regression models, 25(OH)D correlated positively with expression of vitamin D regulated genes, but was only significant in children. An inverse correlation between 25(OH)D and serum IgE levels was observed but only in children. 25(OH)D was significantly inversely correlated with ICS dose, again only in children.	[63]
15 children with SR asthma, 7 with moderate asthma, & 6 non-asthmatic controls.	6–16	London, England	52° N	Children with SR asthma had significantly higher levels of VDBP in BALF but not in serum compared with moderate asthmatics and controls. VDBP concentration in BALF correlated negatively with asthma control and %FEV_1 but positively with ICS usage.	[67]
39 children with controlled asthma and 30 age- and sex-matched controls.	6–16	El Manar, Tunisia	37° N	VDD was higher in asthma compared to control, VDS was lower in asthma than control. Th1/Th2 ratio and CD25(+) Foxp3(+) T-reg cells were positively related to 25(OH) D level while IL-17 was negatively correlated.	[109]
Of 25,616 Norwegian adults who participated in 2 health surveys 1995-1997 and 2006-2008, a nested case-control study included 584 new-onset asthma cases and 1958 non-asthma controls.	19–55	Nord-Trøndelag, Norway	63° N	After adjustment for potential asthma risk factors, baseline VDD was not significantly correlated with asthma in either women or men. Co-existent allergic rhinitis modified the association in men only.	[110]
263 asthmatic children & 284 healthy controls.	2–19	Worchester, USA	42° N	No significant difference in 25(OH)D between cases and controls. 25(OH)D did not relate to asthma severity.	[120]
42 non-severe asthmatic children, 11 with severe asthma and 15 healthy, non-asthmatic children.	8–17	Padova, Italy	45° N	A metabolomic approach to exhaled breath condensate (breathomics) revealed that the absence of ercalcitriol, (active metabolite of vitamin D_2) differentiated severe asthma from both non-severe asthma and healthy children.	[29]

Table 2 (*continued*)

Population	Age (years)	Location	Latitude	Main findings	Reference
30 infants with recurrent wheezing and 45 healthy, similar aged infants without any history of acute or chronic illness	Infants	Ankara, Turkey	40° N	25(OH)D was not statistically different between the groups. However, the sample size was small, mean 25(OH)D was lower in cases than controls and VDI was common (90% of wheezers, 77.8% of controls).	[133]
Prospective cohort study of 20 asthmatics and 19 non-asthmatics followed for ~1y.	Not reported	Minnesota, USA	44° N	Overall negative correlation between 25(OH)D and decreased pneumococcal antibody titers during follow-up, especially significant among those with asthma and/or atopy.	[141]
85 asthmatic children & 85 non-asthmatic children.	2–14	Tekirdag, Turkey	37° N	25(OH)D was significantly lower in asthmatic children. There was a negative correlation between 25(OH)D and ER/hospital admissions, RTI incidence, asthma attacks and asthma severity.	[162]
50 asthmatic children & 25 non-asthmatic children.	1–15	Lucknow, India	29° N	VDI was correlated with asthma incidence and decreased asthma control.	[7]
35 children with AAR, and 11 patients with AR & 28 healthy controls.	8–13	Palermo, Italy	39° N	25(OH) was highest in controls followed by AR and then AAR, while plasma IL-31 and 33 were lowest in controls followed by AR and AAR. Neither plasma IL-31 or IL-33 correlated with 25(OH)D. 25(OH)D correlated negatively with IgE levels and total atopy index only in AAR.	[20]
40 wheezy infants; 30 age-and-gender matched healthy infants.	1–3	Samsun, Turkey	41° N	25(OH)D levels were lower in wheezy infants vs. controls. There was a negative relationship between 25(OH)D and IgE levels.	[46]
120 asthamtic children and 74 age & gender matched, non asthmatic controls.	4.4 ± 1.2	Istanbul, Turkey	41°N	Mean 25(OH)D level was slightly but not significantly lower in cases than controls. Among cases, the total number of exacerbations, asthma severity and systemic GCS need in the previous year were significantly higher in the VDD group.	[50]
69 active asthamics (wheezing in the past 12 months and ever asthma on the ISAAC questionnaire) and 671 controls (no hisotry of wheeinzg of asthma).	16–17	Cyprus	35° N	In adjusted models, mean 25(OH)D levels were significantly lower amongst asthamtics compared to controls. Within asthmatics, there was a negative trend between 25(OH)D and the number of reported asthma severity indicators.	[93]
68 asthmatics and 77 healthy women.	14–65	North Jordan	32° N	The prevalence of low 25(OH)D (<37.5 nmol/L) was non statistically higher in asthmatic women compared with controls. Decreased 25(OH)D correlated posisitvely with number of asthma medications, whereas 25(OH)D directly correlated with ACT and GINA classification. After adjusting for age, the odds of having VDD for asthmatic women were 35.9 times higher than that for control women	[143]
44 asthmatic children and 44 healthy controls.	5–13	Bangalore, India	32° N	25(OH)D levels were significnatly lower in asthmatics vs. controls. 25(OH)D was significantly positively correlated with % FEV_1 and FEV_1/FVC%.	[149]
30 children with acute wheeze and 101 age-matched controls with no history of wheeze or sensitization to airborne allergens.	0.5–4	Stockholm, Sweden	62° N	VDI was correlated with 270% increased risk of acute wheeze. No correlation between 25(OH) and atopy, presence of virus/bacteria or recurrent RTI.	[152]
73 wheezing children and 75 controls	Not reported	Istanbul, Turkey	41° N	No significant difference in 25(OH)D between cases & controls. However, 25(OH)D was significantly lower in recurrent wheezers (>3 wheezing attacks) & children with a positive Asthma Predictive Index.	[162]

Abbreviations: 25(OH)D = 25-hydroxyvitamin D; AAR = allergic rhinitis + allergic asthma; ACT = asthma control test; AR = allergic rhinitis; BALF = *bronchoalveolar lavage fluid*; ER = emergency room; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; GCS = glucocorticoids; GINA = global initiative for asthma; ICS = inhaled corticosteroid; IgE = immunoglobulin E; IL = interleukin; ISAAC = International Study of Asthma and Allergies in Childhood; RTI = respiratory tract infection; SR = steroid resistant; T-reg cells = regulatory T cells; VDBP = vitamin D binding protein; VDD = vitamin D deficiency; VDI = vitamin D insufficiency; VDS = vitamin D sufficiency.

regarding the metabolomics of exhaled breath condensate (breathomics) in severe asthmatic children vs. non-severe asthmatic children and healthy children. They observed that the absence of ercalcitriol (an active metabolite of vitamin D_2) differentiated severe asthma from both children with non-severe asthma and healthy children. This is perhaps the first report of vitamin D being recovered specifically in the lung. The authors speculate that children with severe asthma and treated with high-dose inhaled corticosteroids (ICS) may have insufficient vitamin D in the airways [29].

Observational studies, including case-control studies have several well-known limitations. Choice of controls can determine the observations and therefore even when efforts to match for confounding variables are made, the results can be biased. Further, even those with statistical adjustments, observational studies are limited by potential confounding. Therefore, it is impossible to ascertain whether an insufficient 25(OH)D level is responsible for reduced asthma control or that poor asthma control leads to decreased 25(OH)D status through acute inflammation as has been reported post-orthopedic surgery [138,168] or reduced sun exposure due to asthma related inactivity. A recent *in vivo* study demonstrated that acute lung inflammation induced by exposure to house dust mite did not lead to altered 25(OH)D levels [33] suggesting that altered vitamin D status is not caused by allergic inflammation. However, children with wheezing, shortness of breath or allergy may avoid sunlight and outdoor activities [14,15,162] and therefore present with lower 25(OH)D.

Existing case-control studies regarding vitamin D and asthma have compared asthmatics to healthy controls by assessing measurements which were collected simultaneously and only at a single time point. Therefore it is not possible to determine temporal relationships between exposure and outcome. Further, many of these study populations exhibit widespread VDD and VDI and therefore it is difficult to comment on the effect of higher 25(OH)D on asthma parameters.

Importantly, more than being interested in whether vitamin D intake and 25(OHOD status differs between asthmatic cases and non-asthmatic controls, the key question is whether vitamin D can influence asthma pathogenesis, severity and control. Because case-control studies can not answer these questions, these studies must be interpreted with caution. Hence, case-control studies are therefore placed low in the hierarchy of scientific evidence.

3.1.4. Cross-sectional studies of vitamin D status in asthma

Although, vitamin D may be of importance in adult asthma [105,154], the association of vitamin D deficiency with severity of asthma is reported to be particularly strong in children [63] – however this observation is not consistent [88]. Nevertheless, available cross-sectional data from 36 studies, involving 386,584 subjects suggest that low 25(OH)D is associated with poor control, increased exacerbation, reduced lung function and, increased medication usage in asthmatics (Table 3).

These cross-sectional studies suffer from many of the same limitations as case-control studies. In particular, assessments were conducted simultaneously and typically only at a single time point only. Further, the widespread nature of VDD and VDI prevents the assessment of high 25(OH)D on asthma parameters. Similar to case-control studies, the results of cross-sectional reports must be interpreted with caution. Ultimately, these observational studies provide associations between vitamin D and asthma but can not determine cause or effect and hence are only a step in understanding relationships between vitamin D and respiratory outcomes.

3.1.5. Prospective studies of vitamin D status and asthma outcomes

In contrast to case-control and cross-sectional studies, prospective studies follow subjects who are similar but differ with respect to certain factors. These factors can be studied to determine how they affect certain outcomes. There are 7 post-natal prospective studies regarding asthma, involving a total of 14,041 subjects followed for 1–31 years (Table 4).

Compared to observational studies, prospective cohort studies are superior regarding assessment of sequence between exposure and outcome. However, the longitudinal design of these studies means there is a lag between assessment of exposure and assessment of outcome. Because many factors influence both asthma pathogenesis and 25(OH)D levels and because 25(OH)D levels ae known to fluctuate over time, prospective studies too are limited in this context. Therefore interventional trials are best suited to study the effects of vitamin D and asthmatic disease.

3.1.6. Interventional data of vitamin D in asthma

Case-control, cross-sectional and prospective studies designs are interesting and provide insights into any potential relationship between vitamin D and asthma outcomes. However, intervention data, particularly from randomized, controlled trials designed to specifically assess the impact of vitamin D on asthma parameters provide far more robust information. There are 17 published trials of vitamin D supplementation in asthma involving 1578 asthmatics with varying doses and preparations of vitamin D followed for 4–52 weeks (Table 5).

The idea that vitamin D therapy could be therapeutic in asthma and allergic disease dates back to the early 20th century. Vitamin D was only discovered around this time. This led to a successful treatment of rickets and interest in other conditions, including asthma and allergy. Viosterol (which contained ergosterol, the precursor to ergocalciferol – vitamin D_2) was the vehicle of choice for these early investigations into asthma.

An early pilot study involving a heterogenous group of 11 subjects with either non-atopic asthma (n = 3), chronic uriticaria (n = 2) or ragweed allergy + asthma (n = 6) treated with very large doses of viosterol (up to 1,380,000 IU bi-weekly for weeks to months) reported variable results in *the Journal of the American Medical Association* in 1933. In this pilot study, non-atopic asthmatics and subjects with uriticaria showed little improvement while subjects with ragweed allergy showed varying but obvious improvements [137].

These observations led the same investigators to conduct a subsequent larger study focusing on 212 patients specifically with asthmatic allergic to ragweed. The treatments were high dose viosterol (120,000–300,000 IU/day, n = 68) or high dose viosterol and pollen injection (n = 144). In the viosterol only group, 82.4% experienced definite significant relief. In the viosterol + pollen group, 96.5% had comparable degrees of relief. The authors wrote that: '92% of the entire series were definitely and significantly relieved'. Interestingly, despite the massive doses of vitamin D_2 utilized, hypercalcemia was not evident [136].

These early American studies were followed up by some publications in small European journals in the mid 20th century [28,85]. In 1976, a German group reported a double-blind, crossover trial of oral calcium + vitamin D_2 (undescribed doses) on 12 patients with allergic bronchial asthma and airway obstruction. Within 60 min of application, a statistically significant reduction of airway resistance and intrathoracic gas volume, as well as an increase of FEV_1 and forced inspiratory volume in 1 s (FIV_1) was observed compared to placebo. It was concluded that calcium, given orally in combination with vitamin D_2, causes a decrease of airway obstruction in patients with allergic bronchial asthma [161].

These early trials are limited by the large doses of vitamin D used, use of vitamin D_2 as opposed to vitamin D_3, sub-optimal trial design and missing details. Nevertheless and despite the inconsistent beneficial effects observed from these early trials, interest in the therapeutic potential of vitamin D in asthma seemed to decrease and the next asthma specific intervention trial, following multiple reports correlating vitamin D with worse asthma outcomes in human, animal and cell models, was not performed until 2009.

Before these vitamin D intervention trial, reports appeared suggesting an increased risk of atopy with peanut oil + vitamins A and D. The first report of potentially increased risk of atopy with

Table 3
Cross sectional studies of vitamin D status and asthma.

Population	Age (years)	Location	Latitude	Main findings	Reference
18,224 adults.	Not reported	USA wide	28–48° N	25(OH)D was not correlated with allergic sensitization. Risk of AR increased across quartiles of 25(OH)D.	[181]
100 subjects with low 25(OH)D (<25 nmol/L) & 190 VDS subjects attending a weight management centre.	10–73	Massachusetts, USA	41° N	The mean BMI was 44.8 kg/m^2 25(OH)D was not correlated with prevalence of asthma or AR. Low 25(OH)D was correlated with increased AD compared to VDS.	[132]
616 asthmatic children.	6–14	Costa Rica (city not specified)	~10° N	25(OH)D levels were inversely correlated with total IgE, eosinophil count and hospitalization for asthma in the past year.	[23]
7288 adults.	45	UK wide	51–58° N	Non-linear correlation between 25(OH)D & serum IgE, where both low and high 25(OH)D were correlated with elevated IgE.	[83]
1024 asthmatic children.	7–11	USA wide	28–48° N	Lower 25(OH)D levels were correlated with increased ED visits and hospitalizations for asthma.	[24]
100 asthmatic children.	4–10	Denver, USA	40° N	25(OH)D levels were inversely correlated with total IgE, number of positive aeroallergen skin tests and steroid usage but positively correlated with FEV_1 and FEV_1/FVC.	[146]
54 asthmatic adults.	2–49	Denver, USA	40° N	25(OH)D level was inversely correlated with total IgE, number of positive aeroallegen skin tests and use of steroids but positively correlated with FEV_1 and FEV_1/FVC.	[154]
75 asthmatic children.	5–11	Verona, Italy	45° N	25(OH)D correlated positively with FEV_1, FVC and ACT score.	[35,36]
Prospective study of 436 children, with 25(OH)D measured at 2y and supplement usage assessed at age 1, 2 and 6–7 years.	6–7	Maastricht, The Netherlands	51° N	25(OH)D levels and vitamin D supplement use in childhood were not correlated with lung function	[42]
483 asthmatic children.	<15	Doha, State of Qatar	25° N	Lower 25(OH)D was correlated with more allergic disease and elevated serum IgE.	[53]
4979 adults.	>20	USA wide	28–48° N	25(OH)D < 25 nmol/L was positively correlated with prevalence of allergies after adjusting for age, gender, race, smoking, alcohol, and educational status.	[58]
6857 adults & children.	>6	USA wide	28–48° N	25(OH)D level was inversely correlated with both current wheeze and asthma in adjusted analysis. Among those with asthma, lower 25(OH)D was correlated with increased odds of both ED visits and exacerbation in the past year.	[88]
21 subjects with asthma and 23 subjects with AD, or AR and atopic sensitization.	Not reported	Minnesota, USA	46° N	Positive correlation between serum 25(OH)D and positive pneumococcal antibody levels in asthmatic subjects An inverse correlation was observed in non-asthmatic patients.	[103]
435 adults.	>18	Beijing, China	39° N	89% were VDD. After adjustment for confounders, 25(OH)D was positively correlated with FEV_1, % FEV_1, and FEV_1/FVC. No correlation between 25(OH)D and IgE.	[105]
372 4 year olds and 328 8 year olds from the Prevention and Incidence of Asthma and Mite Allergy birth cohort study.	4 and 8	Wageningen, Holland	51° N	25(OH)D level at age 4 was inversely with asthma at age 4-8 but 25(OH)D level at age 8 was positively correlation with asthma.	[164]
22 moderate/severe asthmatics.	18–75	London, England	52° N	25(OH)D levels correlated strongly with CD4(+) Foxp3(+) T-cell numbers.	[31]
16 atopic individuals (9 with asthma).	18–44	Baltimore, USA	39° N	25(OH)D and 1,25 were low in the airways. After allergen challenge, 25(OH)D, 1,25D & LL-37 were increased in BALF compared to saline and correlated with each other. The increase in 25(OH)D and 1,25D correlated with the magnitude of inflammation and increases in LL-37.	[108]
994 participants (asthma prevalence was 5.4%)	≥65	South Korea (city not specified)	~36° N	With multivariate logistic regression, asthma risk increased in proportion to an increased BMI or abdominal subcutaneous adiposity. However, no correlation was found with visceral adiposity, serum adiponectin levels, or 25(OH)D levels	[150]
1024 asthmatic children	7–11	USA wide	28–48° N	VDD was correlated with decreased lung function (prebronchodilator FEV_1) compared to children with VDI or VDS.	[182]
Asthmatic out-patients (number of subjects not specified)	Not reported	San Juan, Puerto Rico	18° N	80% were VDD. 25(OH)D correlated positively with ACT score but negatively with PEFR.	[188]

(*continued on next page*)

Table 3 (*continued*)

Population	Age (years)	Location	Latitude	Main findings	Reference
121 predominantly African-American urban, preschool asthmatic children.	2–6	Baltimore, USA	38° N	23% were VDD, 31% were VDI. There was a modest, statistically significant inverse correlation between 25(OH)D levels and total IgE.	[21]
15,212 individuals.	>19	South Korea (city not specified)	~36° N	After adjusting for potential confounders, 25(OH)D levels were significantly lower in AD than in those without this diagnosis. Compared with VDI, VDD increased the odds of AD. There was no relationship between 25(OH)D and asthma, allergic rhinitis, or IgE sensitization.	[34]
Secondary analyses of 2 cohorts: 6,487 children from NHANES & 226 asthmatic children enrolled in study of asthma control.	12–20	USA wide	28–48° N	25(OH)D level showed either no relation or minor contradictory correlations with asthma severity, treatment requirements, spirometry and atopy/inflammation. 25(OH)D did not differ between asthmatics and non-asthmatics	[61]
1,115 children.	9–10	Toyama, Japan	37° N	60% were VDI. After adjustment for confounders, no relationship between 25(OH)D and asthma, rhinoconjunctivitis, or eczema.	[84]
280 adult asthmatics.	45.0 ± 13.8	Mainz, Germany	50° N	67% were VDD. 25(OH)D levels were related to asthma severity and control. The frequency of VDI or VDD was significantly higher in patients with severe or uncontrolled asthma and was correlated with a lower FEV_1, higher eNO and higher BMI.	[94]
125 asthmatic children.	6–18	Bangkok, Thailand	13° N	VDD was present in 31, 17 and 13% of children with uncontrolled, partly controlled and controlled asthma. However, there was no significant difference in pulmonary function, asthma exacerbation, ICS dose, anti-inflammatory drugs, or ED visit or hospitalization between different vitamin D statuses.	[96]
121 asthmatic adults.	48 ± 16	Costa Rica (city not specified)	~10° N	VDI was correlated with a higher risk of severe asthma. High 25(OH)D levels were inversely correlated with risk of hospitalization or ED visit during the last year. Although there appeared to be a direct relationship between 25(OH)D and FEV_1, it did not reach statistical significance. No relationship between 25(OH)D levels and some allergy markers.	[122]
2478 non-asthmatic, older adults.	≥55	Singapore	1° N	Adjusted multiple regression models dietary fish intake at least thrice weekly was correlated with FEV_1. No significant as with vitamin D supplements was observed.	[127]
1833 children (rates of asthma, allergic rhinitis and wheezing were 38.5%, 34.8% and 35.7%)	<16	Doha, Qatar	25° N	VDD prevalence was significantly higher in children with wheezing, AR, and asthma than in healthy children. VDD was a significant correlate for asthma, AR and wheezing.	[14]
1134 asthmatic children.	14.8	Lima and Tumbes, Peru	3.6–12° S	In stratified analyses of multivariable logistic regression, the correlation between lower 25(OH)D and asthma was limited to children with atopy. No correlations between 25(OH)D and eNO, total serum IgE and pulmonary function.	[32]
308,000 adults. 6.9% (n = 21,237), had physician diagnosed asthma.	22–50	Tel Aviv, Israel	32° N	No correlation between 25(OH)D and asthma incidence. VDD was correlated with a 25% greater risk of asthma exacerbation compared to VDS independent of BMI and smoking.	[40]
32 asthmatic patients during severe exacerbation	47.5 ± 15	Sichuan, China	30° N	Compared to VDS, VDD was correlated with lower FEV_1 and SOD, increased ROS release, increased DNA damage, increased TNF-α, OGG1 and NFκB expression and NFκB phosphorylation.	[100]
760 adults with self reported asthma	19–55	Trondheim, Norway	63° N	44% were VDD but VDD was was not correlated with airway obstruction except in asthmatic men without allergic rhinitis.	[102]
1213 children.	6–12	Canada wide	50–70° N	Children with either VDD & VDS were more likely to report current wheeze and ever asthma in comparison to VDI. The rate of increase in % predicted FEV_1 & FVC with age was greatest in the VDI group.	[128]
92 adult asthmatics.	24–85	New Mexico, USA	31° N	VDS was significantly correlated with decreased total and severe asthma exacerbations, and ER visits.	[142]
2815 children	10	Germany (4 separate cities)	48–51° N	There was no association between 25(OH)D and either asthma or AR.	[169]

Table 3 (*continued*)

Population	Age (years)	Location	Latitude	Main findings	Reference
1315 children.	5–18	Taoyuan, Taiwan	25° N	51% and 90.3% were VDD and VDI. After adjusting for potential confounders. Serum 25(OH)D was not correlated with asthma, rhinitis, eczema, atopy, or total serum IgE.	[184,185]

Abbreviations: 25(OH)D = 25-hydroxyvitamin D; ACT = asthma control test; AD = atopic dermatitis; AR = allergic rhinitis; ASM = airway smooth muscle; BALF = bronchoalveolar lavage fluid; DBRCT = double-blind, randomized, controlled trial; ED = emergency department; ED = emergency department; eNO = exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; ICS = inhaled corticosteroid; IgE = Immunoglobulin E; LL-37 = the C-terminal part cathelicidn; OCS = oral corticosteroid; OGG-1 = 8-Oxoguanine-DNA glycosylase; PEFR = peak expiratory flow rate; ROS = reactive oxygen species; SOD = superoxide dismutases; SR = steroid resistant; VDD = vitamin D deficiency; VDI = vitamin D insufficiency; VDS = vitamin D sufficiency.

vitamin D supplementation came in 1993. Peanut oil used for the pharmacological preparation of vitamin D to prevent peanut sensitization was associated with a markedly increased risk of sensitization to allergen (OR = 9.0; p < 0:003) compared to the supplement without allergen [44]. Later trials of supplementation with vitamins A and D dissolved in peanut oil and particularly when dissolved in water demonstrated increased adverse allergic outcomes, including asthma [45,97,98]. The preparations used contained a combination of peanut oil as well as vitamins A and D, and therefore it is difficult to speculate on the individual contributions.

Since a call to action for vitamin D intervention trials in asthma in 2009 [47], several small trials have been published:

Majak et al. conducted a double-blind, randomized, placebo-controlled trial (DBRCT) to assess specific immunotherapy (SIT) in combination with ICS (prednisone 20 mg daily) + either placebo or vitamin D_3 (1000 IU/week). This was a one-year trial at high latitude (51° N) and enrolled 54 asthmatic children allergic to house dust mites on SIT. Early administration of ICS prevented the benefits of SIT. However, the addition of low dose vitamin D_3 (equivalent to 143 IU/day) preserved the benefits of SIT, despite concomitant ICS use. Indeed, all negative clinical- and immunological-effects of prednisone were prevented by administration of low dose vitamin D_3 [111]. For more detail on the potential of vitamin D as an adjunct to anti-inflammatory therapy in asthma, see section 3.2.6 in part-one of this review.

Urashima et al. conducted a DBRCT to assess the effectiveness of vitamin D_3 (2000 IU/d) vs. placebo in reducing influenza A incidence in 334 Japanese school children. This four-month study included physician diagnosed asthma exacerbations as a secondary outcome. Although an 83% reduction in asthma attacks with vitamin D was observed (RR: 0.17; 95% CI: 0.04, 0.73; p = 0.006),

Table 4
Prospective studies of post-natal cohorts of vitamin D and asthma.

Population	Age (years)	Location	Latitude	Main findings	Reference
5007 subjects born in 1966 assessed at age 31.	31	Finland wide	60–70° N	Atopy, allergic rhinitis and asthma prevalence at age 31 was higher in participants who had received regular vitamin D supplementation during the first year of life, even after adjusting for multiple behavioral and social factors.	[82]
123 neonates followed for 6y. All children were prescribed supplements containing 1000 IU vitamin A and 400 IU vitamin D_3 daily from 6 weeks to 24 months of age.	Neonates	Umeå, Sweden	64° N	High self reported vitamin D intake during their first 10 months was significantly positively correlated with atopic dermatitis and non-significantly correlated with allergic rhinitis and atopic asthma compared to low self reported vitamin D intake.	[8]
Longitudinal study of 989 subjects at age 6; 1380 at age 14; 689 with data at both ages.	6 and 14	Perth, Australia	32° S	25(OH)D level was inversely correlated with asthma and atopy at both age 6 and 14. 25(OH) D level at age 6y was inversely correlated with asthma, rhinoconjunctivitis and atopy development at age 14.	[77]
Prospective study of >2259 children (4% wheezers, 14% asthma, 8% flexural dermatitis). Mean follow up was 5.7y.	9.8 and 15.5	Bristol, United Kingdom	51° N	$25(OH)D_2$ was inversely correlated with flexural dermatitis and wheezing. 25(OH) D_3 was positively correlated with flexural dermatitis and wheezing. $25(OH)D_2$ was weakly positively correlated with FEV_1, and FVC but $25(OH)D_3$ was not correlated with lung function.	[157]
Post hoc analysis of an RCT comparing daily low-dose budesonide to intermittent high-dose budesonide in 120 children with severe intermittent wheezing (71% had diagnosed asthma) participating in a 1-year multicenter DB RCT.	1–4.5	USA wide	28–48°N	VDD was correlated with non-white ethnicity and tobacco exposure. 25(OH)D level at randomization was not correlated with the rate of exacerbations requiring OCS therapy over the 1-year trial. However, VDD participants had a significantly higher mean rate of exacerbations requiring OCS compared with non-VDD participants.	[13]
Prospective study of 3727 adults followed for 10y.	30–60	Copenhagen, Denmark	57° N	No correlation of 25(OH)D with atopy or asthma. Low 25(OH)D was correlation with lower % predicted FEV_1. Correlation between high baseline 25(OH)D and adverse changes in lung function.	[156]

Abbreviations: 25(OH)D = 25-hydroxyvitamin D; DB = double-blind; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; OCS = oral corticosteroid; RCT = randomized, controlled trial; VDD = vitamin D deficiency.

Table 5
Vitamin D intervention studies in asthma.

Design	Duration (weeks)	Population	Dose	Age	Location	Latitude	Main findings	Reference
Pilot study	Varied: weeks to months	3 non-atopic asthmatic, 2 subjects with chronic uriticaria and 6 subjects with ragweed allergy + asthma	Up to 1,380,000 IU vitamin n D_2 bi-weekly	Not specified	USA	Not specified	Non-atopic asthmatics and subjects with uriticaria showed little improvement while subjects with ragweed allergy showed varying but obvious improvements	[137]
Pilot study	Varied: weeks to months	212 patients with ragweed allergy + asthma	vitamin D_2 (120,000-300,000 IU/day) ± pollen injection.	Not specified	USA	Not specified	In the viosterol only group, 82.4% improved, while. 96.5% in the viosterol + pollen group improved	[136]
Acute, crossover DBRCT	Acute administration	12 patients with allergic bronchial asthma	oral calcium + vitamin D_2	Not specified	Germany	Not specified	Within 60 min of application, a statistically significant reduction of airway resistance and intrathoracic gas volume, as well as an increase of FEV_1 and forced inspiratory volume in 1 s (FIV_1) was observed compared to placebo	[161]
3 arm DBRCT to assess the effectiveness of SIT + steroid vs. SIT, steroid + vitamin D_3 vs. SIT, steroid + placebo	52	54 asthmatic children allergic to house dust mites on SIT.	1000 IU vitamin D_3/week	6–12	Lodz, Poland	52° N	ICS prevented the clinical and immunological benefits of SIT. The addition of vitamin D preserved the benefits of SIT, despite concomitant ICS use	[111]
DBRCT to assess the effectiveness of vitamin D in reducing influenza A incidence	16	334 Japanese school children	2000 IU vitamin D_3/d	8–12	Japan wide	34–45° N	42% reduction in influenza A in vitamin D group compared to placebo. In asthmatics, this was associated with an 83% in asthma attacks	[160]
DBRCT ICS + vitamin D_3 vs. ICS + placebo	26	48 children with newly diagnosed asthma	500 IU vitamin D_3/d	5–18	Lodz, Poland	52° N	Significantly lower risk of asthma exacerbation in the vitamin D group. No difference in serum 25(OH)D and ATAQ scores	[112]
DBRCT to examine whether increased 25(OH)D levels either through seasonal variations or supplementation affect asthma	52	20 children with chronic persistent asthma	1000 IU vitamin D_3/d	6–17	Creighton, USA	42° N	At baseline, 95% were VDI. Vitamin D supplementation did not affect ACT score or FEV_1. However, children were well controlled at baseline. Pooled data on all 25(OH)D measurements and corresponding ACT scores revealed a significant positive correlation	[104]
DBRCT standard treatment + vitamin D or placebo	26	100 childhood asthmatics	60,000 IU vitamin D_3 /month	Not specified	New Delhi, India	28° N	Significantly lower risk of asthma exacerbation, steroid requirement and ED visits in the vitamin D group accompanied by significantly increased PEFR	[183]
ICS or ICS plus LABA + vitamin D or placebo	24	130 asthmatics.	100,00 IU bolus IM plus 50,000 IU orally weekly	10–50	Tehran, Iran	36° N	% FEV_1 improved in both groups but to a significantly greater degree in the vitamin D group at 24 weeks	[6]
3 arm RCT of SCIT alone vs. SCIT + vitamin D vs. pharmacotherapy alone	52	50 childhood asthmatics sensitized to house dust mite	650 IU vitamin D_3/day	5–15	Istanbul, Turkey.	41° N	Asthma symptoms were lower in both SCIT groups compared to pharmacotherapy alone. However the vitamin D supplemented group had greater improvements	[12]
DBRCT of mild asthmatics currently not receiving anti-inflammatory therapy and with VDD/VDI	6	39 children	14,000 IU/week	6–18	Haifa, Israel	33° N	No change in IgE, eosinophil count, hs-CRP, FeNO levels, PC_{20}- FEV_1 or exhaled breath condensate cytokines (IL-4, IL-5, IL-10, IL-17, and IFN-γ) between the groups	[11]

DBRCT of ICS + vitamin D or ICS placebo	28	408 adults with symptomatic asthma and VDI	100,000 IU vitamin D_3 followed by 4000 IU/day	40 ± 13	USA wide	28–48° N	Vitamin D supplementation had no significant effect on the overall rate of first treatment failure or exacerbation. Significant reductions in exacerbations and the rate of first treatment failure in the 82% subjects who reached VDS	[30]
Unblinded, uncontrolled pilot	12	28 elderly asthmatics	2000 IU vitamin D_3/day	>65y	Philadelphia, USA	40° N	Mean 25(OH)D increased by 24 nmol/L. There was no correlation between 25(OH)D and ICS dose. Vitamin D was significantly lower in subjects with uncontrolled asthma. In uncontrolled asthma, ACT scores increased significantly at the end of the study but spirometry did not change	[39]
Randomly divided into vitamin D supplementation or no supplementation	Day 1 and 4 post exacerbation.	16 VDD asthmatic patients with severe asthma exacerbation were treated with 80 mg/day of methylprednisolone for 7 days.	7.5 mg vitamin of D_3 IM.	45 ± 15	Sichuan, China.	30° N	Supplemental vitamin D_3 significantly increased the rate of %FEV_1 improvement and decreased airway epithelial ROS as well as DNA damage	[100]
Open label, randomized trial of usual care vs. usual care + vitamin D	14	48 mild to moderate persistent adult asthmatics	?	Not specified	Porur, India.	13° N	% FEV_1 improved in both groups, but to a greater extent in the vitamin D group	[125]
Proof-of-concept DBRCT of 1,25 as adjunct to prednisolone	4	24 severe SR asthmatics	0.25 μg1,25D twice daily	Not specified	London, England	52° N	No significant difference in % FEV_1 between 1,25 and placebo. Within group comparison of OCS +1,25 or placebo revealed a modest but significant improvement in absolute and predicted FEV_1 with 1,25D. There was a trend for a positive correlation between baseline 25(OH)D and change in predicted lung function following OCS. Following prednisolone, there was a greater improvement in % FEV_1in VDS compared to VDI.	[126]
DBRCT	9	44 patients with nonatopic asthma with neutrophilic and/or eosinophilic airway inflammation.	400,000 IU vitamin D_3 bolus	Not specified	Leeuwarden, The Netherlands	52° N	Vitamin D did not significantly affect sputum neutrophils or eosinophils compared with placebo. However, sub group analysis of subjects with airway eosinophilia revealed that eosinophils significantly decreased by 30% after vitamin D compared with a 12% increase in the placebo group. Vitamin D treatment also resulted in slightly better ACQ scores	[43]

Abbreviations; ACQ = asthma control questionnaire; ACT = asthma control test; ATAQ = asthma therapy assessment questionnaire; DB = double-blind; ED = emergency department; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 s; hs-CRP = high sensitivity C reactive protein; ICS = inhaled corticosteroid; IFN-γ = gamma interferon. IgE = immunoglobulin E; IL = interleukin; IU = international unit; LABA = long-acting β-agonist; OCS = oral corticosteroid; PC_{20}- FEV_1 = provocation dose of methacholine require to induce a 20% drop in FEV_1; PEFR = peak expiratory flow rate; RCT = randomized, placebo controlled trial; SCIT = subcutaneous immunotherapy; SIT = specific immunotherapy; VDI = vitamin D insufficiency; VDS = vitamin D sufficiency; VDS = vitamin D sufficiency.

only 26% (n = 110) of the sample had physician diagnosed asthma. Additionally there was no assessment of 25(OH)D status or asthma severity at any stage [160].

Following up on their preliminary work, Majak et al. conducted a small, DBRCT of ICS vs. ICS + vitamin D (500 IU/d). This was a 6 month trial conducted at high latitude (51° N) and enrolled 48 children with newly diagnosed asthma. There was a significant increase in asthma exacerbations in the placebo group (OR, 8.6; 95% CI, 2.1–34.6). However, the difference in serum 25(OH)D and asthma therapy assessment questionnaire (ATAQ) scores between the intervention and placebo group was very small and neither reached statistical significance [112].

Retrospective, secondary analysis of pooled data obtained from previously published DBRCTs on 36 asthmatic children undergoing allergen immunotherapy revealed that higher serum 25(OH)D was associated with a more significant reduction in asthma symptoms and steroid use as well as higher TGF-α production and Foxp3 induction [113].

Lewis et al. conducted a 1 year DBRCT to examine whether increased 25(OH)D levels – either through seasonal variation or supplementation - could affect asthma. In this one year study of 20 children with chronic persistent asthma, half were given 1000 IU vitamin D_3/d while the other half were given placebo and seasonal variation in 25(OH)D was observed. 19 of the 20 enrolled children were VDI at baseline. Although, vitamin D supplementation did not affect ACT score or FEV_1, all children were well controlled at baseline. Further, pooled data on all 25(OH)D measurements and corresponding ACT scores revealed a significant positive correlation ($r = 0.25$, $p < 0.05$) [104].

Yadav & Mittal conducted a DBRCT to assess the effectiveness of vitamin D_3 (60,000 IU/month) vs. placebo in improving asthma parameters. Compared to the placebo group, the vitamin D group experienced reduced exacerbations ($p = 0.011$) and steroid requirements ($p = 0.013$) and increased expiratory flow rate, however there was no report of 25(OH)D levels. The authors concluded: 'Vitamin D has a definite role in the management of moderate to severe persistent bronchial asthma as an adjunct to standard treatment' [183].

Arshi et al. conducted a 3 arm randomized trial of ICS vs. ICS plus long-acting β-agonist (LABA) + vitamin D_3 vs. ICS plus LABA + placebo. This 24 week trial included asthmatics aged 10–50y and the vitamin D dose was 100,00 IU bolus intramuscularly (IM) plus 50,000 IU orally weekly. Although, percentage predicted FEV_1 improved in both groups, the improvement was significantly greater in the vitamin D group at 24 weeks ($p < 0.001$) [6].

Baris et al. conducted a 3 arm, randomized trial of subcutaneous immunotherapy (SCIT) alone (n = 15), or with vitamin D_3 supplementation (650 IU/day; n = 17), or pharmacotherapy alone (n = 18). Although both SCIT groups fared better than pharmacotherapy alone at the end of 1 year, some favorable outcomes in the vitamin D group were noted including better asthma controls as indicated by corticosteroid treatment discontinuation in a greater percentage of patients ($p = 0.02$) [12].

Bar Yoseph et al. conducted a DBRCT of vitamin D supplementation (14,000 IU/week) vs. placebo for 6 weeks in asthmatic children. There was no change in IgE, eosinophil count, high sensitivity C reactive protein, fraction of exhaled nitric oxide levels or provocation dose of methacholine require to induce a 20% drop in FEV_1 between he vitamin D or placebo groups. Exhaled breath condensate cytokines, including IL4, IL5, IL10, IL17, and interferon gamma changed in both groups but there was no difference [11].

Castro et al. reported findings from the large Vitamin D Add-on Therapy Enhances Corticosteroid Responsiveness in Asthma (VIDA). Compared to placebo, a baseline 100,000 IU vitamin D_3 bolus followed by 4000 IU daily for 28 weeks had no significant effect on the overall rate of first treatment failure or exacerbation in patients with asthma and VDI. However, at 28 weeks, there was a significant difference in cumulative ciclesonide (a glucocorticoid) dosing between the vitamin D and placebo groups (111.3 vs. 126.2 μg/day; $p = 0.02$). Additionally, in the 82% of the vitamin D supplementation group who reached VDS, there were significant reductions in exacerbations and the rate of first treatment failure [30]. Due to the baseline bolus dose and the moderate-high daily dose, it was surprising that 18% of the vitamin D group did not reach VDS, which may have affected the results. This may be due to the obese nature of the cohort (mean BMI = 32 kg/m^2) or malabsorption, metabolism, or compliance issues with vitamin D.

Columbo et al. conducted an unblinded, uncontrolled pilot study to assess the potential effect of vitamin D in elderly asthmatics. This 12 week study included 28 elderly asthmatics (>65y) adjunctly treated with 2000 IU vitamin D_3 daily. There was no association between 25(OH)D and ICS dose or spirometric values. However, 25OH)D was significantly lower in subjects with uncontrolled asthma and in uncontrolled asthma, ACT scores increased significantly at the end of the study ($p < 0.04$).

Lan et al. conducted an unblinded pilot study to assess the acute effects of 80 mg/day of methylprednisolone alone vs. combined with 7.5 mg intramuscular vitamin D_3 injection in vitamin D deficient adults (in this study: <75 nmol/L) with severe asthma exacerbation. Vitamin D_3 injections were given on day 1 and day 4. The supplemental vitamin D_3 significantly increased the rate of $\%FEV_1$ improvement and decreased reactive oxygen species as well as DNA damage compared to monotherapy with methylprednisolone [100].

Nageswari et al. conducted an open labeled, RCT of usual care (budesonide and formoterol) vs. usual care + vitamin D_3 (1000 IU/day). Although this trial was short (90 days) and included a small cohort (n = 48), an increase in % predicted FEV_1 was observed in the usual care + vitamin D group compared to the usual care only group [125].

Nanzer et al. conducted a proof-of-concept DBRCT of 1,25D as adjunct to prednisolone in 24 severe SR asthmatics. 0.25 μg 1,25D was administered twice daily to the 1,25D group (n = 13). Although there was no significant difference in $\%FEV_1$, a within-group comparison showing the change in lung function during the initial screening in response to 2-week oral prednisolone vs. the response to an identical course of prednisolone plus either placebo or 1,25D revealed a modest but significant improvement in absolute and predicted FEV_1 with 1,25D compared to placebo ($p = 0.03$). There was no observed benefit in patients randomized to receive 1,25D before the second course of prednisolone, suggesting that 1,25D alone had no effect on lung function. A trend for a positive correlation between baseline 25(OH)D and change in predicted lung function following prednisolone ($r = 0.56$, $p = 0.08$) was observed. Additionally, following prednisolone, there was a greater improvement in % FEV_1 in VDS compared to VDI subjects ($p = 0.03$) [126].

de Groot et al. conducted a DBRCT comparing a large bolus of vitamin D_3 (400,000 IU) to placebo. On a group level, there was no significantly effect on sputum neutrophils or eosinophils with vitamin D or placebo. However, subgroup analysis of subjects with airway eosinophilia at baseline revealed that vitamin D significantly decreased sputum eosinophils from a median of 41%–11.8% compared to an increase from 51.8% to 63.3% in patients receiving placebo ($p = 0.034$). Vitamin D treatment also resulted in slightly better Asthma Control Questionnaire scores ($p = 0.08$) [43].

Although some of these interventional trials suggest a benefit of vitamin D repletion, they are limited by small sample sizes, short duration and potentially inadequate vitamin D dose. Nevertheless, a recent systematic review and meta-analysis in paediatric asthmatics noted a statistically significant reduction in asthma

exacerbation with vitamin D supplementation (RR 0.41, CI 0.27–0.63) [134]. However, the need for adequately powered trials utilizing adequate vitamin D dosing persists.

3.2. Why is data from human studies inconsistent?

The majority of existing epidemiologic and observational data suggest that vitamin D intake and/or status may be of importance in asthmatic disease. However, not all studies are in agreement with some studies demonstrating no benefit from increased vitamin D intake and/or status, while other reports suggest inferior asthmatic outcomes associated with higher vitamin D. Vitamin D represents a unique nutrient with many complexities. Although some studies directly measure vitamin D status, other studies record vitamin D intake through food frequency questionnaires, which can be a poor predictor of both vitamin D intake and 25(OH)D status. Unlike other nutrients, the major source of vitamin D for most people is not through diet, but from exposure to UV-B. Therefore vitamin D status displays marked variation depending on local weather conditions and individual sun behaviors e.g. sunscreen use, time indoors etc. Most studies assess sun habits and vitamin D status or intake at a single time point only. Human behavior and season are variables, which change often and can influence both asthma and vitamin D outcomes. Therefore epidemiologic and observational studies are limited regarding asthma and vitamin D.

Well designed, long term prospective and interventional studies regarding vitamin D and asthmatic disease can provide more robust evidence. To date there is a lack of these studies in asthma (reviewed in Tables 4 and 5 respectively). However, again the results of existing prospective studies are conflicting. These prospective studies have relied on a single measurement of vitamin D status or intake with asthmatic outcomes assessed up to 31 years later. Despite efforts to control for relevant, non-vitamin D confounders, it is impossible to discount variables other than vitamin D contributing to the observations. Similarly, vitamin D intervention studies to date provide inconsistent results. There have been 17 vitamin D intervention trials in asthma to date (Table 5). These intervention trials differed in terms of trial design, vitamin D dosing, outcome measures and trial duration, which may help explain the inconsistencies.

4. Conclusions

4.1. What is the optimal vitamin D intakes and serum 25(OH) level for asthma?

The recommendations for optimal vitamin D intake and serum 25(OH)D levels are controversial. The 2010 IOM report suggests a recommended daily allowance of 600 IU for healthy subjects aged >1y and a target serum 25(OH)D of >50 nmol/L [139]. However this report was based almost exclusively on skeletal considerations and has been criticized by experts in the vitamin D field [69,167]. Some reports observed a plateau effect of serum 25(OH)D at 50 nmol/L regarding exacerbations in asthmatics [13]. However, others suggest a serum 25(OH)D level >100 nmol/L may be required for optimal immunological and respiratory outcomes [17,76,78,79,166]. Conversely, both high and low 25(OH)D levels have been associated with adverse outcomes in terms of increased aeroallergen sensitization [140], elevated IgE levels [83], and adverse changes in lung function [156] raising the possibility that an optimal level of 25(OH)D exists regarding asthma and that levels above or below are detrimental.

It has been argued that in populations with limited sun exposure that the current vitamin D recommendations are inadequate for non-skeletal effects, and that intakes ≥2000 IU/day may be required [74,76]. For example, a 500 IU supplement of vitamin D_3 daily for 6 months was insufficient to increase serum 25(OH)D in asthmatic children at 51° N [113]. In asthmatic children treated with 1000 IU for 12 months only 50% reached vitamin D sufficiency defined as >75 nmol/L [104]. Indeed, the Endocrine Society recommended vitamin D supplements of up to 4000 IU/day for adults [76].

UV-B is the major source of vitamin D for most people, even at high latitude [74] but with lifestyle changes and concerns about sun damage, sun exposure has decreased contributing to widespread VDI. However, achievable sunlight exposure may not be sufficient for adequate 25(OH)D levels, particularly in urban and/or heavily pigmented subjects [21]. Because vitamin D is naturally found in few foods (mainly oily fish) and few food products are fortified adequately (mainly dairy and cereal products), it is difficult to achieve an adequate vitamin D status through diet al.one. Indeed, dietary intake of vitamin D is typically inadequate [18], including among asthmatic cohorts [25]. Further, a randomized controlled trial demonstrated that diet was inadequate to achieve sufficient serum 25(OH)D [41].

Although cod liver oil contains vitamin D_3, its use has been associated with increased asthma incidence [81,110,129] possibly due to its high vitamin D content [27] and therefore may not represent a suitable vehicle to increase vitamin D intake and serum 25(OH)D. Additionally, vitamin D_2 is not as effective as vitamin D_3 in maintaining serum 25(OH) levels [159].

4.2. Future recommendations

Despite, recent widespread publicity, vitamin D deficiency remains highly prevalent throughout the world [74]. Here we have presented human observational and interventional data regarding vitamin D and asthma. Despite the recent advances in our understanding of the vitamin D pathway and its potential implications for allergic and immune disorders such as asthma, many questions remain:

- Is widespread vitamin D supplementation detrimental in asthma as initially hypothesized or beneficial as mechanistic and observational work suggest?
- Has vitamin D replacement therapy a role as an adjunct to anti-inflammatory therapy or immunotherapy in asthma?
- Is the effect of vitamin D supplementation limited to a specific asthma phenotype/endotype? And if so, which one?
- When is the therapeutic age range to exploit the potential benefits of vitamin D supplementation in asthma?
- Should 25(OH)D be routinely measured in asthma?
- What is the desired serum 25(OH)D level for a potential therapeutic effect in asthma?
- What is the best strategy to achieve this desired serum 25(OH)D level?
- Does peri-natal vitamin D supplementation reduce the risk of developing asthma? The focus of the current manuscript was to review existing human evidence that vitamin D may be of importance in asthmatic disease. We have not comprehensively reviewed studies of perinatal studies of vitamin D status or intake. Existing trials in this area are inconsistent, probably owing to important differences in study design for example measuring vitamin D status versus reported vitamin D intake. Additionally vitamin D levels are known to fluctuate over time and are rapidly and significantly altered by modifiable human behaviors such as location, sun behaviors and supplement use. Therefore, the importance of a single vitamin D assessment in early childhood or pregnancy is of debatable importance

regarding future asthmatic outcomes. However manipulating 25(OH)D status holds promise for primary prevention of asthma as recent reviews suggest [121,135].

- Is ultraviolet radiation a powerful immunomodulator in asthmatic disease where 25(OHJ)D status merely reflects ultraviolet exposure? For example acute ultraviolet exposure caused systemic immunosuppression in the absence of increased 25(OH)D in mice [64] This fascinating concept cannot be discounted currently and is supported by several, recent animal studies whereby ultraviolet exposure inhibited asthmatic disease [117,118]. Relevant human evidence comes from inverse associations with diverse respiratory tract symptoms [155], RSV incidence [172,186] and risk of invasive pneumococcal disease associated with UV-B (White et al., 2009). We briefly presented human evidence suggesting a benefit of sunlight in asthmatic disease above in section 3.1.2

New therapeutic options for wheezing disorders, and particularly steroid resistant asthma are needed. Serum 25(OH)D level is a novel and modifiable potential risk marker for severe asthma exacerbations [55]. Taken together existing mechanistic and observational data support a role for vitamin D as an important factor in asthma and infection. However, results from existing clinical trials provide heterogeneous findings.

Vitamin D supplementation potentially represents a low-cost, low-risk method to treat and prevent asthma and therefore further exploration of the effect of vitamin D supplementation is encouraged. Future trials should utilize adequate doses of vitamin D_3 preparations for interventions of sufficient duration. Appropriate trial duration appears likely to be >12 months considering the half life of 25(OH)D is approximately 2–3 weeks [75] as well as the natural seasonal variation in asthma and infection. Additionally, because reported vitamin D intake and sun exposure are unreliable, 25(OH)D should be measured, preferably on more than one occasion. This will also help determine optimal 25(OH)D levels and decrease risk of vitamin D toxicity (VDT). VDT is rare and has most reports of VDT have resulted from industrial accidents [4]. Nevertheless supraphysiological 25(OH)D levels (>375 nmol/L), which are a possibility with extended use of inappropriately high doses of vitamin D (≥10,000 IU/d), can cause hypercalcemia and increased risk of falls [144].

The data reviewed herein suggest that supplementation with moderate doses (e.g. 1000 IU/d) of vitamin D_3 may be appropriate for maintenance of bone health in asthmatics, particularly steroid users. However, existing data does not yet definitively support a role for supplemental vitamin D therapy as a adjunct strategy in asthmatic disease. Despite limited evidence, an adverse effect of widespread vitamin D supplementation can not be discounted and therefore caution is advised until more definitive evidence is available.

Childhood asthma and steroid resistant asthma are key underexplored areas where vitamin D based interventions may provide benefit. Only the results of well-designed, clinical trials can elude as to effects of vitamin D therapy asthma. Indeed there has been a call to action for well-designed intervention trials of vitamin D supplementation to assess its role in preventing and treating asthma [47]. Ongoing longitudinal studies and clinical trials should help ultimately answer some of the existing questions.

Author contributions

- CK made substantial contributions to review design and manuscript collection and interpretation of data; has drafted the submitted article; has provided final approval of the version to be published; and has agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- BE revised the submitted article critically for important intellectual content; has provided final approval of the version to be published.
- JF revised the submitted article critically for important intellectual content; has provided final approval of the version to be published.
- LC revised the submitted article critically for important intellectual content; has provided final approval of the version to be published. and has agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Role of the sponsors

The sponsors were not involved in the design, analysis or reporting of the current trial.

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Guarantor statement: CK and LC guarantee the accuracy and completeness of the reported data, and for the fidelity of the study.

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