Vitamin D for secondary prevention of acute wheeze attacks in preschool and school-age children

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ABSTRACT

Introduction Vitamin D is best known for its role in bone health; however, the discovery of the vitamin D receptor and the expression of the gene encoding the vitamin D 1α-hydroxylase (CYP27B1) enzyme in a wide variety of tissues including immune cells and respiratory epithelium has led to the discovery of potential roles for vitamin D in the prevention of acute wheeze.

Methods We review here the literature concerning the relationships between circulating 25-hydroxyvitamin D (25(OH)D) concentration and secondary prevention of acute wheeze attacks in preschool and school-age children.

Results Epidemiological data suggest that vitamin D insufficiency (25(OH)D <75 nmol/L) is highly prevalent in preschool and school-age children with wheeze. Preschool age children with a history of wheeze attacks and circulating 25(OH)D <75 nmol/L are at increased risk and frequency of future acute wheeze. However, no consistent association between low vitamin D status and risk of acute wheeze is reported in school-age children. Seven randomised controlled trials (RCTs) with relatively small sample sizes (30–430) and variable quality showed inconsistent results regarding the effect of oral vitamin D supplementation during childhood on the risk of asthma attacks, asthma symptom control, inhaled corticosteroid requirements, spirometry and unscheduled healthcare attendances for wheeze. A RCT showed that vitamin D supplementation had no effect on the frequency of unplanned healthcare attendances due to acute wheeze in 22 preschool children.

Discussion An evidence-based recommendation for the use of vitamin D as a preventive therapy for wheeze attacks cannot be made until results of further trials are available. The assessment of circulating 25(OH)D concentration and the optimisation of vitamin D status to prevent acute respiratory tract infections, and to maintain skeletal and general health in preschool and school-age children with acute wheeze is worthwhile in its own right, but whether this will reduce the risk of acute wheeze attacks is unclear.

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INTRODUCTION

Asthma affects 339 million people worldwide and is the most common chronic disease of school-age children.[1] Globally, asthma is among the top 10 chronic conditions for ranking of disability-adjusted life years in children aged 5–12 years. Mortality for asthma and hospital admission rates in children varies across countries.[2] UK asthma outcomes are among the worst in Europe. In London, the mortality rate for all causes of death has been falling except the deaths from respiratory illnesses in preschool and school-age children.[3] The majority of children who died had infrequent asthma attacks which were managed within primary care.[4] Severe acute attacks of wheeze can have serious consequences, including death and impaired quality of life, and are associated with reduced lung growth trajectories.[5] Furthermore, the mean healthcare costs per patient per year are huge, varying from US$ 1900 in Europe to US$ 3100 in USA.[6] Viral respiratory infections are important triggers of acute wheeze,[7] and the efficacy of specific antiviral therapies in the prevention of acute wheeze is under investigation, but currently influenza immunisation is our only effective intervention to reduce incidence of viral respiratory illness.[8]

An increasing number of immunomodulatory effects of vitamin D have been proposed, including antiviral, and the coordinated modulation of inflammatory and anti-inflammatory responses.[9] Cord blood 25-hydroxyvitamin D (25(OH)D) has been inversely associated with early life recurrent wheeze.[10] There is some evidence for a U-shaped association between circulating 25(OH)D concentration and primary prevention of wheeze in children,[11 12] but this is not consistent across studies.[13] There is no evidence for a dose effect relationship on circulating 25(OH)D concentration and the secondary prevention of acute wheeze in children. Vitamin D is an inactive preprohormone, the generic term for ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) which is metabolised to the active form in two steps. In the liver, cholecalciferol undergoes hydroxylation at the C25 position by the cytochrome p450 enzymes CYP27A1, CYP2R1 and CYP3A4 resulting in the formation of 25(OH)D.[14] 25(OH)D is the main circulating vitamin D metabolite in humans, and is the universally accepted measure of vitamin D status. A second hydroxylation step, at the 1α position is catalysed by vitamin D 1α-hydroxylase (CYP27B1), synthesising 1,25-dihydroxyvitamin D or $1,25(OH)_2D$.[15] The optimal 25(OH)D concentration for skeletal health is controversial, and there is no consistent classification for vitamin D deficiency across national guidelines. European experts favours a threshold of 25(OH)D concentration <50 nmol/L for vitamin D deficiency with the exception of the UK experts, who suggest a 25 nmol/L threshold.[16 17] Some experts advocate a 25(OH)D concentration ≥75 nmol/L for bone health but it is still unclear if this level is optimal for antiviral immunity.[17] Furthermore, for any immune effects, tissue levels of 25(OH)D are important; these are challenging to measure, and are likely at best loosely related

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Table 1 In vitro data on the influence of vitamin D on host innate immune responses to pathogens

Effect of vitamin D	Cell type
249.6 nmol/L vitamin D reduces the thickness of the airway smooth muscle, collagen deposition and the alpha-smooth muscle actin via Wnt5a and β-catenin expression in airway smooth muscle (p<0.01)[79]	Mouse primary
10^{-7} M of 25(OH)D and $1,25(OH)_2D$ attenuates rhinovirus-induced expression of intracellular adhesion molecule–1 (3.6-fold, p=0.005) and platelet-activating factor receptor in respiratory epithelial cells (5.1-fold, p=0.001 for 25(OH)D and 4.9-fold for $1.25(OH)_2D$, p=0.001)[80]	Human A549 cell lines
100 nmol $1,25(OH)_2D$ decreases rhinovirus replication and release in bronchial epithelial cells and promotes antiviral activity by the induction of interferon stimulated genes and cathelicidin (p<0.05)[81]	Human primary
12 nM $1,25(OH)_2D$ promotes the differentiation of monocytic precursors into alveolar macrophages by 35%[82]	Mouse primary
10 nM $1,25(OH)_2D$ enhances the synthesis of granulocyte macrophage colony stimulating factor in monocytes by 4.0±0.8-fold (p<0.05)[83]	Human U937 cell lines
$1,25(OH)_2D$ decreases the production of specific surface antigens, human leucocyte antigen ((HLA)-DR, -DP and -DQ) by decreasing the synthesis of major histocompatibility complex (MHC)-II in monocytes[84]	Human primary
1 µM $1,25(OH)_2D$ reduced prostaglandin E_2 synthesis by lung fibroblasts (p<0.01)[85]	Human HFL-1 cell lines
10^{-9} M $1,25(OH)_2D$ facilitates antimicrobial function through the expression of lysosomal enzyme acid phosphatase and hydrogen peroxide in monocytes and neutrophils[86]	Human primary; Calu-3, and U937 cell lines
$1,25(OH)_2D$ increases the production of specific surface antigens by decreasing the synthesis of MHC class II molecules in monocytes.[84]	Human primary
100 nM 25(OH)D reduces dendritic cell capacity to induce proliferation of antigen specific T cells and chemotaxis (p<0.01)[87]	Human primary
10^{-7} M $1,25(OH)_2D_3$ reduces co-receptor of toll-like receptor (TLR)4 expression by 4.8±0.03-fold and upregulates cluster of differentiation (CD)14 expression in monocytes by 3.9±0.1-fold (p<0.001)[88]	Human primary
5 µM $1,25(OH)_2D_3$ inhibits the synthesis of TLR2, –4 and –9 in monocytes by 0.5-fold (p=0.02) and triggers hyporesponsiveness to pathogen-associated molecular patterns[89]	Human primary
5 µM $1,25(OH)_2D_3$ impairs TLR9-induced IL-6 production in monocytes by 0.5-fold (p<0.02)[89]	Human primary
TLR activation of human macrophages upregulates expression of the vitamin D receptor and the 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) genes in macrophages with $1,25(OH)_2D_3$ treatment at 10^{-9} to 10^{-7} M[90]	Human primary
10^{-9} to 10^{-7} M $1,25(OH)_2D_3$ suppresses the synthesis of tumour necrosis factor, interferon-inducible protein 10 (IP10) in monocytes and IL-12 in lymphocytes (p<0.05)[91 92]	Human primary and THP-1 cell lines
10^{-9} M $1,25(OH)_2D$ increases the expression of antimicrobial peptides including cathelicidin and defensin β2 in human monocytes and macrophages[86]	Human primary; Calu-3, and U937 cell lines
0.5–100 nM $1,25(OH)_2D$ negatively regulates dendritic cell maturation, differentiation and immunostimulatory capacity (p<0.05)[93]	Human primary
10 nM $1,25(OH)_2D$ suppresses the synthesis of MHC class II, CD-80 and 86 in monocytes (p<0.05)[94]	Human primary
10 nM $1,25(OH)_2D$ induces anergic T cells by immature dendritic cells. Expresses enhanced levels of forkhead box P3 (FOXP-3) by fourfold and displays T cell antigen unspecific suppressor activity (p=0.03)[95]	Human primary
1–100 nM $1,25(OH)_2D_3$ enhances the expression of inhibitor of I-Kappa-B-Alpha (IkBa) by 247%, a negative regulator for nuclear factor kappa beta (NF-kB) in monocytes (p=0.02)[96]	Human primary
1–100 nM $1,25(OH)_2D_3$ inhibits proinflammatory and anti-inflammatory responses elicited by TLR4 stimulation (by a median of 50%) in monocytes[96]	Human primary

to circulating levels. It may also be that tissue 25(OH)D levels respond only slowly to an increased oral intake of vitamin D. Circulating 25(OH)D concentration varies across countries and studies, and in a meta-analysis of 11 case-control and five cohort studies, 28.5% and 26.7% of children with asthma aged up to 18 years were vitamin D deficient (25(OH)D <50 nmol/L) and insufficient (25(OH)D between 50 and 75 nmol/L) globally.[18] There is seasonal variation in 25(OH)D concentration and biseasonal measurements are vital to determine vitamin D status.[19] This review explores the relationship between 25(OH)D concentration and secondary prevention of acute attacks of wheeze in preschool and school-age children.

Acute attacks of preschool wheeze

Acute wheezing illness in preschool children (<5 years) is heterogeneous with at least two phenotypes (viral-induced and multitrigger wheeze) which are not necessarily stable over time and with treatment.[20] Viral-induced wheeze accounts for two-thirds of all preschool wheezing whereas multitrigger wheezing is less prevalent in early life.[21] Viral-induced wheeze is defined as wheeze in discrete episodes, with the child being well in between,[20] and is triggered by (a usually clinically diagnosed) viral infection. In preschool children, viral-induced wheeze may be difficult to distinguish from bronchitis, bronchiolitis or pneumonia because of the lack of consistent definitions internationally. The factors underlying the frequency and severity of the acute episodes are not fully understood; however, atopy (especially in multitrigger wheeze), prematurity and exposure to tobacco smoke have been implicated.[22 23] Viral-induced wheeze not consistently associated with allergic sensitisation, total serum IgE levels[24] or evidence of airway eosinophilia,[25] but is associated with impaired lung function (spirometry). A study including bronchoalveolar lavage has shown that infants with non-atopic, viral-induced wheeze have predominantly neutrophilic inflammation, especially at the time of acute infection.[26]

By contrast, multitrigger wheeze more resembles school-age asthma and is strongly associated with fixed and variable airway obstruction.[27] Multitrigger wheeze is associated with atopy, a higher risk of persistent wheezing into school-age,[28] and airway eosinophilia.[29] Children with multitrigger wheeze also wheeze between respiratory infections in response to other factors, including allergens, laughing, crying, strong smells or certain foods or drinks.[20] Multitrigger wheeze is often considered as early-onset allergic asthma[30]; however, not all preschool children with multitrigger wheeze have chronic allergic (type 2) airway inflammation.[20] Multitrigger wheeze occurs more commonly at school-age.[31]

Acute attacks of wheeze in school-age children

Wheeze attacks in school-age children (≥5 years) are usually precipitated by respiratory viruses, but bacterial infections are also implicated, as are relative humidity, extreme temperatures, aeroallergens and air pollution.[32] At least 85% of childhood asthma attacks are

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associated with a viral upper respiratory tract infection, with rhinovirus accounting for 61% of the viruses detected.[33] Importantly, and unlike preschool children, most school-age children who have an asthma attack are also sensitised to indoor allergens and have background type 2 airway inflammation.[34] Rarely, a large allergen load alone (pollen/thunderstorm, soya bean) can cause an attack even in the absence of viral infection.[34] School-age children with a history of previous wheeze attacks and persistent asthma symptoms, are at increased risk of future wheeze attack, especially if they have 25(OH)D concentration <75 nmol/L.[35]

The differences between preschool wheeze attacks (no background type 2 inflammation, not abrogated by regular inhaled corticosteroids[36]) and school-age acute wheeze (uncontrolled type 2 inflammation important, attack risk reduced by inhaled corticosteroids[35]) means that effects of vitamin D should be considered separately in the two age-groups. For example, if any beneficial effects of vitamin D were mediated via abrogation of type 2 inflammation, but the antiviral effects of the vitamin were clinically irrelevant, then benefits at school-age only would be anticipated; if on the other hand, antiviral effects were most significant, then benefit across the developmental spectrum would be expected.

Effect of vitamin D on host responses to pathogens

A subgroup analysis conducted within a meta-analysis of individual participant data from 25 randomised controlled trials (RCTs) concluded that vitamin D supplementation significantly reduces the risk of acute respiratory tract infection in a mixed population of 513 children aged 1.1–15.9 years participating in eight studies (adjusted OR: 0.60; 95% CI 0.46 to 0.77, p<0.001).[37] Vitamin D coordinates the immune system both by turning on and off inflammation and modulates inflammatory and anti-inflammatory effects of immune cells. The cellular and molecular mechanisms by which vitamin D may exert in vivo antiviral, antimicrobial and immunomodulatory effects on the host innate and adaptive immune responses are summarised in tables 1 and table 2 and are illustrated in figure 1

Effects of vitamin D on type 2 airway inflammation

The effect of vitamin D on type 2 airway inflammation is complex and controversial.[38 39] In vitro, 1,25(OH)$_2$D induced interleukin 4 (IL-4) and IL-13 synthesis by primary murine T cells in one study[38] and inhibited IL-4 when added from the onset of differentiation in another.[39] Both studies used naïve T cells. In a murine model, early treatment with vitamin D before allergen challenge augmented allergen-induced T-cell proliferation along with IL-4, IL-13 and IgE production.[40] However, the local inflammatory response in bronchoalveolar lavage fluid and lung tissue was ameliorated with impaired eosinophil recruitment and inferior levels of IL-5 when vitamin D treatment was given after the establishment of an early immune response. Administration of 1,25(OH)$_2$D was found to decrease IL-4 in bronchoalveolar lavage fluid and T-cell migration in a study of murine allergic airways disease.[41] This apparent paradox may be resolved by a study showing that vitamin D enhanced the release of the soluble form of the receptor for IL-33, ST2, which by binding IL-33 may reduce alarmin-driven Th2 inflammation.[42]

Search strategy

One investigator (CS) searched Medline, PubMed, the Cochrane Central Registry of Controlled Trials (CENTRAL), Web of Science and ClinicalTrials.gov using electronic search strategies. Searches were regularly updated. No language restrictions were imposed. Collaborators were asked if they knew of any additional studies.

Table 2 In vitro data on the influence of vitamin D on host adaptive immune responses to pathogens

Effect of vitamin D	Cell type
10 nM 1,25(OH)$_2$D$_3$ decreases T helper cell proliferation by 20.9%, and expression of interferon-γ by 9.2%, IL-17 by 1.0% and IL-22 synthesis by 0.7% in CD4$^+$T cells (p<0.001)[97]	Human primary
20 nM 1,25(OH)$_2$D$_3$ suppresses NF-κB family transcription factors, activation, expression and activity in vitamin D receptor (VDR) dependent manner (p<0.001)[98]	Mouse HEK293 cell lines
1 µM 25(OH)$_2$D$_3$ enhances IL-10 expression (3.3-fold) of activated B cells by recruiting VDR (p<0.01)[99]	Human primary
0.5 µM 1,25(OH)$_2$D$_3$ or 25(OH)D increases expression of VDR by T cell antigen receptor[100]	Human primary
0.5 µM 1,25(OH)$_2$D$_3$ upregulates the VDR containing enzyme phosphoinositide phospholipase C-1, the central molecule in the classical T-cell receptor signalling pathway[100]	Human primary
100 nM 1,25(OH)$_2$D$_3$ increases the production of cytotoxic T-lymphocyte associated protein (CTLA)4, FoxP3 protein in the presence of IL-2 in CD4$^+$ T cells (p<0.001)[101]	Human primary
10^{-7} M 1,25(OH)$_2$D$_3$ decreases respiratory syncytial virus induction and the expression of NF-κB driven genes like interferon-β and C-X-C motif chemokine ligand (CXCL)10 by 86% in airway epithelium (p<0.001)[102]	Human primary
4×10^{-8} M 1,25(OH)$_2$D$_3$ promotes T cell shift from T helper (Th)1 to Th2 phenotype and induces cytokines of the Th2 profile (IL-4, IL-5 and IL-10) by 55%[38]	Mouse primary cells
100 nM 1,25(OH)$_2$D$_3$ suppresses Th-17 cells and induces regulatory T cells (Treg) resulting in reduced production of inflammatory cytokines IL-17 and IL-21 (p<0.001)[101]	Human primary
100 nM 1,25(OH)$_2$D$_3$ expresses CLTA-4 and FoxP3, characteristic of Treg cells[101]	Human primary
100 nM 1,25(OH)$_2$D$_3$ upregulates TLR10 synthesis in monocytes[103]	Human cell line
2×10^{-11} M 1,25(OH)$_2$D$_3$ inhibits IgG, IgM production in peripheral blood mononuclear cells (p<0.01)[104]	Human primary
100 nM 1,25(OH)$_2$D$_3$ enhances the production of IL-1 receptor-like 1 (IL1RL1), inhibiting IL-33 action in bronchial epithelial cells (p<0.01)[42]	Human primary
10^{-6} M 1,25(OH)$_2$D$_3$ increases the frequency of IL-10$^+$ CD4+T cells (p<0.05)[105]	Human primary
10^{-7} M 1,25(OH)$_2$D$_3$ reverses steroid resistance, through the upregulation of IL-10 by 15% in airway epithelium, increasing the therapeutic response (p<0.05).[106] Hence in children with atopic, eosinophilic asthma, in whom inhaled corticosteroids (ICS) are indicated, a strategy of combing vitamin D with ICS may be more successful	Human primary
10^{-7} M 1,25(OH)$_2$D$_3$ upregulates CD200 expression by 93% in human peripheral and airway-resident T cells (p<0.05)[107]	Human primary

Vitamin D deficiency and acute wheeze attacks in preschool children with wheeze and school-age children with asthma: epidemiological studies

Cross-sectional and longitudinal epidemiological studies investigating associations between circulating 25(OH)D concentration and the risk of acute wheeze attacks in preschool children with wheeze and school-age children with asthma are summarised in table 3, table 4, and online supplementary file 1

Ten cross-sectional studies in school-age children reported inconsistent results on the association between higher circulating 25(OH)D concentration and the risk of wheeze attacks

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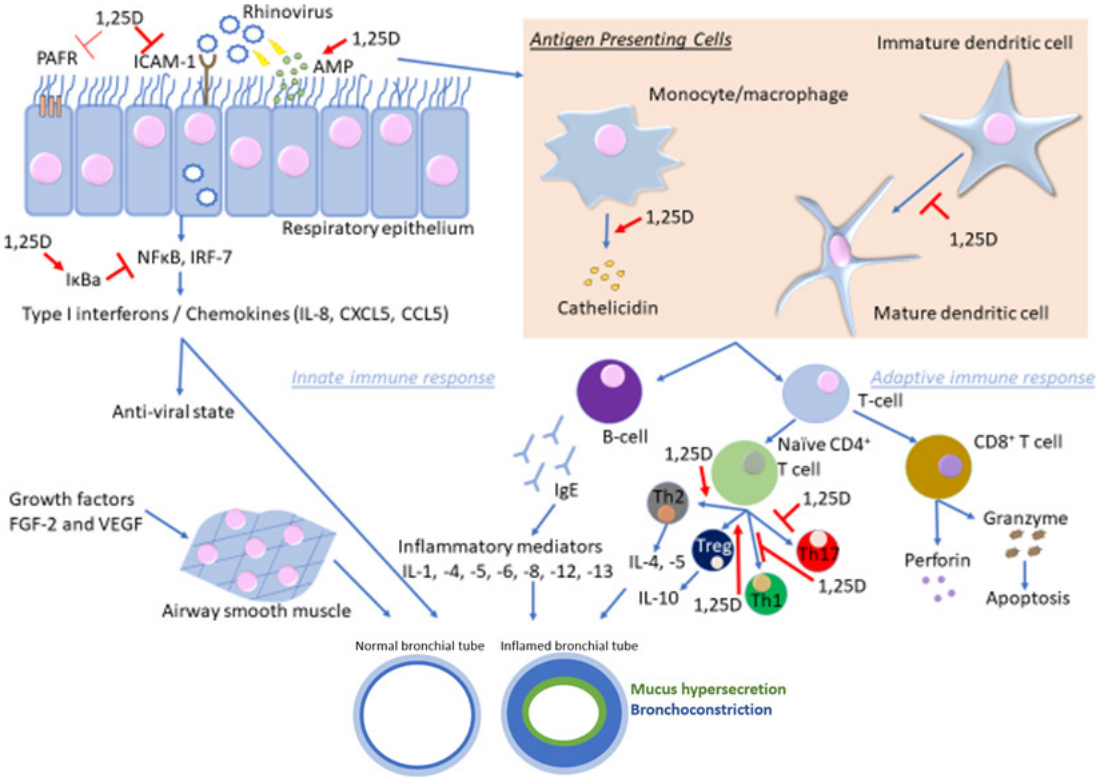


Figure 1 Effect of 1,25(OH)$_2$D on components of host immune response in relation to the pathogenesis of acute wheeze attacks. 1,25D, 1,25-dihydroxyvitamin D or 1,25(OH)$_2$D; PAFR, platelet-activating factor receptor; ICAM-1, intracellular adhesion molecule 1; AMP, Antimicrobial peptides; IκBa, I-Kappa-B-Alpha; NFkB, nuclear factor kappa beta; B cell, B lymphocyte; T cell, T lymphocyte; IL, interleukin; Th, T helper cell; Ig, Immunoglobulin; CD, cluster of differentiation; Treg, T regulatory cell; IRF-7, Interferon regulatory factor 7; CXCL5, C-X-C Motif chemokine ligand 5; CCL5, C-C motif chemokine ligand 5; FGF-2, fibroblast growth factor 2; VEGF, vascular endothelial growth factor;--> stimulation and --|: inhibition. Effects that are reported in just one paper (thin arrows) vs effects that have been reported in more papers (thick arrows).

managed in primary care, childhood asthma control test (c-ACT) score and spirometry. Specifically, in school-age children higher vitamin D status was associated with better controlled asthma,[43] reduced risk of attacks requiring hospitalisation,[44] reduced severity and number of asthma attacks,[45–47] reduced prescription of inhaled corticosteroids,[45] and improved c-ACT scores.[45 48] Better vitamin D status was also associated with higher forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC),[45 48–50] reduced airway reactivity to exercise,[49] and reduced total IgE and IgE antibodies against inhalant allergens.[51] Five studies reported no association between circulating 25(OH)D levels and risk of asthma attack, prescribed dose of inhaled corticosteroids, frequency of unscheduled healthcare attendances due to asthma,[52] total peripheral blood eosinophil count,[48] total IgE[46 50] or spirometry (FEV_1, FEV_1/FVC ratio).[46 48 51 52] In both preschool and school-age children, better vitamin D status was associated with reduced prescribed dose of inhaled corticosteroids and higher FEV_1 and FEV_1/FVC ratio[53] and also with reduced frequency of acute wheeze requiring oral corticosteroids[54] or admission to hospital[55] in preschool children.

Two case-control studies[56 57] reported an association between higher 25(OH)D concentration with reduced frequency of acute wheeze attacks and reduced risk for wheeze episodes in preschool children. Out of two case-control studies in a mixed population of preschool and school-age children with asthma,[58 59] one showed that higher circulating 25(OH)D concentration was associated with reduced frequency and duration of wheeze attacks[59] and the other showed no association between circulating 25(OH)D concentration and asthma control.[58] Their observational nature makes it impossible to ascertain causality and the temporal order of vitamin D deficiency and risk of wheeze attack; reverse causality cannot therefore be excluded as a potential cause of the reported associations. Furthermore, these studies only measure circulating concentration of 25(OH)D at enrolment. In a study of 1024 children aged 7–10 years with mild to moderate asthma, after adjustment for age, sex, body mass index, treatment group and season of vitamin D sampling, 25(OH)D concentration was associated with reduced odds of a wheeze attack precipitating a visit to the emergency department unit or hospitalisation.[60] However, this study is limited by having only one measure of circulating 25(OH)D concentration.

In general, observational studies report associations between low vitamin D status and worse respiratory outcomes in preschool children with wheeze and school-age children with asthma. However, these reported associations are inconsistent, and may remain subject to confounders, bias and reverse causality.

Effect of vitamin D supplementation on the secondary prevention of acute wheeze attacks/asthma control in preschool and school-age children

RCTs investigating effects of vitamin D supplementation on the secondary prevention of acute wheeze attacks in preschool and school-age children are presented in table 5 and online supplementary file 2, respectively.

RCTs in school-age children showed mixed results on the effect of oral vitamin D supplementation on asthma control and the risk of an asthma attack. Specifically, in some studies

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Table 3 Cross-sectional and case-controls studies: vitamin D and acute wheeze in preschool children with wheeze

Author	Sample size	Age range (months)	Setting	Phenotype of wheeze (n)	Subtype of wheeze (n %)	Confounding variables	Main finding
Beigelman *et al* [54]	278	12–53	USA	Recurrent wheeze and at least four episodes of acute wheezing illness (278)	Positive to at least one allergen (58.4%)	Race, tobacco smoke exposure	Vitamin D deficiency (25(OH)D <50 nmol/L) was associated with higher mean rate of acute episodes of wheezing illness requiring oral corticosteroids compared with vitamin D sufficiency (25(OH)D ≥50 nmol/L) (1.46 vs 0.93 attacks/child-year, p=0.035; rate ratio 1.56 (95% CI 1.03 to 2.37)
Uysalol *et al* [55]	148	3–24	Turkey	Recurrent wheeze and at least one wheeze attack (73) Healthy controls (75)	Allergic rhinitis and atopic dermatitis	Not reported	Lower 25(OH)D concentration was associated with increased frequency of severe wheeze attacks (p=0.011) and hospitalisations (p=0.026)
Stenberg Hammar *et al* [57]	231	6–48	Sweden	Wheeze group (130) Healthy controls (101)	Positive to at least one airborne or food allergen (not reported) None	Age, sex, ethnicity, sampling month, >6 respiratory infections a year, history of respiratory syncytial infection	Vitamin D insufficiency (25(OH)D <75 nmol/L) was associated with higher risk for acute episodes of wheezing illness (OR, 95%; 2.7 CI 1.1 to 6.2, p=0.02)
Turkeli *et al* [56]	204	1–4* 1–4*	Turkey	Mild to moderate asthma (102) Healthy controls (102)	Not reported	Not reported	Number of wheeze attacks significantly lower in the vitamin D sufficient group (25(OH)D >75 nmol/L) compared with the deficient group (25(OH)D ≤50 nmol/L) and the insufficient group (25(OH)D: 50–75 nmol/L) p=0.03 for comparison of vitamin D sufficient group against vitamin D insufficient and deficient

*Age in years

in school-age children vitamin D supplementation reduced the risk of an asthma attack managed in primary care,[61–63] improved c-ACT scores,[64 65] reduced frequency of asthma attacks precipitating a visit to the emergency department unit,[63] reduced school absences due to asthma[66] and improved asthma symptoms.[67] Supplementation also improved FEV_1[67] and FEV_1/FVC ratio.[66] However, three trials failed to show an effect of vitamin D supplementation on asthma control, unscheduled healthcare visits due to asthma, number of prescribed oral steroid courses,[66] FEV_1[64], FVC%, IgE[66] and fractional exhaled nitric oxide.[67] In preschool children, vitamin D supplementation had no effect on the risk of acute episodes of wheezing illness leading to a healthcare visit.[68] However, these are small trials (22–430 participants)[62–67]; in addition some have important

Table 4 Cross sectional and case-control studies: vitamin D and acute wheeze in a mixed population of preschool children with wheeze and school-age children with asthma

Author	Sample size	Mean age (range) years	Setting	Phenotype of asthma (n)	Subtype of asthma (n %)	Confounding variables	Main finding
Searing *et al* [53]	100	(0–18)	USA	Doctor diagnosis of asthma (100)	Positive aeroallergens (9%)	Not reported	Association between 25(OH)D concentration <75 nmol/L) and increased inhaled steroid use (p=0.0475). Positive association between 25(OH)D concentration and FEV_1 and FEV_1/FVC ratio
Dogru *et al* [59]	120	4.4 (3–8.5) 4.6 (3–8)	Turkey	Asthma group (120) Healthy controls (74)	Atopy (50%)	Not reported	Inverse association between vitamin D deficiency (25(OH)D ≤50 nmol/L) and total number of attacks, number of attacks in the previous year and duration of acute episodes of wheezing illness (p<0.05)
Esfandiar *et al* [58]	106	5.6±3.2* 5.5±3.9*	Iran	Diagnosis according to global initiative for asthma guideline (53) Healthy controls (53)	Not reported	Not reported	No association between circulating 25(OH)D and asthma control scores

*Mean age ± Standard deviation

FEV_1, forced expiratory volume in one second; FVC, forced vital capacity.

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Table 5 A randomised controlled trial: vitamin D and secondary prevention of acute wheeze in preschool age children

Author	Sample size	Mean age (years)	Setting	Mean baseline 25(OH)D level (nmol/L)	Low 25(OH)D entry criterion	Attained 25(OH)D >75 nmol/L at the end of the trial (%)	Oral vitamin D_3 dose (IU)	Phenotype of wheeze (n)	Subtype of wheeze (n %)	Covariates	Risk of bias	Primary outcome	Secondary outcome	Adjustment for multiple testing
Jensen *et al*[68]	22	2.2	Canada	62.0	No	100	100 000 bolus-dose followed by 400/day for 6 months	Asthma diagnosis (11), persistent (45.5%), episodic (54.5%)	Multi-trigger (27.3%) and un-trigged (72.7%), positive to at least one allergen (72.7%)	Baseline asthma classification (episodic vs persistent), asthma treatment, and dietary vitamin D	Low	Vitamin D significantly increased serum 25(OH) D concentration at 10 days after the bolus-dose (mean difference from baseline 25(OH)D concentration 110.3 nmol/L; 95% CI 64.0 to 156.6); however, there was no significant effect on serum 25(OH)D concentration at 3 months	Vitamin D had no significant effect on healthcare visits for an asthma attack compared with placebo (RR, 95% CI 0.88, 0.32 to 2.41)	No adjustment for testing multiple comparisons
		3.1		68.0		54.5	Placebo	Asthma diagnosis (11), persistent (72.7%), episodic (27.3%)	Multi-trigger (36.4%) and un-trigged (63.6%), positive to at least one allergen (18.2%)					

limitations including high dropout rates,[61 63 64] no assessment of circulating 25(OH)D concentration,[61 63] and a vitamin D dosing regimen that failed to elevate circulating 25(OH)D concentration above 75 nmol/L.[62 64–66] Furthermore, two trials were underpowered to test the primary outcome.[66 68] In a single study lack of power meant that interactions within subgroups could not be evaluated.[65] Four trials in school-age children reported no adverse effects of the studied vitamin D supplementation regimen,[61 65–67] whereas three trials provided no safety data.[62–64] No toxic circulating 25(OH)D concentration was reported in the trial in preschool-age children.[68] Three systematic reviews and meta-analyses concluded that vitamin D supplementation led to a reduction in the risk of wheeze attacks managed in primary care[69–71] in children aged 5–18 years. However, all three reviews based their conclusions on the same RCTs. Two RCTs were included in the pooled estimate effect for a meta-analysis (relative risk (RR), 95% CI 0.26, 0.11 to 0.59).[70] These two RCTs and a further trial were included in meta-analyses of the pooled estimate effect meta-analyses (RR, 95% CI 0.41, 0.27 to 0.63).[69 71] None of these analyses presented subgroup analyses and it is unclear if the conclusions were valid for preschool children. A meta-analysis of individual participant data of five RCTs concluded that there was no statistically significant effect of vitamin D supplementation on wheeze attacks requiring treatment with systemic corticosteroids in a mixed population of 290 preschool and school-age children (adjusted incidence rate ratio, 95% CI 0.64, 0.34 to 1.20, p=0.16, note the wide CIs).[72] Individual participants' data from an eligible study that showed a strong positive effect of vitamin D supplementation on the risk of asthma attacks were not available for inclusion in this meta-analysis. In addition, limited power was reported for some of the subgroup analyses.

In summary, only one small (n=22) RCT (the DIVA pilot) tested the effect of vitamin D supplementation on attacks of wheeze in preschool children as an exploratory outcome (RR, 95% CI 0.88, 0.32 to 2.41, note the wide CIs), from which little can be concluded.[68] There are more RCTs of vitamin D supplementation in children with asthma, but there is diversity in study design, treatment protocols and outcome definitions. Furthermore, they are too small-sized, and of variable quality; some show a signal for protection while others do not. This phenomenon may relate to variation in the prevalence of vitamin D deficiency among participants at baseline. Meta-analysis of individual participant data from RCTs of vitamin D for the prevention of acute respiratory infections and severe exacerbations of chronic obstructive pulmonary disease (COPD) reveals stronger protective effects of vitamin D supplementation in those with baseline 25(OH)D levels <25 nmol/L.[37 73] In patients with asthma, a similar trend of greater vitamin D-induced protection against exacerbation among participants with baseline 25(OH)D <25 nmol/L was seen, although the p value for interaction was >0.05.[72] Therefore, a firm recommendation for vitamin D supplementation as a preventive therapy for wheeze attacks in preschool and school-age children cannot be made until further well-designed and conducted clinical trials become available. Two trials in Canada and the USA are testing the efficacy of oral vitamin D_3 on the secondary prevention of acute wheeze in preschool[74] and school-age children.[75] However, the Celedon[75] trial has been stopped. A summary of the trials is shown in table 6.

Should vitamin D status be measured in all children who experience an acute wheeze attack?

There is clearly no point in measuring anything if useful action does not result. The evidence of benefit from vitamin D

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Table 6 Ongoing randomised controlled trials on the effect of vitamin D supplement on the secondary prevention of acute wheeze in preschool and school-age children

Author	ClinicalTrials.gov Identifier	Setting	Age range (years)	Phenotype of asthma (n)	Oral vitamin D_3 dose (IU)	Primary outcome measure	Expected completion date	Comment
Ducharme et al[74]	NCT03365687	Canada	1–5	Viral-induced wheeze (865)	100 000 at baseline and at 3.5 months with a daily dose of 400 for 7 months for 7 months Placebo	Number of asthma attacks treated with oral corticosteroid	December 2022	–
Celedon *et al*[75]	NCT02687815	USA	6–16	Asthma treated with inhaled corticosteroids and 25(OH)D <75 nmol/L (400)	4000/day for 48 weeks Placebo	Number of asthma attacks requiring systemic corticosteroids, or an increase in maintenance dose for at least 3 days or an unplanned healthcare visit due to asthma	November 2020	Trial has been stopped

supplementation to prevent acute wheeze is weak at best, but there are in vitro studies (effects on innate immunity and type two inflammation) and adult data which are suggestive that there may be a true effect.[72] Also, the risks of supplementing vitamin D to achieve normal 25(OH)D levels are practically zero.

Vitamin D supplements at daily doses up to 2500 IU for preschool and up to 3000 IU daily for school-age children are safe. Doses of up to 4000 IU vitamin D per day are well tolerated in children over the age of 9 years without signs of intoxication.[76] Vitamin D intoxication has not been reported where 25(OH)D concentrations are <220 nmol/L.[77] Since there is unequivocal evidence that vitamin D deficiency is common in children with acute wheeze, whatever the reason may be, and good reason to optimise levels for non-respiratory reasons, we recommend measuring levels and supplementing those who are deficient. Whether this as an added bonus will reduce future risk of wheezing attacks awaits further trials.

SUMMARY AND CONCLUSIONS

There is conflicting evidence for the use of vitamin D supplementation as adjuvant therapy for the secondary prevention of acute wheeze in school-age children with asthma, and limited evidence for the use of vitamin D to reduce risk of wheezing attacks in preschool children. However, there is evidence that vitamin D reduces the risk of asthma exacerbations in adults, and also reduces the risk of acute respiratory tract infections in preschool and school-age children. There are good in vitro studies which lend biological plausibility for a beneficial effect on acute wheeze. Screening circulating 25(OH)D concentration and maintaining optimal vitamin D status may reduce wheeze risk in preschool and school-age children with a history of acute wheeze. Further studies are needed to ascertain the daily oral dose of vitamin D that is necessary to reach optimal 25(OH)D for the prevention of acute wheeze in children, to examine the efficacy of vitamin D supplementation on incidence and severity of acute wheeze in preschool children and school-age children, and to evaluate the mechanisms of any effect of vitamin D supplementation on the pathogenesis of acute wheeze in both preschoolers and school-age children. One approach to synthesising information from diverse studies would be for a clinical trials group such as the Inner-City Asthma Consortium use existing mechanistic and population-based evidence to construct definitive designs to answer the open questions of greatest interest.[78]

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