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REVIEW ARTICLE

Efficacy of high-dose vitamin D in pediatric asthma: a systematic review and meta-analysis

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Abstract

Context: Observational studies have suggested a relationship between vitamin D status and asthma-related respiratory outcomes. The benefit of vitamin D supplementation for pulmonary function, symptoms and exacerbations is not well established. *Objective*: To systematically review paediatric clinical trials investigating the role of vitamin D on asthma-related respiratory outcomes. *Data sources*: MEDLINE, EMBASE and CENTRAL were searched until January 2014. No date or language restrictions. *Study selection*: Clinical trials reporting asthma-related respiratory outcomes following vitamin D administration at a dose equal or greater than 500 IU per day were included and reviewed independently by two authors for full systematic review eligibility. *Data extraction*: Two reviewers independently extracted and verified pre-defined data fields. *Results*: We identified five studies that met study eligibility and assessed final data synthesis. The median trial size was 48 participants (range 17–430) and the average daily dose of cholecalciferol ranged from 500 to 2000 IU/day. Overall study methodological quality was high, but some heterogeneity in population and vitamin D dosing regimen was evident. Meta-analysis suggested a statistically significant reduction (RR 0.41, CI 0.27–0.63) in asthma exacerbation with vitamin D therapy. *Limitations*: Due to variability in outcome selection and missing data, it was not possible to perform meta-analysis for pulmonary function testing and asthma symptom scores. Vitamin D-related adverse events were not considered in four of five papers. *Conclusions*: Available evidence from this systematic review suggests that high dose vitamin D may prevent asthma exacerbation. This should be confirmed through larger well-designed randomised controlled trials.

Keywords

Asthma, asthma-related respiratory outcomes, children, systematic review, Vitamin D

History

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Introduction

Asthma is a chronic inflammatory disorder of the airways affecting approximately 10% of children, with prevalence varying by definition and country of origin [1]. Moreover, there is evidence to suggest that asthma prevalence has increased in many Western countries over the past few decades [2]. An armamentarium of medications and drug delivery devices has been developed to control long-term symptoms and prevent asthma exacerbations. Despite significant research and improvements in health care delivery, current asthma management remains imperfect with many children suffering from either inadequate symptom control or prevention at the expense of excess medication use with the risk of side effects. Consequentially, there remains considerable interest in the identification of modifiable risk factors that contribute to the development or control of asthma.

In recent years, vitamin D has been hypothesised as an effect modifier of asthma severity and medication response [3]. Long known for its role in calcium and bone metabolism, vitamin D is now recognised to have potentially clinically relevant anti-infective and immunomodulatory functions [4]. Several observational studies have suggested a potential relationship between vitamin D levels and pulmonary function in asthma [5,6]. In addition, an inverse relationship between vitamin D levels and hospitalisation, anti-inflammatory medications use and total immunoglobulin E (IgE) and eosinophil counts has been reported, as has a relationship between lower vitamin D levels and reduced efficiency of asthma control [5,7]. The potential relevance of vitamin D status to asthma is amplified by concerns over widespread vitamin D insufficiency in both the general and asthmatic pediatric populations.

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Although suggestive, results from observational studies cannot be used to confirm causality. A number of clinical trials have reported on the administration of vitamin D to children and evaluated asthma-related respiratory outcomes. A well-done systematic review with meta-analysis could provide information on the efficacy of vitamin D in asthma [8]. The first objective of this systematic review was to comprehensively evaluate the number, design and quality of paediatric clinical trials investigating the role of vitamin D in asthma-related respiratory outcomes. The second objective was to evaluate and synthesise the current literature on the efficacy of vitamin D on pulmonary function, asthma symptoms and exacerbations.

Methods

Study authors (DM, SP) developed a study protocol which included the research question, eligibility criteria, study objectives and analytical approach. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9] to report the methods and results of this systematic review, including implementation of a protocol, search and selection of studies.

Eligibility criteria

Studies were included if the following eligibility criteria were met: (i) described a population of infants, children or adolescents (18 years old or less), (ii) reported on the prospective administration of cholecalciferol or ergocalciferol at a dose equal to or greater than 500 IU (averaged per day), (iii) reported on one or more asthma-related respiratory outcomes. Studies were excluded if the described population was determined to be primarily: (i) children with a wheezing disorder other than asthma (e.g. cystic fibrosis, bronchiolitis), (ii) pregnant adolescents or (iii) children with genetic or metabolic conditions involving the vitamin D axis. Studies evaluating the short-term impact of vitamin D administration to infants admitted to NICU (e.g. prematurity or low birth weight infants) were also excluded. Studies or study arms were also excluded if the vitamin D dosing regimen included: (i) prescription of ultraviolet (UV) exposure, (ii) vitamin D was administered as a food and intake quantity not controlled and (iii) the dosing regimen included the fixed administration of another drug or vitamin without an appropriate control arm.

Data sources and study selection

An electronic search was performed on the following databases: MEDLINE (1946–2014 January Week 2), EMBASE (1974–2014 January Week 3) and the Cochrane Central Register of Controlled Trials (December 2013) using the Ovid interface. The MEDLINE search strategy was developed by a librarian experienced in systematic review searching (MS), and peer reviewed by another librarian (LK), using the PRESS standard (Supplementary Appendix 1). The MEDLINE search was then adapted for the other databases. The initial search was performed in April 2013, with an update performed January 2014. No date or language restrictions were applied.

Study eligibility was determined through three screening levels, and each citation was independently assessed by a minimum of two reviewers (Supplementary Appendix 2). Level 1 screening was performed using Mendeley (Mendeley Desktop, version 1.10.3, Mendeley Inc., New York, NY), and those citations that could not be excluded were uploaded to DistillerSR™ (Evidence Partners Incorporated, Ottawa, ON, Canada) for level 2 and 3 screening. Level 2 screening was performed with the goal of identifying all prospective interventional trials of ergocalciferol or cholecalciferol that included children. At the third screening level, abstracts and full text articles were reviewed independently by two authors for full systematic review eligibility. Disagreements between reviewers were resolved by discussion, with a third author available to resolve disagreement.

Data extraction and risk of bias assessment

A data extraction form was prepared as part of protocol development (Supplementary Appendix 3). Variables extracted included authors, study and population characteristics, asthma control and vitamin D drug regimens, pre- and post-study drug 25-hydroxyvitamin D (25OHD) levels, vitamin D related outcomes including adverse events (hypercalcemia, hypercalciuria) and asthma-related respiratory outcomes. The *a priori* identified asthma-related respiratory outcomes of primary interest were pulmonary function tests (PFTs) and asthma exacerbations. PFT was selected due to well established role in clinical practice and frequent application in asthma research. FEV_1 or forced expiratory volume in 1 s was the primary PFT chosen for reporting and analysis; other relevant PFT measurements (e.g. peak expiratory flow rates) would be extracted, reported and utilised when FEV_1 was not available. Asthma exacerbation was selected as an important clinical outcome measure and more relevant patient-centred outcome. As children under the age of 6 cannot reliably perform pulmonary function testing [10], asthma symptom scores (ASS) were collected and considered an alternative primary asthma-related respiratory outcome in this subpopulation. Data were extracted from text and tables, and where necessary were extracted from figures (using Digitizelt Digitizer Software, http://www.digitizeit.de/Germany). All author groups responded to a request for additional or missing data and four provided one or more pieces of additional information. Once extraction was complete, the data was reviewed to identify duplicate reporting of trials and study populations; only the study containing the most complete data was retained. Methodological quality was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials [11].

Data analysis and reporting

Search strategy and results were reported as per PRISMA recommendations (Supplementary Appendix 4). We provided a narrative synthesis of findings from eligible studies, including study characteristics, population characteristics, intervention regimens and outcomes as text, tables and figures. Heterogeneity was assessed clinically and statistically using the I-squared statistic. Where possible, meta-analysis was performed using Review Manager (RevMan5.2, Denmark,

Copenhagen). For dichotomous outcomes, meta-analysis was performed using risk ratio, and continuous variables were evaluated using mean difference. Random effect was used if heterogeneity was evident, and statistical significance was defined as a *p*-value less than 0.05.

Results

Screening

Results of the citation search are presented in Figure 1. The electronic database search identified 2113 citations after duplicate removal, and an additional 146 citations were ascertained through a review of relevant systemic reviews and eligible articles. In total, level one screening was performed on titles and abstracts of 2254 citations, resulting in exclusion of 1892. Assessment of full text at level 2 removed another 111 articles, identifying 256 articles as prospective clinical trials. In level three screening, 250 were excluded as not meeting full eligibility criteria for this systematic review and one additional article identified as a duplicate [12]. In total, five articles met inclusion and exclusion criteria and were included in this review [13–17]. The numbers of conflicts documented were 23 (6.3%) and 5 (1.95%) at level two and three, respectively.

Description of included studies

Study population, dosing regimen and methodological characteristics for the five studies meeting our initial eligibility criteria are shown in Tables 1 and 2.

Study characteristics

The five studies were published between 2003 and 2013 [13–17]. Only one of five trials, Urashima et al. was conducted in more than one centre [14]. Four of the five studies were conducted in industrialised countries [13–16], with the remaining study performed in India [17]. Four of the five studies were conducted in university associated hospitals, while one trial was conducted at a non-academic children hospital in Denmark [13]. All five studies were randomised

Figure 1. PRISMA flow diagram.

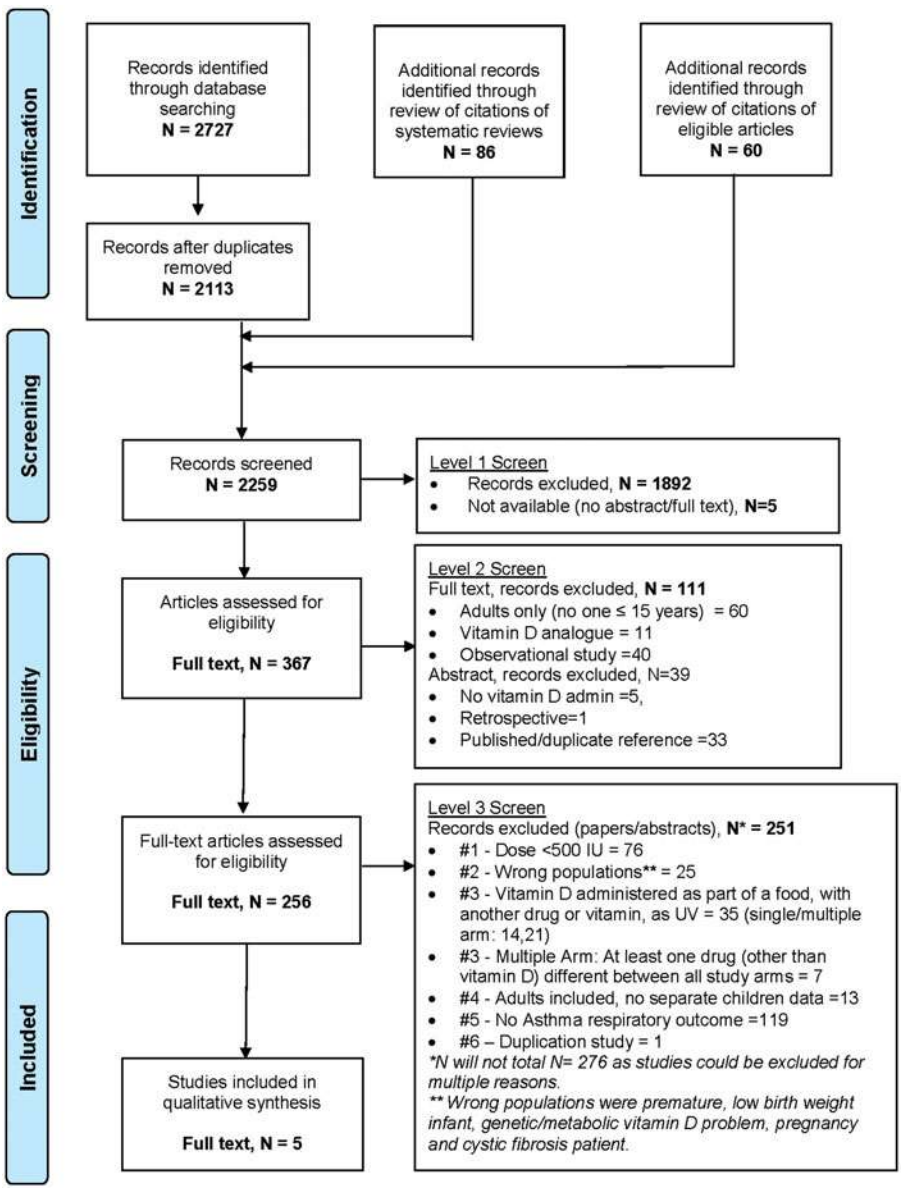

Table 1. Descriptive characteristics of study setting and population.

Trial, year	Location	Study setting	Patient population, severity	Age range (years)	No. of total participants	Pre-study drug 25OHD level[a] (ng/ml)
Included studies in final data analysis						
Schou et al. [13]	Denmark	Outpatient	Asthma (severity not specified)	6.1–14.4	17	Not provided
Urashima et al. [14]	Japan	Outpatient	School children (26% asthma)	6–15	430	Not provided
Majak et al. [15]	Poland	Outpatient	Newly diagnosed asthma (severity not specified)	5–18	48	35.6 ± 15.3
Lewis et al. [16]	United States	Outpatient	Asthma (severity not specified)	6–17	30	13.0 ± 1.2
Yadav and Mittal [17]	India	Outpatient	Asthma (moderate to severe severity)[b]	5–13	100	Not provided

[a]Mean ± SD.
[b]Severity as defined by The Global Initiative for Asthma (GINA) [18].

controlled trials (RCT), with all studies including 2 arms. Median trial size was 48 participants (range 17–430), and only the trial reported by Urashima enrolled more than 100 participants [14].

Study participants

The age of included patients ranged from 5 to 18 years. Four of the five studies enrolled exclusively, asthmatic patients. The one remaining study enrolled 430 school children, of which 26% were classified as asthma [14]. Among the primary asthmatic studies only one provided specific diagnostic criteria (GINA) [17,18], one described participants as newly diagnosed [15] and the other one reported the population as having moderate to severe asthma [17,18]. Baseline PFT measurements were available in three studies, with one trial reporting values consistent with well-controlled disease (forced expiratory volume in 1 s [FEV_1] % predicted >90%) [15]. Baseline vitamin D status was reported in two studies, with one population having average 25OHD levels below 50 nmol/l (20 ng/ml) [16].

Study intervention

All studies compared enterally administered cholecalciferol to a comparator arm, with identical asthma control therapy in both arms. Four studies used a daily dosing regimen of cholecalciferol [13–16] and the remaining study provided a monthly dose of 60 000 IU [17]. The average daily dose of cholecalciferol ranged from 500 IU [15] to 2000 IU [17]. Duration of therapy and length of follow-up ranged from 4 to 52 weeks. All studies reported concurrent corticosteroid with inhaled corticosteroid (budesonide) with doses ranging from 400 to 800 μg/day [13,15].

Risk of bias of included trials

The results of the risk of bias assessment use the Cochrane tool and are presented in Table 3. Overall assessment of quality determined one study [16] as having moderate risk of bias and four studies as low risk of bias [13–15,17].

Asthma and vitamin D-related outcomes

An asthma-related respiratory outcome was reported as the primary outcome in three studies [15–17] and secondary outcome in two studies [13,14]. Further evaluation and synthesis of outcome data was limited to five studies. Among these five studies, at least one measure of post-intervention PFT was reported in four studies [13,15–17], with both asthma symptom scores [13,15,16] and exacerbations reported in three studies [14,15,17]. Post-drug 25OHD values were reported in three studies [13,15,16]. Only one study reported on any vitamin D-related adverse events [15]. Table 4 summarises the respiratory and vitamin D adverse event outcomes for the five studies.

Three studies evaluated asthma exacerbations following study drug initiation, on a total of 482 participants [14,15,17]. Although none of the studies provided clear case definitions asthma exacerbations, two did indicate that use of short-acting β_2 agonists was part of the evaluation [14,15]. Statistical evaluation of the outcome did not identify heterogeneity between studies ($I^2 = 0\%$, $p = 0.42$). As shown in Figure 2, both fixed and random effects meta-analysis determined the pooled effect of cholecalciferol in the reduction of asthma exacerbations was highly statistically significant (RR 0.41, CI 0.27–0.63, $p < 0.0001$). Sensitivity analysis determined that the calculated risk ratio retained statistical significance with the removal of any one of the three trials (See forest plot, Supplementary Appendix 5). More specifically, the meta-analysis retained statistical significance with the removal of the largest study. Although all three studies reported a statistically significant reduction in exacerbations, the upper 95% CI for the study by Majak study (500 IU/day) approached 1 (CI: 0.13–0.98). Meta-analysis performed by removing this study only decreased the calculated risk ratio from 0.44 to 0.42 (CI: 0.26–0.67).

Our systematic review presents the individual trial PFT, asthma symptom score and vitamin D related outcome data (Supplementary Appendix 6). Three of the four reported PFTs using FEV_1 (% predicted or absolute) [13,15,16], with the remaining study reporting peak expiratory flow rates (PEFR) [17]. Two of the four studies reported greater improvements in PFTs for the vitamin D group [16,17]. Meta-analysis was not considered appropriate as only two of the four studies, totalling 78 participants, provided sufficient pre- and post-intervention data for pooling [15,16]. Type and study findings for asthma symptom scores are also summarised in Supplementary Appendix 6. The three studies all used different symptom scores [13,15,16] and only two reported pre- and post-intervention [15,16]. Of these two trials, one reported no difference in symptom score between groups [16] and the other reporting a greater reduction in asthma symptoms in the placebo group [15]. As there was insufficient data and none of the trials included children under 5, meta-analysis of asthma symptom score results was not pursued. Finally, three studies

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Table 2. Trials meeting systematic review eligibility.

Trial	Methodology	Number of arms	Vitamin D arm (type, dose and route)	Oral vitamin D calculated daily dose (IU/day)	Comparator arm	Study primary outcome	Duration of therapy and follow-up (Weeks)
Studies in final data analysis							
Schou et al. [13]	RCDBCT Two period cross over	2	600 IU D3 oral daily (includes drug in comparator arm)	600	Budesonide ICS 400 µg/day	Bone turnover	4
Urashima et al. [14]	RCDBCT	2	Vitamin D3 1200 IU oral daily (includes drug in comparator arm)	1200	Placebo (asthma control drug not protocolised)	Incidence of influenza A	15–17
Majak et al. [15]	RCDBCT	2	Vitamin D3 500 IU oral daily (includes drug in comparator arm)	500	Budesonide ICS 800 µg/day	Asthma exacerbation	26
Lewis et al. [16]	RCT	2	Vitamin D3 1000 IU oral daily (includes drug in comparator arm)	1000	Placebo (asthma control drug not protocolised)	Asthma control (FEV_1, Asthma Control Test)	26, 52
Yadav and Mittal [17]	RCDBCT	2	Vitamin D3 60 000 IU per month oral (includes drug in comparator arm)	2000	Placebo (asthma control drug not protocolised)	Level of severity	26

Abbreviations: FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroid; RCT, randomised controlled trial; RDBCT, randomised controlled double blind clinical trial; vitamin D3,Cholecalciferol.

Table 3. Methodological quality of trials.

Trial	Sequence generation described	Allocation concealment	Blinding of participants, personnel and outcome	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Studies in final data analysis						
Schou et al. [13]	Yes (Computer generated, Balanced blocks)	Identical boxes labeled	Placebo described as having the same identical appearance	Complete outcome data	Outcome reporting complete	Source of funding not reported
Urashima et al. [14]	Yes (Computer generated, Blocks of 4)	Not described	Participants, personnel and outcome assessors blinded Placebo described as having the same identical appearance	Complete outcome data	Outcome reporting complete	Detail of side effects not reported, Lack of urine calcium data
Majak et al. [15]	Yes (Computer generated)	Not described	Randomised double-blind but placebo detail not described	Complete outcome data	Outcome reporting complete	None identified
Lewis et al. [16]	Reported as randomised but detail not described	Not described	Not described	Complete outcome data	Outcome reporting complete	None identified
Yadav and Mittal [17]	Yes, reported as randomised trial	Sealed opaque envelop	Participants and investigator blinded Drug and placebo were given in sachet, implied same apperance	Complete outcome data	Outcome reporting complete	Lack of 25OHD reported

Table 4. Outcomes and adverse events reported in the included trials.

Trial	FEV_1% predicted, PEFR	Asthma symptom score	Exacerbation	ED visit	Hospitalisation	Drug control usage	Post-study drug 25 OHD	Level of control	Severity	Bone	Influenza a infection	Immunological outcome	Hypercalcemia, Hypercalciurea
Studies in final data analysis													
Schou et al. [13]	X (FEV_1, Liters)	X (Diary card)					X			X			
Urashima et al. [14]			X								X		
Majak et al. [15]	X	X (ATAQ)	X		X		X			X			X
Lewis et al. [16]	X	X (ACT)					X						
Yadav and Mittal [17]	X (PEFR)		X	X		X		X	X				

Blank means that data was not reported. Abbreviations: ACT, Asthma Control Test; ATAQ, Asthma Therapy Assessment Questionnaire for children; ED, emergency department; FEV_1, forced expiratory volume in one second; PEFR, peak expiratory flow rate; NC, Not collected; 25OHD, 25-hydroxyvitamin D.

reported post-intervention vitamin D levels, and in all three the 25OHD point estimate was lower in the placebo (comparator) group [13,15,16]. The range of post-study difference in 25OHD levels ranged from 5.7 to 11.2 ng/ml.

Discussion

This systematic review identified five studies with independent data on children receiving average daily cholecalciferol doses at or exceeding 500 IU [13–17]. All but one of the RCTs was considered to be at low risk for bias [13–15,17] Inspection of the five RCTs identified some heterogeneity in population, vitamin D dosing and duration of therapy. Meta-analysis was possible for the asthma exacerbation outcome, and the pooled data suggested a statistically significant benefit to vitamin D therapy. Descriptive evaluation of results from individual studies suggested improved PFTs in specific population-dosing regimen combinations.

Our systematic review identified five RCTs, and no uncontrolled studies, addressing our research question. Overall, the RCTs were determined to be of high methodological quality and there were no concerns about influence from the pharmaceutical industry. Studies were evaluated for evidence of heterogeneity in population and vitamin D dosing regimens. With the exception of one study [14], all studies considered solely asthmatic patients. Despite only one quarter of their population being asthmatic, the study by Urashima and colleagues [14] had the largest total number of asthmatic patients. Few studies provided details on how asthma was diagnosed or confirmed or used objective criteria to define baseline disease severity. Indirect evaluation of severity of baseline asthma control using PFT measurements was possible for three studies [15–17]. Among these three, Majak and colleagues reported a baseline FEV_1% predicted well in excess of 90%, which would leave little room for improvement following vitamin D administration [15].

Evaluation of vitamin D dosing regimens identified that all but one of the final five trials reviewed used daily dosing, and the average daily dose was determined to be between 500 and 2000 IU. The ability of daily dosing in this range to sufficiently elevate 25OHD levels is dependent upon the baseline levels and duration of therapy [19,20]. Numerous paediatric clinical trials have identified that two or more months of daily administration in this range may be required to normalise vitamin D levels in severely deficient children [21–26]. For example, the decision by Schou and colleagues to evaluate outcomes after one month of therapy may not have allowed appropriate time for both the separation of 25OHD levels and subsequent changes to organ structure and function [13]. In contrast, the decision by Yadav and Mittal [17] to administer 60 000 IU/monthly over 6 months would have better allowed for separation of 25OHD levels and evaluate for differences between groups.

As described in the results, there was sufficient data to pool study results for the asthma exacerbation outcome. Our meta-analysis identified a statistically significant reduction (RR 0.41, CI 0.27–0.63) in asthma exacerbation with high-dose vitamin D dosing. Importantly, our sensitivity analysis demonstrated that no one study was driving the effect. Although combining data was not possible for the PFT

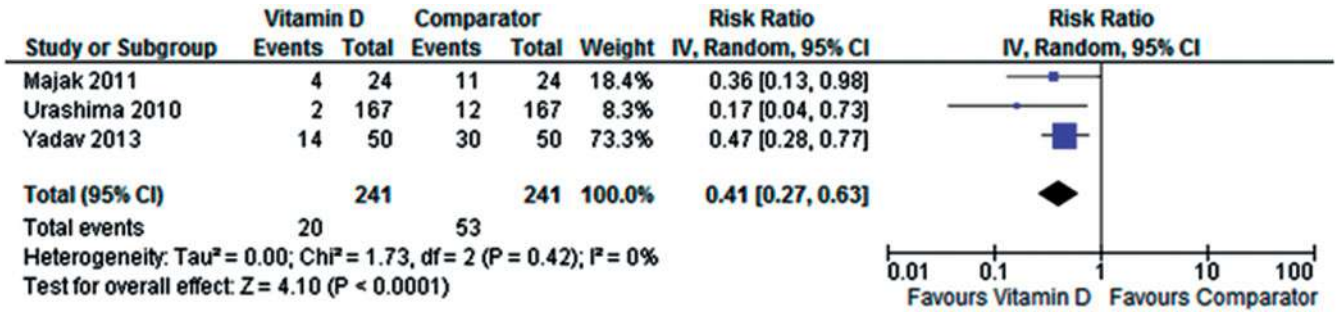

Figure 2. Meta-analysis evaluating efficacy of vitamin D supplementation for asthma exacerbations.

outcome due to missing data and variability in outcome measures, some observations were possible. First, two of the four studies evaluating PFTs reported significantly greater change in PFT's in their vitamin D groups [16,17]. Evaluation of the two studies that did not demonstrate PFT differences between groups identified that they used lower vitamin D doses, one had near normal pre-drug PFT values [15], and one only administered vitamin D for 1 month [13]. With this combination of population and dosing regimen characteristics, it is not surprising that no difference was observed. Overall, the available data suggest that high-dose vitamin D supplementation may improve asthma-related respiratory outcomes in specific population-dosing combinations.

Our study findings are consistent with those observational studies documenting a relationship between vitamin D levels and asthma exacerbations, pulmonary function results and medication utilisation [5,27]. For example, a recent retrospective study in adults reported that vitamin D sufficiency was significantly associated with decreased frequency and severity of asthma exacerbation [28]. Our systematic review similarly demonstrates vitamin D supplementation had a significant benefit by decreasing asthma exacerbations in asthmatic children. The suggested benefits of vitamin D in asthmatics has biological plausibility as Vitamin D Receptors are widespread in the immune system (T cell, B cell, monocytes and macrophages) and respiratory epithelial cells [29,30]. Available basic science research supports immunomodulatory actions for vitamin D through inhibition of T cell proliferation [31], cytokine synthesis and release and enhancement of interleukin-10 (IL-10) synthesis by regulatory T cells [32]. Vitamin D is also potentially anti-microbial, with a well-established role in the regulation of antimicrobial peptides (e.g. cathelicidin) and defence against respiratory tract pathogen [33,34]. Finally, other data support interactions between vitamin D and glucocorticoid signaling pathways that may help explain the greater therapeutic response to glucocorticoids in asthmatics treated with vitamin D [6,35].

An important objective of this study was to evaluate variability in selection and/or reporting of asthma-related respiratory outcomes. Overall, four studies provided PFT, three studies reported on exacerbations and three had asthma symptom scores. Other asthma systematic reviews evaluating different interventions have also considered these same outcomes and shown comparable results [36,37]. For example, Massingham et al. [36], reported PFT's in 87%, exacerbation in 100% and asthma symptom score in 25% of trials. Incorporation of exacerbations and asthma symptom scores into clinical trials and systematic reviews is supported by research showing that in addition to mortality and quality of life, these two outcomes are the most important ones for clinicians, patients and parents [38]. Although PFT's may be less important to families, the familiarity, reliability and repeatable nature of this measure almost assures its ongoing use in trials [10,39]. Although some consistency in selection of outcome type was observed, variability in the measurement technique was clear with both PFT and asthma symptom scores determined using three different scales. Unfortunately, this variability combined with missing relevant data prevented meta-analysis for PFT and asthma symptom score. Based on the findings from our systematic review, we support the suggestion by others [38] that asthma clinical research would benefit from a common set of outcomes, including the unit of measure or score.

There are some factors limiting the ability of this systematic review to provide a definitive answer regarding the risk and benefits of high-dose vitamin D in paediatric asthma outcomes. Although meta-analysis did suggest benefit for high-dose vitamin D in the prevention of asthma exacerbations, supporting evidence from PFT meta-analysis was not possible due to inconsistent use and reporting of outcome measures. Second, there was some potentially relevant heterogeneity in population and dosing regimen selection and these variations have the potential to compromise the validity of the calculated point estimate for the effect of vitamin D treatment on asthma exacerbations. Third, as with most paediatric systematic reviews, the total number of RCTs did not permit meta-regression to evaluate the impact of factors with the potential to moderate the treatment effect. Fourth, given that there were a limited number of studies with small sample sizes, an assessment of bias via funnel plots and/or Egger's tests was not undertaken. Finally, lack of data on vitamin D-related adverse outcomes such as hypercalcemia and hypercalciuria does not allow for a proper evaluation of risk and benefit. Although doses between 1000 and 4000 IU are considered safe in healthy children [19], this might not be true for asthmatic children receiving one or more other medications.

Altogether our findings support the completion of a large phase III RCT evaluating the role of high dose vitamin D supplementation in the asthma management. We would recommend evaluating a pediatric population over the age of 2 years with moderate to severe asthma who present with

vitamin D deficiency (25OHD < 50 nmol/L). To achieve maximum therapeutic benefit, vitamin D status should be rapidly normalised using age-based loading therapy (100 000–300 000 IU) and participants should be followed regularly and continue to receive monthly maintenance dosing to eliminate potential problems with drug compliance. As asthma exacerbations are patient centred and have the greatest impact on morbidity, cost of care, and risk of mortality, we believe that future studies should include exacerbations as a key outcome variable [40]. Further, it is essential that exacerbations be defined in a standardised and clinically important fashion; most studies have used emergency department visits, hospitalisation and/or need for systemic steroid therapy as indicators of a clinically important exacerbation [41]. In addition to asthma exacerbations, participants should be evaluated for differences in PFT change and controller medications as vitamin D may work to reduce inhaled corticosteroids or other medication requirements. Estimating a baseline asthma exacerbation rate of 25%, the clinical trial would need to randomise 300–400 children to be sufficiently powered to detect the RR reduction of 50% predicted by the meta-analysis. However, as the confidence interval suggested the true effect size could be as low as 33% (still a clinically important difference), a larger sample size could be rationalised.

Conclusion

Our systematic review on vitamin D supplementation in children suggests that high-dose vitamin D may have a role in improving asthma control by prevention of asthma exacerbations. Our review supports the need for a well-designed RCT on the effects of high-dose vitamin D supplementation in children with asthma.

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Declaration of interest

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Supplementary material available online

Supplementary Appendix Tables SA1–SA6