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Vitamin D for the management of asthma (Review)

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Williamson A, Martineau AR, Sheikh A, Jolliffe D, Griffiths CJ.
Vitamin D for the management of asthma.
Cochrane Database of Systematic Reviews 2023, Issue 2. Art. No.: CD011511.
DOI: 10.1002/14651858.CD011511.pub3.

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[Intervention Review]

Vitamin D for the management of asthma

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Editorial group: Cochrane Airways Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 2, 2023.

Citation: Williamson A, Martineau AR, Sheikh A, Jolliffe D, Griffiths CJ. Vitamin D for the management of asthma. *Cochrane Database of Systematic Reviews* 2023, Issue 2. Art. No.: CD011511. DOI: 10.1002/14651858.CD011511.pub3.

ABSTRACT

Background

Since the previous Cochrane Review on this topic in 2016, debate has continued surrounding a potential role for vitamin D in reducing risk of asthma exacerbation and improving asthma control. We therefore conducted an updated meta-analysis to include data from new trials completed since this date.

Objectives

To evaluate the effectiveness and safety of administration of vitamin D or its hydroxylated metabolites in reducing the risk of severe asthma exacerbations (defined as those requiring treatment with systemic corticosteroids) and improving asthma symptom control.

Search methods

We searched the Cochrane Airways Group Trial Register and reference lists of articles. We contacted the authors of studies in order to identify additional trials. Date of last search: 8 September 2022.

Selection criteria

We included double-blind, randomised, placebo-controlled trials of vitamin D in children and adults with asthma evaluating exacerbation risk or asthma symptom control, or both.

Data collection and analysis

Four review authors independently applied study inclusion criteria, extracted the data, and assessed risk of bias. We obtained missing data from the authors where possible. We reported results with 95% confidence intervals (CIs). The primary outcome was the incidence of severe asthma exacerbations requiring treatment with systemic corticosteroids. Secondary outcomes included the incidence of asthma exacerbations precipitating an emergency department visit or requiring hospital admission, or both, end-study childhood Asthma Control Test (cACT) or Asthma Control Test (ACT) scores, and end-study % predicted forced expiratory volume in one second (FEV1).

We performed subgroup analyses to determine whether the effect of vitamin D on risk of asthma exacerbation was modified by baseline vitamin D status, vitamin D dose, frequency of dosing regimen, form of vitamin D given, and age of participants.

Main results

We included 20 studies in this review; 15 trials involving a total of 1155 children and five trials involving a total of 1070 adults contributed data to analyses. Participant ages ranged from 1 to 84 years, with two trials providing data specific to participants under five years (n = 69) and eight trials providing data specific to participants aged 5 to 16 (n = 766). Across the trials, 1245 participants were male and 1229

were female, with two studies not reporting sex distribution. Fifteen trials contributed to the primary outcome analysis of exacerbations requiring systemic corticosteroids. The duration of trials ranged from three to 40 months; all but two investigated effects of administering cholecalciferol (vitamin D3). As in the previous Cochrane Review, the majority of participants had mild to moderate asthma, and profound vitamin D deficiency (25-hydroxyvitamin D (25(OH)D) < 25 nmol/L) at baseline was rare.

Administration of vitamin D or its hydroxylated metabolites did not reduce or increase the proportion of participants experiencing one or more asthma exacerbations treated with systemic corticosteroids (odds ratio (OR) 1.04, 95% CI 0.81 to 1.34; I^2 = 0%; 14 studies, 1778 participants; high-quality evidence). This equates to an absolute risk of 226 per 1000 (95% CI 185 to 273) in the pooled vitamin D group, compared to a baseline risk of 219 participants per 1000 in the pooled placebo group.

We also found no effect of vitamin D supplementation on the rate of exacerbations requiring systemic corticosteroids (rate ratio 0.86, 95% CI 0.62 to 1.19; I^2 = 60%; 10 studies, 1599 participants; high-quality evidence), or the time to first exacerbation (hazard ratio 0.82, 95% CI 0.59 to 1.15; I^2 = 22%; 3 studies, 850 participants; high-quality evidence). Subgroup analysis did not reveal any evidence of effect modification by baseline vitamin D status, vitamin D dose, frequency of dosing regimen, or age. A single trial investigating administration of calcidiol reported a benefit of the intervention for the primary outcome of asthma control.

Vitamin D supplementation did not influence any secondary efficacy outcome meta-analysed, which were all based on moderate- or high-quality evidence. We observed no effect on the incidence of serious adverse events (OR 0.89, 95% CI 0.56 to 1.41; I^2 = 0%; 12 studies, 1556 participants; high-quality evidence). The effect of vitamin D on fatal asthma exacerbations was not estimable, as no such events occurred in any trial. Six studies reported adverse reactions potentially attributable to vitamin D. These occurred across treatment and control arms and included hypercalciuria, hypervitaminosis D, kidney stones, gastrointestinal symptoms and mild itch. In one trial, we could not ascertain the total number of participants with hypercalciuria from the trial report.

We assessed three trials as being at high risk of bias in at least one domain; none of these contributed data to the analysis of the outcomes reported above. Sensitivity analyses that excluded these trials from each outcome to which they contributed did not change the null findings.

Authors' conclusions

In contrast to findings of our previous Cochrane Review on this topic, this updated review does not find evidence to support a role for vitamin D supplementation or its hydroxylated metabolites to reduce risk of asthma exacerbations or improve asthma control. Participants with severe asthma and those with baseline 25(OH)D concentrations < 25 nmol/L were poorly represented, so further research is warranted here. A single study investigating effects of calcidiol yielded positive results, so further studies investigating effects of this metabolite are needed.

PLAIN LANGUAGE SUMMARY

Does vitamin D reduce risk of severe asthma attacks or improve control of asthma symptoms?

Key messages

1) In contrast to our previous Cochrane Review on this topic, this updated review does not find that vitamin D offers protection against severe asthma attacks or improves control of symptoms.

2) Further trials are required in people with frequent severe asthma attacks and those with very low baseline vitamin D status, and into the potential for calcidiol (a particular form of vitamin D) to offer protective effects.

Why did we think that vitamin D might benefit patients with asthma?

Low blood levels of vitamin D (the 'sunshine vitamin') have been linked to an increased risk of severe asthma attacks, defined as those requiring oral (systemic) steroid medications.

Our previous Cochrane Review on this topic in 2016 found that vitamin D reduced the risk of asthma attacks, yet debate has continued, and some subsequent trials found vitamin D to have no effect. We therefore conducted an updated meta-analysis to include data from new trials completed since our last review.

What did we want to find out?

We wanted to find out if vitamin D supplementation:

• reduces the risk of severe asthma attacks;

• improves control of asthma symptoms;

• leads to any negative side effects.

What did we do?

We searched for randomised controlled trials that assessed the effect of vitamin D supplementation on the risk of severe asthma attacks and asthma symptom control. We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods.

We also analysed whether effects of vitamin D supplementation differed according to baseline vitamin D status, the dose or form of supplements administered, how often people took the supplements, or the age of participants.

What did we find?

We included data from 20 clinical trials in this review that involved a total of 2225 people; nine of these were included in the previous Cochrane Review on the topic and 11 were published since then. Of the 20 studies, 15 reported data on severe asthma attacks. The trials lasted between three and 40 months, and all but two investigated a particular form of vitamin D called cholecalciferol or vitamin D3. This is the most common form of vitamin D tablet.

• People given vitamin D supplements did not have a lower risk of severe asthma attacks compared to those given placebo (dummy medication).

• Vitamin D supplementation did not influence measurements of asthma control or breathing capacity; neither did it affect risk of serious harmful side effects.

What are the limitations of the evidence?

• People with severe asthma and those with very low vitamin D levels prior to supplementation were poorly represented, so we cannot assess whether vitamin D supplements might help these individuals.

• A single study investigating effects of calcidiol, an alternative form of vitamin D, showed a protective effect. Further investigation of this form of vitamin D is needed.

How up to date is this evidence?

This review updates our previous review. The evidence is up to date to September 2022.

Summary of findings 1. Summary of findings table - Vitamin D compared to placebo for the management of asthma

Vitamin D compared to placebo for the management of asthma

Patient or population: children and adults with predominantly mild to moderate asthma
Setting: primary and secondary care
Intervention: vitamin D
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with vitamin D				
Proportion of participants with one or more exacerbations treated with systemic corticosteroids follow-up: range 3 months to 40 months	219 per 1000	**226 per 1000** (185 to 273)	**OR 1.04** (0.81 to 1.34)	1778 (14 RCTs)	⊕⊕⊕⊕ High[a]	
Proportion of participants with one or more exacerbations requiring emergency department visit or hospitalisation, or both	79 per 1000	**46 per 1000** (22 to 94)	**OR 0.56** (0.26 to 1.21)	1070 (9 RCTs)	⊕⊕⊕⊖ Moderate[b]	
End-study asthma control test score assessed with: childhood Asthma Control Test, or linearly transformed Asthma Control Test Scale from: 0 to 27	The mean end-study asthma control test score was **22.98** points	MD **0.23 points higher** (0.26 lower to 0.73 higher)	-	1271 (7 RCTs)	⊕⊕⊕⊖ Moderate[c]	
End-study forced expiratory volume in 1 second, % predicted	The mean end-study forced expiratory volume in 1 second, % predicted was **93.80** %	MD **0.2 % higher** (1.24 lower to 1.63 higher)	-	1286 (11 RCTs)	⊕⊕⊕⊕ High	
Proportion of participants with one or more serious adverse events due to any cause	55 per 1000	**49 per 1000** (32 to 76)	**OR 0.89** (0.56 to 1.41)	1556 (12 RCTs)	⊕⊕⊕⊕ High	
Proportion of participants with fatal asthma exacerbation	0 per 1000	**0 per 1000** (0 to 0)	Not estimable	1976 (16 RCTs)	⊕⊕⊖⊖ Low[d]	
Withdrawals from trial	86 per 1000	**90 per 1000** (68 to 119)	**OR 1.05** (0.77 to 1.43)	2225 (20 RCTs)	⊕⊕⊕⊕ High	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_436923543367697621.

[a] Each of these GRADE assessments is discussed in full under Quality of the evidence.
[b] Downgraded one level due to imprecision, as 95% CI ranged from 0.26 to 1.21 and evidence drew on fewer studies than the primary outcome
[c] Downgraded one level due to heterogeneity, as $I^2 = 29\%$
[d] Downgraded two levels due to imprecision, as no events occurred in either arm of any trial considered

BACKGROUND

Description of the condition

Asthma is a chronic inflammatory condition of the airways, characterised by recurrent attacks of breathlessness, wheezing, cough, and chest tightness, commonly termed exacerbations. The prevalence of asthma varies widely between countries, ranging from 2.20% (China) to 12.1% (Tonga) (Soriano 2020). It can be diagnosed by respiratory pulmonary function testing showing reversible airway obstruction, including spirometry with bronchodilator reversibility or diurnal peak flow variation. Raised fractional exhaled nitric oxide levels can also be used to inform asthma diagnosis (Reddel 2009). Exacerbations represent the major cause of morbidity and mortality in people with asthma (Briggs 2021; Johnston 2006). Asthma exacerbations are commonly classified as severe when they require treatment with systemic corticosteroids or when they result in emergency department attendance, hospitalisation, or death (Reddel 2009). Severity of exacerbations may also be classified by patient symptoms, or by peak expiratory flow relative to patient baseline. Common precipitants of asthma exacerbation include acute respiratory infections and exposure to allergens and particulates (Singh 2006). Beyond exacerbations, asthma may also affect patient quality of life through ongoing symptoms such as breathlessness, functional impairment, financial burden of treatment, and emotional impacts (Reddel 2009).

Description of the intervention

Vitamin D is a fat-soluble micronutrient that has two parent forms: cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2). Cholecalciferol is synthesised in human skin from its precursor molecule 7-dehydrocholesterol on exposure to ultraviolet B (UVB) radiation in sunlight; it may also be ingested, either in the diet (primarily from eating oily fish or vitamin D-fortified foods) or as vitamin D supplements. Ergocalciferol is the plant and fungal form of the vitamin, which may be ingested in the diet (primarily by eating fungi) or as vitamin D supplements. In situations where cutaneous exposure to UVB radiation of appropriate intensity is limited (for example, during winter at latitudes above 34°N or below 34°S, or in settings where people do not regularly expose their skin to sunlight), dietary sources of vitamin D or vitamin D supplements may be required to meet the body's vitamin D requirement (Holick 2007).

Following cutaneous synthesis or ingestion, both forms of parent vitamin D undergo metabolism to form 25-hydroxyvitamin D (25(OH)D), the major circulating vitamin D metabolite whose serum concentration indicates vitamin D status. 25-hydroxylation may occur in the liver and in extra-hepatic tissues, including leucocytes (Holick 2007). Serum 25(OH)D concentrations less than 50 nmol/L are widely accepted to indicate vitamin D deficiency; concentrations less than 25 nmol/L represent profound deficiency. Concentrations of 50 nmol/L to 74 nmol/L may represent a milder state of inadequate vitamin D status, commonly termed 'vitamin D insufficiency' (Holick 2007). 25(OH)D undergoes a second hydroxylation step at the 1-alpha position to form 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), the steroid hormone and active vitamin D metabolite that mediates the biological actions of vitamin D by binding the vitamin D receptor to regulate gene expression (Holick 2007). This 1-alpha hydroxylation step is catalysed by the enzyme CYP27B1, which is expressed in many tissues including the kidney, leucocytes, and pulmonary epithelium; expression of CYP27B1 in leucocytes and pulmonary epithelium is up-regulated in response to infection and inflammation (Greiller 2015).

This review included randomised controlled trials evaluating the effects of administration of vitamin D_3, vitamin D_2, 25(OH)D, or $1,25(OH)_2D$, by any route and at any dose. Vitamin D_3, vitamin D_2, and 25(OH)D are usually administered orally; the 'parent compounds' vitamin D_3 and vitamin D_2 may also be given intramuscularly. Intramuscular administration of a bolus dose of vitamin D induces a slower increase and a lower peak in serum 25(OH)D than oral administration of the same dose (Romagnoli 2008); consequently, this route of administration is not widely employed in clinical trials of vitamin D. The functional in vivo half-life of 25(OH)D in the circulation is one to two months; accordingly, it takes at least three months to attain steady-state concentrations of 25(OH)D in response to daily administration of vitamin D (Heaney 2003). Due to the relatively long half-life of 25(OH)D, parent vitamin D and 25(OH)D may be administered intermittently as well as daily; weekly and monthly dosing regimens are often employed, and more widely spaced dosing regimens are also sometimes used. However, intermittent bolus dosing may result in large non-physiological fluctuations in serum 25(OH)D concentration, which may cause undesirable effects including increased risk of recurrent pneumonia, falls and fractures (Hollis 2013; Martineau 2012; Sanders 2010; Vieth 2009).

How the intervention might work

About one billion people worldwide are estimated to have 25(OH)D levels of less than 75 nmol/L (Holick 2007). Inadequate vitamin D status has been reported to be common among people with asthma in a variety of settings. Cross-sectional (Brehm 2012; Shahin 2017) and cohort (Brehm 2010; Confino-Cohen 2014) studies have demonstrated independent associations between inadequate vitamin D status and increased risk of exacerbations. Administration of vitamin D_3, vitamin D_2, or 25(OH)D results in increased circulating concentrations of 25(OH)D. This 25(OH)D acts as a substrate for CYP27B1 expressed in the kidney and multiple extra-renal tissues. Of particular relevance for asthma, CYP27B1 expression in the airway and leucocytes is induced during infection and inflammation, so that the active vitamin D metabolite $1,25(OH)_2D$ is synthesised locally in the lung. $1,25(OH)_2D$ ligates the vitamin D receptor (VDR) to induce antimicrobial activity, (for example, by induction of antimicrobial peptide expression) (Greiller 2015; Martineau 2007), and exert anti-inflammatory activity (for example by induction of the anti-inflammatory cytokine IL-10, suppression of pro-inflammatory tumour necrosis factor and interferon-γ inducible chemokines, and inhibition of lipopolysaccharide-induced synthesis of reactive oxygen species) (Coussens 2012; Lan 2014; Mann 2014). This combination of antimicrobial, antiviral, and anti-inflammatory activity might decrease the risk of exacerbations, which are often precipitated by respiratory infection and which are characterised by dysregulated pulmonary inflammation. Of particular relevance to asthma, $1,25(OH)_2D$ has been shown to inhibit TH17 cytokine production and enhance responsiveness to inhaled corticosteroids for production of interleukin-10 ex vivo in people with asthma (Nanzer 2014; Xystrakis 2006). These findings raise the possibility that administration of vitamin D or its hydroxylated metabolites

may have a role in reducing exacerbation risk and improving symptom control in combination with inhaled corticosteroids, as well as independently. However, controversy exists regarding what dose of vitamin D, if any, is optimal for reducing the risk of asthma exacerbations, and whether benefits of supplementation are restricted to those with baseline vitamin D deficiency.

Why it is important to do this review

There is considerable interest in the therapeutic potential of vitamin D in asthma to improve symptom control and reduce exacerbation risk. Our 2016 Cochrane Review on this topic found that vitamin D offers protection against severe asthma attacks in adults with mild to moderate asthma (Martineau 2016), defined as requiring Global Initiative for Asthma (GINA) step 4 treatment or below (GINA 2022). However, it identified several research gaps, identifying a need for further trials focusing on children, those with profoundly deficient baseline vitamin D status (< 25 nmol/L), and those experiencing frequent severe exacerbations. Debate regarding a potential therapeutic role for vitamin D in asthma has continued due to inconsistency of outcomes of randomised controlled trials conducted since January 2016 (the end-date of our literature search for the previous review). We therefore conducted an updated meta-analysis to include data from these new trials (Aglipay 2019; Andújar-Espinosa 2021; Camargo 2021; Ducharme 2019; Forno 2020; Jat 2020; Jerzynska 2016; Jiang 2017; Kerley 2016; Ramos-Martínez 2018; Thakur 2021).

OBJECTIVES

To evaluate the effectiveness and safety of administration of vitamin D or its hydroxylated metabolites in reducing the risk of severe asthma exacerbations (defined as those requiring treatment with systemic corticosteroids) and improving asthma symptom control.

METHODS

Criteria for considering studies for this review

Types of studies

We reviewed double-blind, randomised, placebo-controlled trials of at least 12 weeks' duration as per the previous Cochrane Review on this topic. We included studies reported as full text and unpublished data. Where eligible studies were published as abstracts only, we contacted the authors to request the full text of the trial report; where the full text was unavailable, we listed such studies as 'ongoing'.

Types of participants

We included children and adults with a clinical diagnosis of asthma, based on the presence of characteristic symptoms and signs (i.e. wheeze, shortness of breath, chest tightness, or cough), variable airflow obstruction, or both. We imposed no restrictions regarding disease severity, baseline vitamin D status, or duration of treatment with asthma medication.

Types of interventions

The review was open to studies in which vitamin D_3, vitamin D_2, 25(OH)D or 1,25$(OH)_2$D were administered at any dose.

Types of outcome measures

Primary outcomes

1. Incidence of severe asthma exacerbations, defined as those requiring treatment with systemic corticosteroids

Secondary outcomes

1. Incidence of asthma exacerbations precipitating an emergency department visit or requiring hospital admission, or both
2. End-study Childhood Asthma Control Test (cACT) or Asthma Control Test (ACT) score
3. End-study % predicted forced expiratory volume in one second (FEV1)
4. Incidence of any severe adverse event, any cause
5. Incidence of adverse reactions attributed to administration of vitamin D or its metabolites
6. Incidence of fatal asthma exacerbation
7. Incidence of asthma exacerbation as defined in the study protocol
8. End-study % lower airway eosinophils
9. End-study log10 total IgE, IU/ml
10. End-study % predicted forced vital capacity (FVC)
11. End-study peak expiratory flow rate (PEFR)
12. Proportion of participants withdrawing from the trial

We integrated cACT and ACT scores into a single composite scale to allow for comparison, following the standardised linear transformation outlined in Han 2021: ACT' = c*(ACT-a)/(b-a) where a denotes the ACT minimum score; b denotes the ACT maximum score; and c denotes the cACT maximum score.

We would have meta-analysed the following secondary outcomes had sufficient data been available.

1. Time off school or work due to asthma symptoms
2. Beta2-agonist inhaler use
3. End-study asthma quality of life as judged by use of a validated instrument
4. End-study fractional exhaled nitric oxide (FeNO) concentration
5. End-study airway reactivity (PC20)
6. Costs from the perspective of healthcare providers

Results for these outcomes are instead presented in narrative form where data are available.

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group's Specialised Register (CAGR), which is maintained by the information specialist for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Allied and Complementary Medicine (AMED), and PsycINFO, and hand-searching of respiratory journals and meeting abstracts (please see Appendix 1 for further details). We searched all records in the CAGR using the search strategy in Appendix 2.

We also conducted searches of ClinicalTrials.gov (www.ClinicalTrials.gov) the World Health Organization trials portal (www.who.int/ictrp/en/), the ISRCTN registry (www.isrctn.com/), the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au/), and the UMIN Clinical Trials Registry (www.umin.ac.jp/ctr/). We searched all databases from their inception to 8 September 2022, and imposed no restriction on language of publication.

Searching other resources

We checked reference lists of all primary studies and review articles for additional references. We searched relevant manufacturers' websites for trial information.

We searched for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) at the time of our final database search on 8 September 2022. We included these alongside the relevant trials.

We also contacted a panel of international experts for information on trials in progress.

Data collection and analysis

Selection of studies

Four review authors assessed eligibility. Anne Williamson (AW) and Adrian R Martineau (ARM) independently screened the titles and abstracts of all the potentially relevant new studies identified by the search, coding them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We then retrieved the full-text study reports/publication, and two people (AW and ARM) independently screened the full text, identifying studies for inclusion and identifying and recording reasons for exclusion of the ineligible studies. Any disagreements were resolved through discussion, or by consultation with other members of the review team (Christopher J Griffiths (CJG) and Aziz Sheikh (AS)), or both. Three review authors (AW, AS, CJG) assessed eligibility of one new study co-authored by ARM (Camargo 2021). We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009). The eligibility of studies included in the previous review was not re-assessed, with all studies previously assessed as eligible being included in this current review.

Data extraction and management

We used the same data collection form for study characteristics and outcome data as for our previous review (Martineau 2016). Two review authors (AW, ARM, and/or DJ) extracted study characteristics from each included study. We extracted the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: number, mean age, age range, sex, body mass index, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (AW and ARM) independently extracted outcome data from each newly included study, except for the new study co-authored by ARM (Camargo 2021), for which AW and CJG extracted data. If studies did not report outcome data in a usable way, we noted this in the 'Characteristics of included studies' table. We resolved disagreements by consensus or by involving a third person (CJG or AS). One review author (AW) transferred data into the RevMan 2020 file. We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports.

Assessment of risk of bias in included studies

Two review authors (ARM and AW) independently assessed the risk of bias for each newly included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We resolved any disagreements by discussion or by involving another review author (CJG, AS, or DJ). AW and CJG performed the risk of bias assessment for the study co-authored by ARM (Camargo 2021). We assessed the risk of bias according to the following domains.

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other biases, including study size.

We graded each potential source of bias as high, low, or unclear and provide a quote from the study report together with a justification for our judgement in the risk of bias table. We summarised the risk of bias judgements across different studies for each of the domains listed. Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the risk of bias table. When considering treatment effects, we took into account the risk of bias for the studies contributing to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to a published protocol (Martineau 2021), and have reported any deviations from it in the Differences between protocol and review section.

Measures of treatment effect

We analysed dichotomous data as odds ratios (OR), event rates as rate ratios (RR), and times to first event as hazard ratios (HR). We took RRs directly from the trial results, where reported; otherwise, we calculated ratios from the published number of events and participant years of follow-up as per Section 9.4.8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022). This was required for four studies: Andújar-Espinosa 2021; Jat 2020; Jensen 2016; Thakur 2021. We analysed other continuous outcome measures as mean difference (MD) or standardised mean

difference (SMD). Where results were presented as a median and interquartile range (IQR) with symmetrical data (Jat 2020), we converted this to mean and standard deviation (SD) following Section 7.7.3.5 of the *Cochrane Handbook* (Higgins 2022). We used generic inverse variance meta-analysis where adjusted measures of treatment effect from individual trials were included. We entered data presented as a scale with a consistent direction of effect. For analyses of outcomes in which no events occurred in some studies, we also calculated risk differences (RD).

Unit of analysis issues

Where multiple trial arms were reported in a single trial, for instance people with asthma versus people with chronic obstructive pulmonary disease (COPD), we included only the relevant arms (Aglipay 2019; Camargo 2021; Jerzynska 2016). If two comparisons (for example drug A versus placebo and drug B versus placebo) had been combined in the same meta-analysis, we would have halved the control group to avoid double-counting.

For outcomes measured at different time points, we included the longest time point after randomisation.

If data had been expressed in unconventional units of analysis, we would have converted them to conventional units, liaising with the authors if required.

Dealing with missing data

We contacted investigators to verify key study characteristics and to obtain missing numerical outcome data where possible. We asked all investigators to provide data relating to exacerbations requiring treatment with systemic corticosteroids or emergency department attendance/hospitalisation, or both, where these were not reported in the manuscript or abstract.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity and inconsistency among the trials in each analysis, following the *Cochrane Handbook*, Section 10.10.2 (Higgins 2022).

Assessment of reporting biases

We created and examined funnel plots for outcomes with more than 10 trials to explore possible small study biases.

Data synthesis

We used a random-effects model for the primary analysis and performed sensitivity analyses using fixed-effect models for the primary outcome. We analysed all data by intention-to-treat where possible. We synthesised dichotomous data as ORs, event rates as RRs and times to first event as HRs. We synthesised other continuous outcome measures as MD or SMD. We would have calculated the number needed to treat for an additional beneficial outcome (NNTB) using the Visual Rx NNT calculator if meta-analysis of dichotomous outcomes had revealed a beneficial effect of allocation to vitamin D (www.nntonline.net/visualrx/). We would have similarly calculated the number needed to treat for an additional harmful outcome (NNTH) if meta-analysis of dichotomous outcomes had revealed a harmful effect of vitamin D.

Subgroup analysis and investigation of heterogeneity

We carried out the following prespecified subgroup analysis for the outcome of asthma exacerbation treated with systemic corticosteroids.

1. Baseline vitamin D status (serum 25(OH)D < 25 nmol/L versus 25 to 49.9 nmol/L versus 50 to 74.9 nmol/L versus ≥ 75 nmol/L).
2. The dose (daily equivalent of < 2000 IU versus > 2000 IU) and form of vitamin D administered (cholecalciferol versus calcidiol versus calcitriol).
3. The frequency of administration (daily versus intermittent bolus doses).
4. The mean age of participants in the trial (< 5 years versus 5 to 16 years versus > 16 years).

Studies administering an initial bolus dose followed by subsequent daily doses were included in the daily dosing subgroup (Castro 2014; Jensen 2016). Where studies reported data on participants which did not wholly fit into a prespecified age category, we included the results in the subgroup appropriate for median participant age (Jat 2020; Majak 2011).

We formally assessed for heterogeneity across subgroups using the Borenstein 2013 test in RevMan 2020. If this had suggested significant differences in effect size between subgroups including more than one study, we would have conducted a multivariable meta-regression analysis.

We prespecified that we would also carry out the following subgroup analyses for the outcome of asthma exacerbation treated with systemic corticosteroids.

1. Further subgroups for daily dose equivalent (< 400 IU versus 400 to 2000 IU).
2. Severity of asthma and concomitant asthma treatment being taken (e.g. taking versus not taking inhaled corticosteroids, taking versus not taking leukotriene receptor antagonists).
3. Genetic variation in pathways of vitamin D metabolism, transport, and signalling (e.g. GC 2/2 versus 2/1 versus 1/1 genotype for the GC polymorphism of the vitamin D binding protein).
4. Body mass index (e.g. < 25 kg/m^2 versus ≥ 25 kg/m^2).

However, limitations of the available data (for example, where data for participants within different subgroups could not be disaggregated, or where numbers of participants or events or both within a subgroup were small) precluded the conduct of such subgroup analyses.

Sensitivity analysis

We carried out the following sensitivity analyses.

1. Exclusion of data from publications assessed as being at high risk of bias in one or more of the following domains: sequence generation, allocation concealment, blinding, completeness of outcome data, or selective outcome reporting.
2. Analysis of our primary outcome using fixed-effect models rather than random-effects models.

Summary of findings and assessment of the certainty of the evidence

We created a summary of findings table presenting all primary and secondary outcomes that were meta-analysed. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the body of evidence as it related to the studies that contributed data to the meta-analyses for the prespecified outcomes.

Where data from primary studies conducted by review authors contributed to a given outcome, the quality of the evidence was assessed by review authors who were not involved with those primary studies (AW and CJG). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022), using GRADEpro GDT software. We justified all decisions to downgrade or upgrade the quality of studies using footnotes where necessary.

RESULTS

Description of studies

Results of the search

We identified a total of 1055 new references by searching the Cochrane Airways Group Register and clinical trial registries, and in consultation with international experts. The most recent search was run on 8 September 2022. After removing 478 duplicate references (459 by automated screening and 19 manually), we screened 382 references to 321 different studies for eligibility. We excluded 290 studies on the basis of their titles or abstracts or both. We assessed the remaining 32 studies for eligibility by consulting the full text of associated references or contacting study authors, or both. We then excluded 13 further studies which did not meet eligibility criteria for inclusion, and classified eight newly identified studies as ongoing. This resulted in 11 new included studies, in addition to the nine studies analysed in the previous Cochrane Review on this topic. Thus, we included 20 studies in the final analysis (Figure 1). We have presented the reasons for excluding potentially relevant studies in the Characteristics of excluded studies table.

Figure 1.

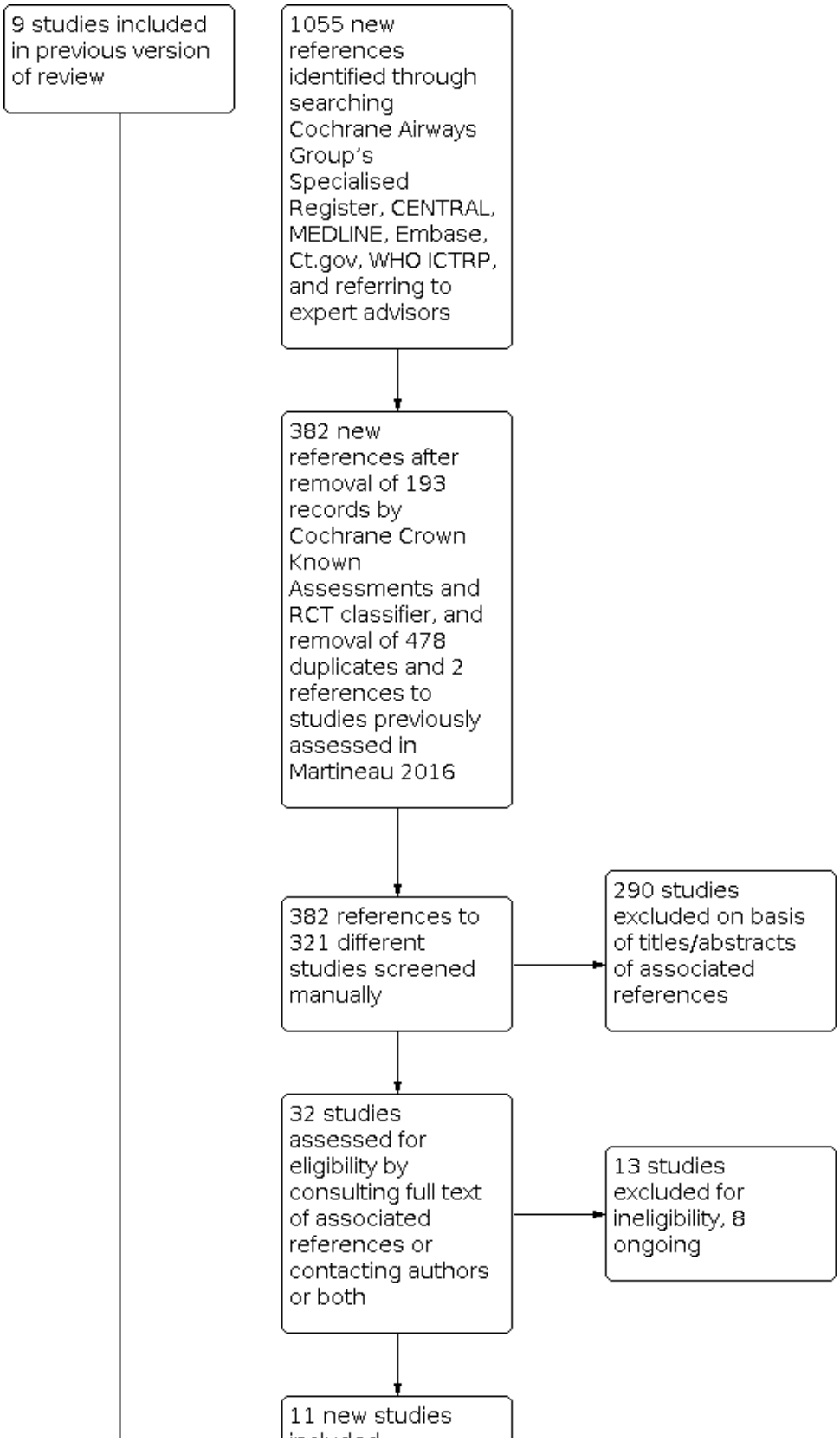
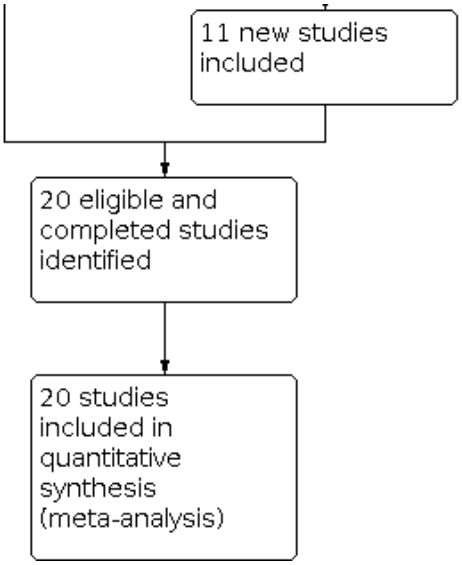


Figure 1. (Continued)



Included studies

See Characteristics of included studies for full details. Twenty studies including a total of 2225 participants with asthma met the inclusion criteria for this review (Aglipay 2019; Andújar-Espinosa 2021; Camargo 2021; Castro 2014; Ducharme 2019; Forno 2020; Jat 2020; Jensen 2016; Jerzynska 2016; Jiang 2017; Kerley 2016; Lewis 2012; Majak 2009; Majak 2011; Martineau 2015; Ramos-Martínez 2018; Tachimoto 2016; Thakur 2021; Urashima 2010; Yadav 2014).

Study design

All included studies were double-blind randomised placebo-controlled trials with a parallel-group design, open to male and female participants of any ethnic background. Thirteen were conducted at a single centre (Andújar-Espinosa 2021; Ducharme 2019; Jat 2020; Jensen 2016; Jerzynska 2016; Jiang 2017; Kerley 2016; Lewis 2012; Majak 2009; Majak 2011; Ramos-Martínez 2018; Thakur 2021; Yadav 2014), and seven were multicentre studies (Aglipay 2019; Camargo 2021; Castro 2014; Forno 2020; Martineau 2015; Tachimoto 2016; Urashima 2010). Seventeen studies recruited only in secondary care, two studies recruited only in primary care (Aglipay 2019; Camargo 2021), and one study recruited in both settings (Martineau 2015). Duration of follow-up ranged from three months (Thakur 2021) to an average of 3.3 years (Camargo 2021).

All trials were restricted to individuals with a physician diagnosis of asthma; three trials additionally based eligibility on evidence of reversible or variable airway obstruction (Castro 2014; Forno 2020; Martineau 2015), and one also required participants to have an FEV1 of at least 70% of predicted (Forno 2020). Two also required recurrent upper respiratory tract infections (Ducharme 2019; Ramos-Martínez 2018), and another was restricted to those with a concomitant clinical diagnosis of grass-related moderate-to-severe rhinoconjunctivitis (Jerzynska 2016).

Current or recent treatment with inhaled corticosteroids was a requirement for six trials (Castro 2014; Forno 2020; Jat 2020; Kerley 2016; Majak 2009; Martineau 2015), and an exclusion criterion for two trials (Jerzynska 2016; Majak 2011). One trial excluded participants who had received oral corticosteroid therapy in the year prior to enrolment (Urashima 2010), and another excluded those who were receiving chronic oral corticosteroid therapy prior to enrolment (Forno 2020). Conversely, three trials required one or more exacerbations requiring rescue oral corticosteroids in the preceding six months or year (Ducharme 2019; Forno 2020; Jensen 2016). All the remaining trials included at least some participants who were taking inhaled corticosteroids.

Six trials included baseline vitamin D status as an eligibility criterion; one restricted eligibility to people with baseline 25(OH)D concentration of 50 nmol/L or less (Jat 2020), two restricted eligibility to those with baseline 25(OH)D concentration less than 75 nmol/L (Andújar-Espinosa 2021; Castro 2014), one excluded those with a baseline 25(OH)D concentration less than 30 nmol/L (Thakur 2021), and one excluded those with a baseline 25(OH)D concentration that was either less than 35 nmol/L or greater than or equal to 75 nmol/L(Forno 2020). Fourteen trials had exclusion criteria relating to maximum permitted pre-trial or concomitant supplemental vitamin D intake, or both (Andújar-Espinosa 2021; Camargo 2021; Castro 2014; Ducharme 2019; Forno 2020; Jat 2020; Jensen 2016; Jerzynska 2016; Jiang 2017; Majak 2009; Majak 2011; Martineau 2015; Tachimoto 2016; Thakur 2021).

Participants

Fifteen studies involved a total of 1155 children (Aglipay 2019; Ducharme 2019; Forno 2020; Jat 2020; Jensen 2016; Jerzynska 2016; Jiang 2017; Kerley 2016; Lewis 2012; Majak 2009; Majak 2011; Tachimoto 2016; Thakur 2021; Urashima 2010; Yadav 2014), and five studies involved 1070 adults (Andújar-Espinosa 2021; Camargo 2021; Castro 2014; Martineau 2015; Ramos-Martínez 2018). Participants were ethnically diverse, reflecting the broad range of geographic settings: Canada (Aglipay 2019; Ducharme 2019; Jensen 2016), India (Jat 2020; Thakur 2021; Yadav 2014), Japan (Tachimoto 2016; Urashima 2010), Poland (Jerzynska 2016; Majak 2009; Majak 2011), the UK (Martineau 2015), Spain (Andújar-Espinosa 2021), New Zealand (Camargo 2021), China (Jiang 2017), Ireland (Kerley 2016), Mexico (Ramos-Martínez 2018), and the USA (Castro 2014; Forno 2020; Lewis 2012). The majority of participants

had mild to moderate asthma, defined as requiring GINA step 4 treatment or below, and a minority had severe asthma. Where measured, mean/median baseline serum 25(OH)D concentration ranged from 28 nmol/L (Jat 2020) to 89 nmol/L (Majak 2011). A minority of participants had serum 25(OH)D concentrations in the profoundly deficient range (less than 25 nmol/L).

Intervention

All studies but two (Andújar-Espinosa 2021; Ramos-Martínez 2018) administered oral vitamin D_3 (cholecalciferol) to participants in the intervention arm. Ramos-Martínez 2018 instead administered oral calcitriol (1,25-$(OH)_2D_3$) to participants in the intervention arm, at a dose of 0.25 µg/day. Andújar-Espinosa 2021 administered oral calcidiol, at a dose of 16,000 IU per week. There was considerable heterogeneity in vitamin D dosage regimens employed. Twelve studies exclusively used daily dosing regimens (Aglipay 2019; Forno 2020; Jat 2020; Jerzynska 2016; Jiang 2017; Kerley 2016; Lewis 2012; Majak 2011; Ramos-Martínez 2018; Tachimoto 2016; Thakur 2021; Urashima 2010). Of the other studies, two used weekly dosing (Andújar-Espinosa 2021, Majak 2009), one used monthly dosing (Yadav 2014), one used two-monthly dosing (Martineau 2015), two gave a bolus dose at the start of the study, followed by daily dosing (Castro 2014; Jensen 2016), one gave a bolus dose followed by monthly dosing (Camargo 2021), and one administered a bolus at baseline and a bolus at 3.5 months (Ducharme 2019).

One study administered low-dose vitamin D (400 IU/day) to participants in both the control and intervention arms; participants in the intervention arm of this study received an additional bolus of 100,000 IU vitamin D at the start of the study (Jensen 2016). Another study administered low-dose vitamin D (400 IU/day) to participants in the control arm, and high-dose vitamin D (2000 IU/day) to participants in the intervention arm (Aglipay 2019). One study also administered an additional grass pollen extract to both intervention and control arms (Jerzynska 2016). For the 14 trials in which vitamin D was given daily (with or without additional bolus doses) (Aglipay 2019; Castro 2014; Forno 2020; Jat 2020; Jensen 2016; Jerzynska 2016; Jiang 2017; Kerley 2016; Lewis 2012; Majak 2011; Ramos-Martínez 2018; Tachimoto 2016; Thakur 2021; Urashima 2010), the median daily dose was 1000 IU/day, ranging from 400 IU/day (Jensen 2016) to 4000 IU/day (Castro 2014; Forno 2020).

Where serum 25(OH)D concentration was assessed, the intervention resulted in an inter-arm difference in follow-up concentration on at least one follow-up time point in 12 studies (Andújar-Espinosa 2021; Camargo 2021; Castro 2014; Ducharme 2019; Forno 2020; Jat 2020; Jensen 2016; Jerzynska 2016; Kerley 2016; Martineau 2015; Tachimoto 2016; Thakur 2021), but not in three others (Lewis 2012; Majak 2009; Majak 2011).

Outcomes

Seventeen trials reported asthma exacerbation as an outcome measure (Aglipay 2019; Andújar-Espinosa 2021; Camargo 2021; Castro 2014; Ducharme 2019; Forno 2020; Jat 2020; Jensen 2016; Jerzynska 2016; Kerley 2016; Majak 2009; Majak 2011; Martineau 2015; Tachimoto 2016; Thakur 2021; Urashima 2010; Yadav 2014). Definitions of exacerbation varied significantly between trials. Fifteen trials reported data on exacerbations requiring treatment with systemic corticosteroids (Andújar-Espinosa 2021; Camargo 2021; Castro 2014; Ducharme 2019; Forno 2020; Jat 2020; Jensen 2016; Jerzynska 2016; Kerley 2016; Majak 2009; Majak 2011; Martineau 2015; Tachimoto 2016; Thakur 2021; Urashima 2010).

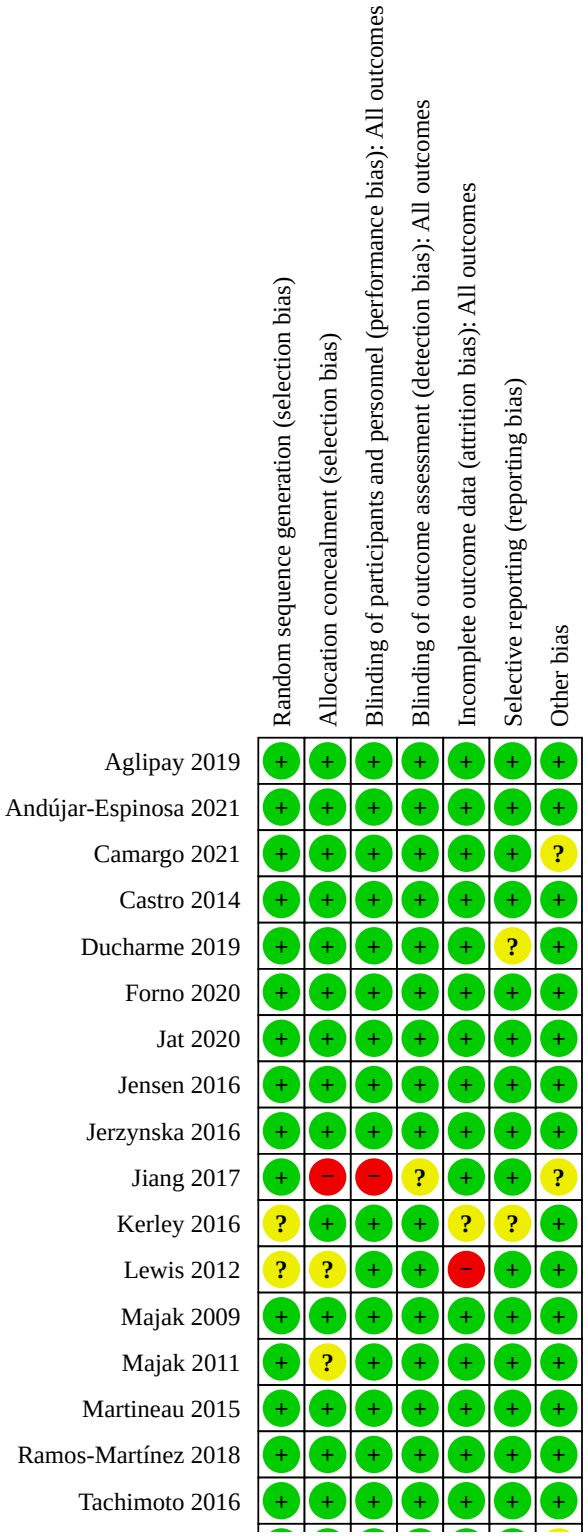
Excluded studies

We excluded 35 studies with reasons. See Characteristics of excluded studies for full details.

Risk of bias in included studies

An overview of risk of bias judgements is shown in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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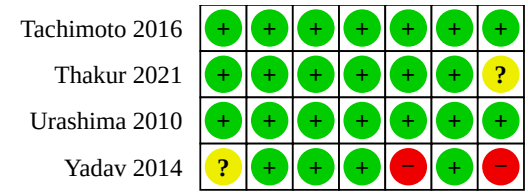


Allocation

Three studies did not report the method of sequence generation (Kerley 2016; Lewis 2012; Yadav 2014), and two studies did not report the method of allocation concealment (Lewis 2012; Majak 2011). We have therefore classified the risk of selection bias for these studies as 'unclear'. One study (Jiang 2017) stated that investigators were divided into planning and dispensing, and those in charge of planning did not disclose the experimental and placebo medications to the dispenser and participants. We classified this as high risk of bias, as it suggested that those in charge of allocating participants may not have been blinded. We assessed the risk of selection bias for the remaining studies as low.

Blinding

Participants and study personnel, including those who administered the intervention, were effectively blinded to allocation for all studies with the possible exception of Jiang and colleagues, as outlined above (Jiang 2017). Accordingly, we assessed the risk of performance and detection bias as low for all studies except for Jiang 2017. We classified this study as being at high risk of bias for blinding participants and study personnel, and unclear risk of bias for blinding of outcome assessment.

Incomplete outcome data

One-third of participants (10 out of 30) in the study by Lewis and colleagues were lost to follow-up (Lewis 2012); we have therefore assessed the risk of attrition bias as high for this study. The study by Yadav and colleagues reports that 18 out of 100 participants were lost to follow-up, but follow-up data for 100 participants were presented for the final follow-up visit (Yadav 2014). This discrepancy led us to assess the risk of attrition bias as being high for this study.

We also assessed Kerley 2016 as being at unclear risk of attrition bias, as there was a high rate of loss to follow-up (12 of 51 participants, 7 prior to randomisation and 5 postrandomisation) but similar rates of loss to follow-up between arms (7 out of 24 intervention arm, 5 out of 27 control arm). We assessed the risk of attrition bias for the remaining studies as low.

Selective reporting

The study by Ducharme and colleagues reported different primary and secondary outcomes to those prespecified in the study protocol as a result of premature trial cessation due to partial funding (Ducharme 2019). However, the study presented and explained this clearly. We therefore assessed the risk of reporting bias as unclear. The study by Kerley and colleagues reported its primary outcome prespecified in the trial protocol, but did not report two secondary outcomes; height velocity and a parental diary of child asthma symptoms (Kerley 2016). These were not outcomes assessed by our review, but this discrepancy led us to assess the risk of reporting bias as unclear.

We found no evidence of selective reporting for any of the remaining studies and have therefore assessed the risk of reporting bias as low.

Other potential sources of bias

The study by Camargo and colleagues defined an asthma exacerbation as “any prescription of oral corticosteroids more than 20 days apart for a short period”, yet participants may have been prescribed oral corticosteroids for other reasons, including rescue packs to treat future exacerbations (Camargo 2021). Investigators sought to minimise this by excluding participants with conditions other than asthma in which systemic corticosteroids may be indicated (e.g. autoimmune disease), but there may still have been residual non-asthma causes of steroid prescriptions. However, this risk was unlikely to differ between intervention and control arms in a way that systematically biases results. Therefore, we assessed this study as being at unclear risk of misclassification bias. In the study by Yadav and colleagues, we noted a change in classification of asthma severity between the six-month time point and earlier time points (Yadav 2014). This suggested a high risk of misclassification bias operating at the final follow-up time point. We assessed the study by Jiang and colleagues (Jiang 2017) as being at unclear risk of other bias, as only participants who completed the trial were analysed in baseline outcomes, with baseline characteristics of those lost to follow-up not presented. Lastly, the study by Thakur and colleagues found baseline cACT scores differed significantly between treatment and placebo groups (Thakur 2021). However, this meta-analysis considers the change in cACT from baseline to end-study, minimising potential for bias to operate. We therefore classified this study as being at unclear risk of other bias. We identified no other potential sources of bias for the remaining included trials.

Effects of interventions

See: **Summary of findings 1** Summary of findings table - Vitamin D compared to placebo for the management of asthma

See: Summary of findings 1. This review was based on a published protocol, Martineau 2021.

Vitamin D versus placebo: all eligible trials

Twenty trials with a total of 2225 participants (1155 children and 1070 adults) contributed to this comparison for at least one outcome. Fifteen trials contributed to this comparison for analysis of the primary outcome of exacerbations requiring systemic corticosteroids; 14 contributed data on whether vitamin D administration influenced the proportion of participants experiencing one or more asthma exacerbations treated with

systemic corticosteroids (Analysis 1.1), with one further study contributing evidence on the rate of asthma exacerbations treated with systemic corticosteroids (Analysis 1.2).

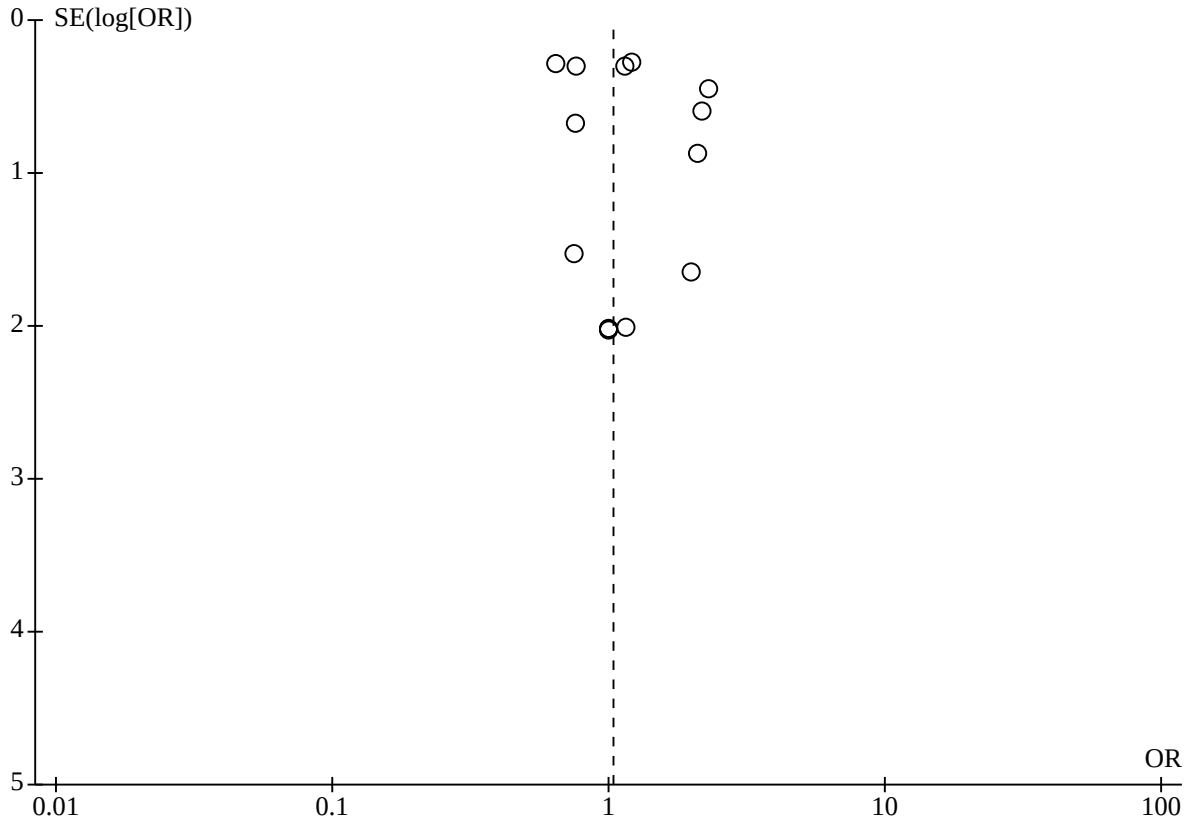
Primary outcome

Incidence of severe asthma exacerbations, defined as those treated with systemic corticosteroids

Analyses including all participants

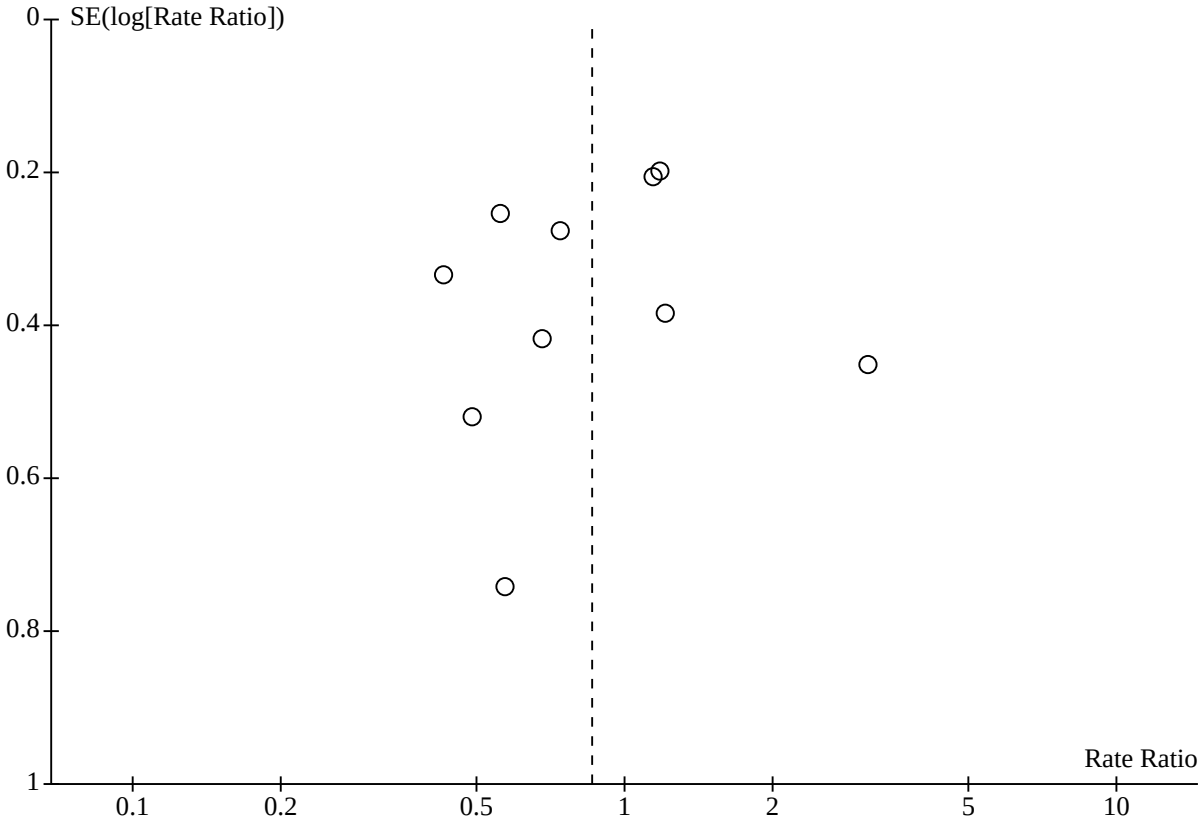
Administration of vitamin D did not reduce or increase the proportion of participants experiencing one or more asthma exacerbations treated with systemic corticosteroids (OR 1.04, 95% CI 0.81 to 1.34; I^2 = 0%; 14 studies, 1778 participants; high-quality evidence; Analysis 1.1). There was low heterogeneity across studies for this outcome, with I^2 = 0%. A funnel plot of included studies for this outcome is presented in Figure 3. This appears approximately symmetrical, with no evidence of small-study or publication bias.

Figure 3. Forest plot of comparison: vitamin D versus placebo (all studies), outcome 1.1: proportion of participants experiencing one or more asthma exacerbations treated with systemic corticosteroids



We also found no evidence that vitamin D administration affected the rate of asthma exacerbations treated with systemic corticosteroids (rate ratio 0.86, 95% CI 0.62 to 1.19; I^2 = 60%; 10 studies, 1599 participants; high-quality evidence; Analysis 1.2). A funnel plot of included studies for this outcome is presented in Figure 4.

Figure 4. Funnel plot of comparison 1: Vitamin D versus placebo (all studies), outcome 1.2 Rate ratio, exacerbation requiring corticosteroids



Finally, we found no evidence to suggest a benefit of vitamin D for the outcome of time to first exacerbation treated with systemic corticosteroids (hazard ratio 0.82, 95% CI 0.59 to 1.15; I^2 = 22%; 3 studies, 850 participants; high-quality evidence; Analysis 1.3).

Subgroup analyses

We conducted four prespecified subgroup analyses for our primary outcome.

First, we stratified by participant baseline vitamin D status (Analysis 1.4; serum 25(OH)D < 25 nmol/L versus 25 to 49.9 nmol/L versus 50 to 74.9 nmol/L versus ≥ 75 nmol/L). Vitamin D administration did not influence the proportion of participants experiencing one or more asthma exacerbations treated with systemic corticosteroids in any of these subgroups; baseline < 25 nmol/L (OR 0.78, 95% CI 0.15 to 3.96; I^2 = 63%; 4 studies, 198 participants; low-quality evidence), 25 to 49.9 nmol/L (OR 0.91, 95% CI 0.57 to 1.44; I^2 = 0%; 8 studies, 515 participants; low-quality evidence), 50 to 74.9 nmol/L (OR 1.16, 95% CI 0.60 to 2.25; I^2 = 29%; 7 studies, 419 participants; low-quality evidence), or ≥ 75 nmol/L (OR 0.98, 95% CI 0.49 to 1.95; I^2 = 0%; 5 studies, 142 participants; low-quality evidence). However, we note only a limited number of studies provided data stratified by baseline vitamin D status, and thus downgraded this evidence by two levels due to imprecision. Testing for heterogeneity across subgroups revealed no evidence of a significant difference in outcomes (Chi^2 = 0.44, df = 3 (P = 0.93), I^2 = 0%) (Borenstein 2013). We could not analyse the outcomes rate of exacerbations and time to first exacerbation by baseline vitamin D subgroup due to lack of access to individual participant data for relevant trials.

Second, we conducted subgroup analyses based on the dose and form of vitamin D administered. We converted studies which provided only regular bolus doses of oral vitamin D_3 into their daily equivalent and then stratified results into two prespecified categories (Analysis 1.5; daily vitamin D dose ≤ 2000 IU versus > 2000 IU). Some studies combined bolus and daily dosing strategies and could not be classified; they were excluded from this subgroup analysis (Camargo 2021; Castro 2014; Jensen 2016). Vitamin D supplementation had no significant effect on the proportion of participants experiencing one or more asthma exacerbations treated with systemic corticosteroids in the lower dose subgroup (OR 1.13, 95% CI 0.75 to 1.69; I^2 = 0%; 10 studies, 942 participants; low-quality evidence). Only one study provided regular doses of vitamin D_3 greater than 2000 IU (Forno 2020); it also reported no significant effect (OR 1.15, 95% CI 0.63 to 2.07; I^2 = 0%; 1 study, 192 participants; low-quality evidence). Testing for heterogeneity across subgroups found no significant difference between groups (Chi^2 = 0.00, df = 1 (P = 0.97), I^2 = 0%).

Andújar-Espinosa 2021 administered oral calcidiol ($25[OH]D_3$) at a dose of 266 µg (one 1.5 mL ampoule) per week, and reported on the rate of asthma exacerbations treated with systemic corticosteroids. All other studies reporting on this outcome considered administered oral vitamin D_3 (cholecalciferol)

to participants in the intervention arm. When this analysis was stratified, we found that administration of oral vitamin D_3 did not significantly influence the rate of severe exacerbations (rate ratio 0.93, 95% CI 0.68 to 1.28; I^2 = 54%; 9 studies, 1487 participants; low-quality evidence; Analysis 1.6). Oral calcidiol did significantly reduce the rate of exacerbations (rate ratio 0.43, 95% CI 0.22 to 0.82; 1 study, 112 participants; low-quality evidence). The formal test for subgroup differences was significant (Chi^2 = 4.42, df = 1 (P = 0.04), I^2 = 77%). We could not carry out subgroup analyses on the proportion of participants experiencing at least one severe exacerbation and time to first severe exacerbation based on the form of vitamin D administered, as only studies administering oral cholecalciferol reported on these outcomes.

Third, we stratified our primary outcome by frequency of dosing regimen. Two categories were used; daily dosing versus intermittent bolus dosing at monthly or greater than monthly frequency (Analysis 1.7). One further study reporting on the primary outcome followed a dosing regimen of 1000 IU weekly (Majak 2009), but this study reported no events in either arm and thus an OR was not estimable for this dosing regimen category. We found that vitamin D did not influence the proportion of participants experiencing one or more asthma exacerbations treated with systemic corticosteroids when administered daily (OR 1.23, 95% CI 0.91 to 1.66; I^2 = 0%; 10 studies, 1201 participants; moderate-quality evidence), or when administered using intermittent bolus doses (OR 1.09, 95% CI 0.68 to 1.77; I^2 = 31%; 3 studies, 511 participants; moderate-quality evidence). The formal test for subgroup differences found no significant difference in the effect of allocation between groups (Chi^2 = 0.16, df =1 (P = 0.69), I^2 = 0%).

Fourth, we stratified our primary outcome by the mean age of participants, in three categories; < 5 years versus 5 to 16 years versus > 16 years (Analysis 1.8). Vitamin D supplementation had no significant effect on the proportion of participants experiencing one or more asthma exacerbations treated with systemic corticosteroids in the subgroup of children < 5 years (OR 2.15, 95% CI 0.82 to 5.64; I^2 = 0%; 2 studies, 69 participants; moderate-quality evidence), the subgroup of children aged 5 to 16 years (OR 1.28, 95% CI 0.83 to 1.97; I^2 = 0%; 9 studies, 837 participants; moderate-quality evidence), or the subgroup aged over 16 years (OR 0.85, 95% CI 0.58 to 1.24; I^2 = 31%; 3 studies, 872 participants; moderate-quality evidence). The formal test for subgroup differences found no significant difference in the effect of allocation between groups (Chi^2 = 4.13, df =2 (P = 0.13), I^2 = 51.5%).

Lack of access to individual participant data precluded conduct of prespecified subgroup analyses for the outcome of severe asthma exacerbation according to asthma severity, concomitant asthma treatment, body mass index, and genetic variation in the vitamin D pathway.

Sensitivity analysis excluding trials at high risk of bias

We assessed three trials as being at high risk of bias (Jiang 2017; Lewis 2012; Yadav 2014). None of these contributed data relating to incidence of exacerbation treated with systemic corticosteroids or exacerbation precipitating emergency department attendance or hospitalisation, or both. We assessed a further five trials which contributed to the primary outcome as being at unclear risk of bias (Camargo 2021; Ducharme 2019; Kerley 2016; Majak 2011; Thakur 2021). Excluding these trials in a sensitivity analysis, the overall finding remained null (OR 0.96, 95% CI 0.71 to 1.30; I^2 = 0%; 9 studies, 1365 participants; high-quality evidence; Analysis 1.9). One trial assessed as being at high risk of bias reported effects of vitamin D on the proportion of participants experiencing at least one study-defined exacerbation (Yadav 2014). When we excluded this trial in a sensitivity analysis, the overall finding was still null (OR 0.90, 95% CI 0.62 to 1.30; I^2 = 42%; 11 studies, 1439 participants; high-quality evidence; Analysis 1.10).

Sensitivity analyses using fixed-effect models

Sensitivity analyses using fixed-effect models to evaluate the effect of vitamin D on risk of severe asthma exacerbation all yielded null results (Table 1). The proportion of participants experiencing one or more asthma exacerbations treated with systemic corticosteroids measured by risk difference also returned a null result (RD 0.00, 95% CI -0.02 to 0.03; I^2 = 0%; 14 studies, 1778 participants; Analysis 1.11).

Secondary outcomes

Incidence of asthma exacerbations precipitating emergency department visit or requiring hospitalisation or both

Administration of vitamin D did not reduce or increase the proportion of participants experiencing at least one asthma exacerbation precipitating an emergency department visit or hospital admission, or both (OR 0.56, 95% CI 0.26 to 1.21; I^2 = 33%; 9 studies, 1070 participants; moderate-quality evidence; Analysis 1.12).

End-study cACT or ACT score

We saw no effect of vitamin D on asthma control scores. Different studies used the cACT for participants under 12 years (scale 0 to 27, 27 representing optimal control) or the ACT for 12 years and over (scale 0 to 25, 25 representing optimal control). As outlined in Methods, we used a linear scale transformation to convert ACT scores to the cACT scale for direct comparison. End-study mean difference between arms was not significant (MD 0.23 higher in vitamin D arm, 95% CI -0.26 to 0.73; I^2 = 29%; 7 studies, 1271 participants; moderate-quality evidence; Analysis 1.13). The standard minimally important difference for this score is three (Schatz 2009).

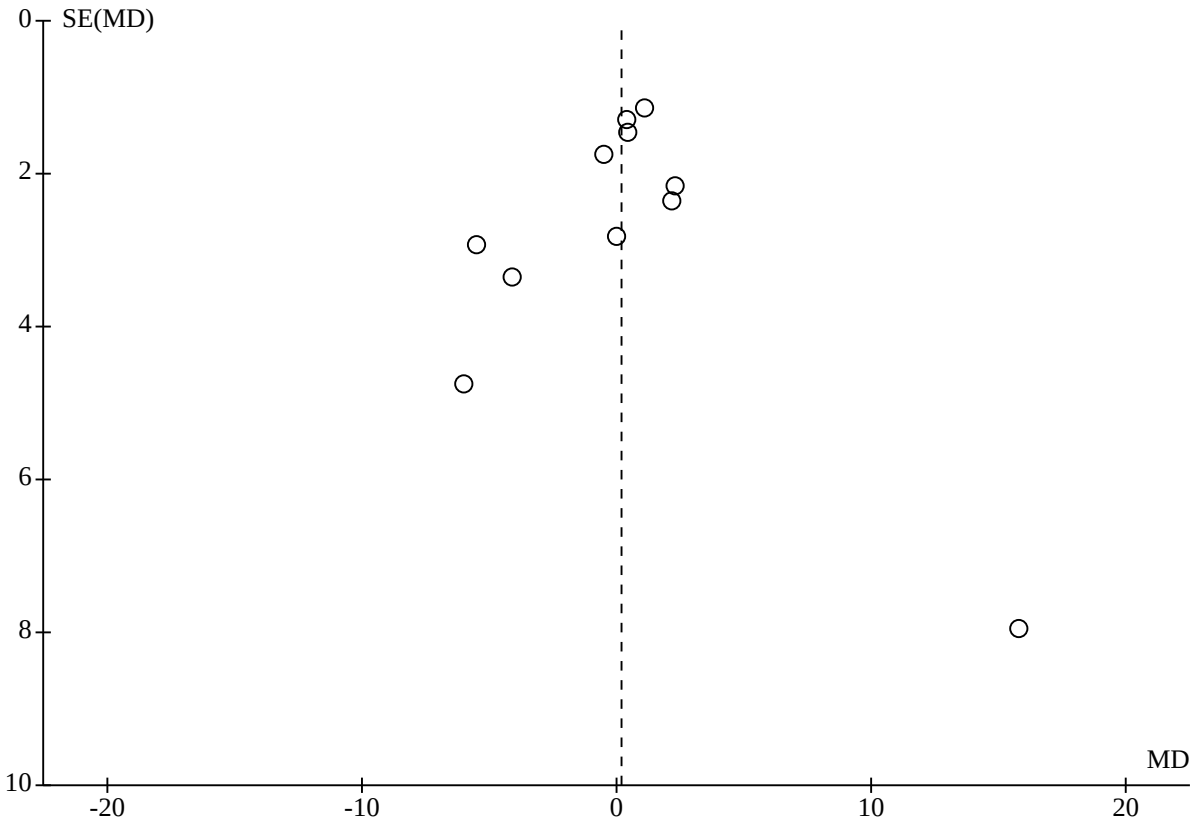
Two other studies provided data on the change in ACT scores within arms rather than end-study scores (Jiang 2017; Kerley 2016), which we have summarised narratively as they could not be meta-analysed with the other eight studies above. Jiang 2017 showed a mean increase of 0.325 (SD 0.80) from baseline in the intervention arm and a mean decrease of -0.025 (SD 0.79) in the placebo arm, with a mean difference of 0.35 (standard error 0.17). Kerley 2016 presented outcomes as median (IQR), with a median change in ACT score of 2 (-2 to 4) in the intervention arm and 3.5 (0 to 5) in the control arm (P = 0.34).

End-study % predicted FEV1

There was no overall effect of vitamin D on end-study % predicted FEV1 (MD 0.20 higher in vitamin D arm, 95% CI -1.24 to 1.63; I^2 = 25%; 11 studies, 1286 participants; high-quality evidence; Analysis 1.14). A funnel plot of included studies for this outcome is presented in Figure 5, which is approximately symmetrical aside from one large study (Camargo 2021), and shows no evidence of small-study bias. Two other trials investigated FEV1 as an outcome measure in a different format, which we have reported narratively. Jiang 2017

reported the end-study proportion of participants with FEV1 < 80% predicted, with no significant difference (14 out of 43 in intervention arm versus 15 out of 40 in control arm). Kerley 2016 reported no significant change in % predicted FEV1 within arms, with a median (IQR) change of -4 (-6.3 to -1) in the intervention arm and 2.5 (-4.3 to 6.5) in the control arm (P = 0.06).

Figure 5. Funnel plot of comparison: Vitamin D versus placebo (all studies), outcome: 1.11 End-study FEV1, % predicted



Incidence of any serious adverse event, any cause

Administration of vitamin D did not influence the proportion of participants experiencing one or more serious adverse events of any cause (OR 0.89, 95% CI 0.56 to 1.41; I^2 = 0%; 12 studies, 1556 participants; high-quality evidence; Analysis 1.15). One other study reported the rate of adverse events rather than the number of participants experiencing one or more such events (Jat 2020), and found that one participant in the intervention arm experienced altered sensorium, which was not defined further, and one in the placebo arm experienced a seizure.

Incidence of adverse reactions attributed to administration of vitamin D or its metabolites

Two trials reported occurrences of hypercalciuria, an event that is recognised as a potential adverse reaction to vitamin D. In the study by Jensen and colleagues, this event arose in one participant in the intervention arm and one participant in the control arm (Jensen 2016). This trial involved administration of 400 IU vitamin D_3 to both study arms, and an initial 100,000 IU bolus for the intervention arm. In Ducharme 2019, at least one participant in the intervention arm experienced borderline hypercalciuria (Ca:Cr 1.02) following treatment with vitamin D, but we could not ascertain the total number of events in either arm from the trial report.

Camargo and colleagues reported 11 participants with adverse reactions potentially attributable to vitamin D (Camargo 2021). Two participants in the intervention arm experienced hypervitaminosis D (defined as 25(OH)D > 220 nmol/L) and six experienced kidney stones, whilst three participants in the control arm experienced kidney stones. Andújar-Espinosa and colleagues reported five participants experiencing gastrointestinal symptoms (Andújar-Espinosa 2021); three in the intervention arm and two in the control arm. Jat and colleagues reported that one participant from the control arm withdrew from the study due to mild itch (Jat 2020). Jerzynska and colleagues narratively reported sublingual itching, headaches, and stomachaches occurring in both arms, without incidence detail specific to the asthma cohort (Jerzynska 2016). No other studies reported any adverse reactions potentially attributable to vitamin D.

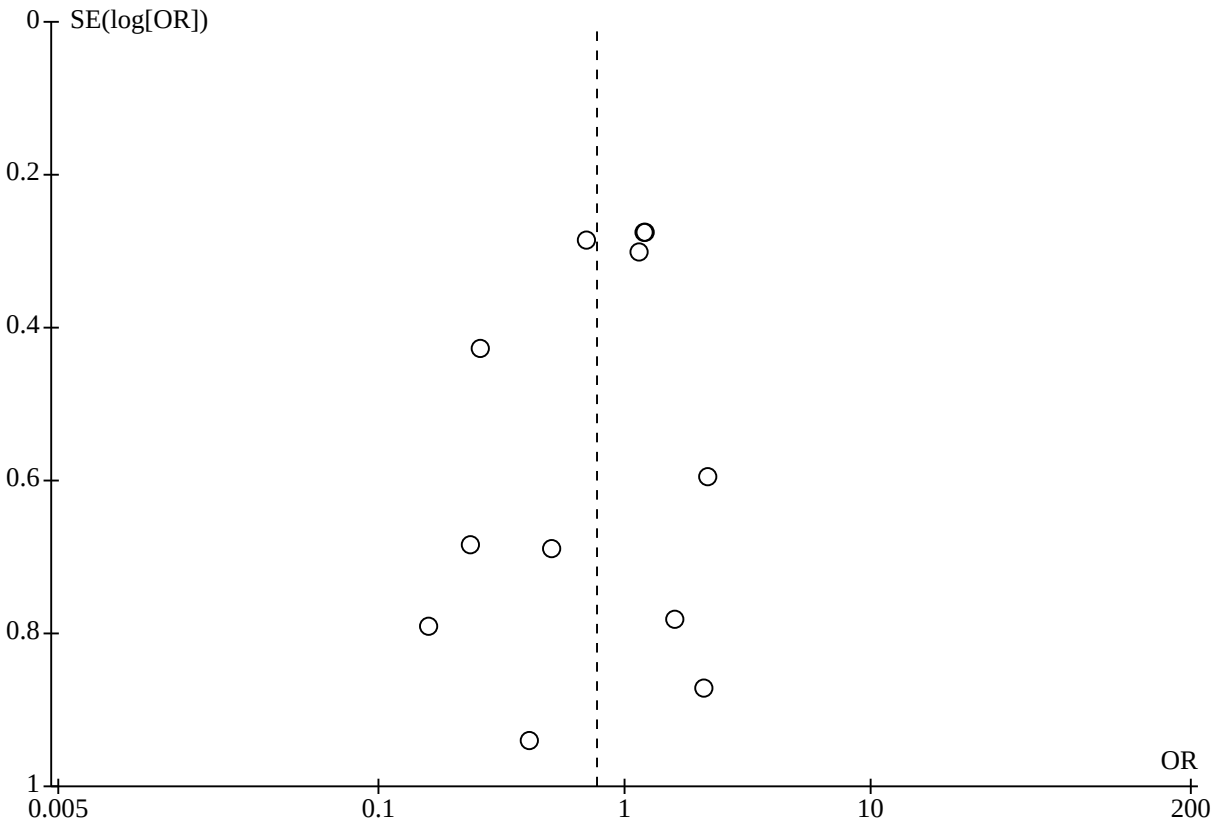
Incidence of fatal asthma exacerbation

No participant in any of the included trials suffered a fatal asthma exacerbation, therefore the effect of the intervention on this outcome could not be evaluated (risk difference 0.00, 95% CI -0.01 to 0.01; I^2 = 0%; 16 studies, 1976 participants; low-quality evidence; Analysis 1.16).

Incidence of asthma exacerbation as defined in primary trials

The definitions of asthma exacerbations used in individual trials are summarised in Table 2. Administration of vitamin D did not significantly affect the proportion of participants experiencing at least one study-defined exacerbation, though there was considerable heterogeneity in study definitions of exacerbation (OR 0.77, 95% CI 0.51 to 1.17; I^2 = 57%; 12 studies, 1539 participants; high-quality evidence; Analysis 1.17). A further study reported no difference between placebo and vitamin D groups (30.4% vs 35.5%; P = 0.431) but did not report absolute numbers (Jat 2020). The funnel plot, shown in Figure 6, was approximately symmetric.

Figure 6. Funnel plot of comparison: 1 Vitamin D versus placebo (all studies), outcome: 1.9 People with one or more study-defined exacerbations



End-study % lower airway eosinophils

Vitamin D did not influence mean end-study % eosinophil count in the lower airway (MD -0.38, 95% CI -1.92 to 1.15; I^2 = 43%; 3 studies, 525 participants; moderate-quality evidence; Analysis 1.18). One further study narratively reported no significant effect of vitamin D on mean end-study % eosinophils (Kerley 2016). However, another study reported only the absolute volume of end-study eosinophils following administration of calcitriol, and found that this active form of vitamin D did reduce the outcome (vitamin D arm 0.77 ± 1.3 x 10^3/µl, control arm 1.29 ± 2.5 x 10^3/µl) (Ramos-Martínez 2018).

End-study log10 total IgE, IU/ml

Three trials reported data on end-study log total IgE levels (IU/ml), showing no significant effects of vitamin D administration (MD 0.07 higher in vitamin D arm, 95% CI -0.13 to 0.26; I^2 = 0%; 3 studies, 366 participants; high-quality evidence; Analysis 1.19) (Andújar-Espinosa 2021; Forno 2020; Ramos-Martínez 2018). Two further trials reported no significant effect on IgE levels, but did not present data on this outcome (Kerley 2016; Tachimoto 2016).

Kerley 2016 also found that vitamin D had no effect on total IgA, IL10 or LL37 biomarkers. Another trial conducted in adults investigated the effects of vitamin D on concentrations of inflammatory markers in induced sputum supernatants. Martineau and colleagues reported that administration of vitamin D had no effect on supernatant concentrations of a panel of 17 inflammatory markers whose concentrations were detectable, measured at 2 and 12 months (Martineau 2015). Castro and colleagues investigated the effects of vitamin D on function of myeloid cells and CD4+ T cells in peripheral blood but found no effect on this outcome (Castro 2014). Ramos-Martínez and colleagues found end-study serum concentrations of IL-10 and INF-γ were higher in the intervention than the control arm (difference in means IL-10 24.92 pg/ml, INF-γ 53.33 pg/ml), while end-study IL-5, IL-9, and IL-13 were lower in the intervention arm (difference in means IL-5 33.72 pg/ml, IL-9 36.92 pg/ml, IL-13 181.45 pg/ml) (Ramos-Martínez 2018).

End-study % predicted FVC

Vitamin D did not influence mean end-study FVC (MD 1.84 higher in vitamin D arm, 95% CI -3.60 to 7.29; I^2 = 73%; 4 studies,

476 participants; moderate-quality evidence; Analysis 1.20). Two further studies reported FVC data in a different format, which we have presented narratively. Jiang 2017 reported end-study proportion of participants with FVC < 80% predicted, with no significant difference (13 out of 43 in intervention arm versus 11 out of 40 in control arm). Kerley 2016 reported no significant change in FVC % predicted within arms, with a median (IQR) change of -2.5 (-8.3 to 3) in the intervention arm and 0 (-5 to 4.5) in the control arm (P = 0.36).

End-study PEFR

Vitamin D did not influence mean end-study PEFR (MD 4.84 higher in vitamin D arm, 95% CI -8.95 to 18.62; I^2 = 79%; 3 studies, 476 participants; moderate-quality evidence; Analysis 1.21). One further study presented PEFR in graphical form only, with end-study mean of approximately 185 L/min for the vitamin D arm and 165 L/min for the control arm, but did not report standard deviations (Yadav 2014).

Proportion of participants withdrawing from the trial

We saw no difference in the proportion of participants withdrawing from trials between intervention and control arms (OR 1.05, 95% CI 0.77 to 1.43; I^2 = 0%; 20 studies, 2225 participants; high-quality evidence; Analysis 1.22).

Sensitivity analysis excluding trials at high risk of bias

All three trials assessed as being at high risk of bias reported effects of vitamin D on the proportion of participants withdrawing from the trial (Jiang 2017; Lewis 2012; Yadav 2014). When these trials were excluded, the effect of vitamin D on this outcome remained null (OR 1.11, 95% CI 0.80 to 1.53; I^2 = 0%; 17 studies, 2003 participants; Analysis 1.23).

Narrative outcomes

Time off school or work

One trial conducted in adults investigated the outcome of work absence due to asthma exacerbation or upper respiratory infection (Martineau 2015). Allocation to vitamin D did not influence such work absence when measured as time to first event (adjusted HR 0.77, 95% CI 0.53 to 1.10), event rate (adjusted RR 0.86, 95% CI 0.50 to 1.46), or proportion of participants with at least one such absence (adjusted OR 0.77, 95% CI 0.45 to 1.30). One trial conducted in children did find an effect on the outcome of time off school due to asthma symptoms (Kerley 2016). Vitamin D supplementation was associated with a median of one (IQR 0 to 5) school day missed over the 15 weeks follow-up, compared with a median of five days (IQR 2 to 10) for the control arm (P = 0.04). Meta-analysis across these two trials was not possible due to results being presented in different formats.

Beta2-agonist inhaler use

One trial conducted in adults investigated the effects of vitamin D on the number of uses of inhaled relief medication per 24 hours (Martineau 2015). Allocation to vitamin D did not influence this outcome at 12 months (adjusted ratio of geometric means 1.00, 95% CI 0.77 to 1.28). Another trial assessed the effects of vitamin D on the intensity of beta2-agonist use per episode, measured as the cumulative number of puffs (Ducharme 2019). Allocation to vitamin D did not influence this outcome, with a mean difference of 1.4 fewer puffs required per episode in participants randomised to intervention versus placebo (95% CI -13.5 to 10.7, P > 0.05).

End-study asthma quality of life

Five trials investigated the effects of vitamin D on respiratory quality of life. Andújar-Espinosa and colleagues reported a significant improvement in Asthma Quality of Life Questionnaire (AQLQ) score (MD 0.70 higher in vitamin D arm, 95% CI 0.15 to 1.25) (Andújar-Espinosa 2021). The minimum clinically important difference for this score is 0.5 points (Juniper 2005). Conversely, Kerley and colleagues stated that vitamin D administration had no significant effect on AQLQ scores in the text of their paper, though they did not present the associated data (Kerley 2016). A supplementary analysis by Forno and colleagues also reported that vitamin D administration had no significant effect on AQLQ scores, presenting this result as a multivariate regression coefficient of 0.12 (95% CI -0.27 to 0.51) (Forno 2020). Martineau and colleagues reported that administration of vitamin D modestly improved respiratory quality of life as evidenced by adjusted inter-arm differences in total St George's Respiratory Questionnaire (SGRQ) score of -3.9 points at two months (P = 0.005), -3.7 points at six months (P = 0.038), and -3.3 points at 12 months (P = 0.060; P for allocation time interaction = 0.026). These differences were associated with statistically significant decreases in component scores for the impacts dimension of the SGRQ at two months (P = 0.05) and six months (P = 0.005; P for allocation-time interaction = 0.030) (Martineau 2015). Of note, the minimum clinically important difference for this score is around four points (Jones 2005). Castro and colleagues reported no effect of the intervention on the Asthma Bother Profile score: the adjusted mean change in score was -1.0 (95% CI -2.7 to 0.7) in the intervention arm versus -2.4 (95% CI -4.0 to -0.7) in the placebo arm; P = 0.16) (Castro 2014). Data from these different instruments were unsuitable for pooling and were therefore not meta-analysed.

End-study FeNO

Two trials investigated the effects of vitamin D on FeNO. Martineau and colleagues reported that administration of vitamin D had no effect on mean FeNO concentrations at 12 months (ratio of geometric means −1.4, 95% CI −6.8 to 3.9) (Martineau 2015). Thakur and colleagues similarly reported that administration of vitamin D had no effect on median FeNO concentrations at three months, with an end-study median of 16 parts per billion (ppb) (IQR 10 to 24.5) in the intervention arm and a median of 10 ppb (IQR 8.3 to 21.8) in the control arm (P = 0.2) (Thakur 2021). The skewness of these results precluded a conversion from median to mean and standard deviation.

End-study airway reactivity (PC20)

Two trials investigated the effects of vitamin D on airway reactivity. Castro and colleagues reported that administration of vitamin D had no effect on the provocative concentration of methacholine at which FEV1 decreased by 20% (PC20): the adjusted mean change in log base 2 transformed PC20 (doubling dilutions) was 0.70 mg/ml (95% CI 0.38 to 1.03) in the intervention arm versus 0.74 mg/ml (95% CI 0.41 to 1.07) in the placebo arm; a difference in mean change of 0.04 mg/ml (P = 0.87) (Castro 2014). Jerzynska and colleagues also reported in text format that vitamin D administration had no significant effect on PC20, but did not present data for this outcome (Jerzynska 2016).

Costs from the perspective of healthcare providers

One trial conducted in adults investigated the effects of vitamin D on health economic outcomes. Martineau and colleagues reported that administration of vitamin D had no effect on total costs associated with asthma/upper respiratory infection over 12 months (adjusted mean difference GBP 66.78, 95% CI GBP -263.47 to GBP 397.03) (Martineau 2015).

DISCUSSION

Summary of main results

This systematic review and meta-analysis incorporated data from 1155 children and 1070 adults enrolled in 20 double-blind randomised placebo-controlled trials of vitamin D supplementation in participants with asthma. Overall, we found that administration of vitamin D had no significant effect on any primary or secondary outcomes considered, both in aggregate and in the majority of subgroup analyses conducted. This is in contrast to the findings reported in our previous Cochrane Review on this topic (Martineau 2016).

Fifteen studies contributed data to analyses of the primary outcome of asthma exacerbations requiring systemic corticosteroids (severe exacerbations). Administration of vitamin D had no effect on the proportion of participants experiencing one or more asthma exacerbations treated with systemic corticosteroids (OR 1.04, 95% CI 0.81 to 1.34; I^2 = 0%; 14 studies, 1778 participants; high-quality evidence; Analysis 1.1). We note the lower bound of the 95% confidence interval of 0.81, such that we can state with 97.5% certainty that vitamin D supplementation leads to no more than a 19% reduction in the odds of experiencing one or more severe exacerbations. There was low heterogeneity across studies for this primary outcome, with I^2 = 0%.

Administration of vitamin D did not influence the rate of severe asthma exacerbations (RR 0.86, 95% CI 0.62 to 1.19; I^2 = 60%; 10 studies, 1599 participants; Analysis 1.2). We note, however, that there was a high degree of heterogeneity across studies for this outcome, with I^2 = 60%. This heterogeneity may be due to differences in populations, such as variation in baseline vitamin D status, genetics, adherence to the intervention, or different background treatments. It may also arise due to differences in interventions, including the dose of vitamin D given and the dosing regimen. An additional possible factor is that this outcome includes data from the single study which administered calcidiol rather than vitamin D_3, and reported a significant protective effect from this metabolite (Andújar-Espinosa 2021). Conversely, Analysis 1.1 and Analysis 1.3 could not include this study as it did not publish data on the relevant outcomes. Following the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 10 (Higgins 2022), the random-effects model used should account for any such heterogeneity.

Vitamin D did not influence time to first severe asthma exacerbation (HR 0.82, 95% CI 0.59 to 1.19; I^2 = 22%; 3 studies, 850 participants; high-quality evidence; Analysis 1.3).

We also found that vitamin D was not associated with a significant difference in risk of asthma exacerbations in any subgroup considered, except for form of vitamin D administered. No effect of giving cholecalciferol was seen, but oral calcidiol did significantly reduce the rate of exacerbations in the single study which utilised this form of vitamin D (Andújar-Espinosa 2021). Further research is therefore warranted to investigate whether calcidiol has a significant effect on risk of asthma exacerbation.

Overall completeness and applicability of evidence

This review incorporated evidence from 20 trials, across a wide range of patient populations in terms of age, country, baseline vitamin D status, and vitamin D dosing regimens. We included papers published in both English and Chinese, and sought supplementary unpublished data from authors as per the published protocol where required (Martineau 2021). This was a result of rigorous search criteria using a range of Cochrane and other databases to maximise completeness of evidence. This large pool of studies increases the generalisability of our findings relative to other reviews (Chen 2021; Fares 2015; Jolliffe 2017; Kumar 2022; Luo 2015; Martineau 2016; Nitzan 2022; Pojsupap 2015; Riverin 2015; Xiao 2015). It allowed for subgroup analyses by baseline vitamin D status, vitamin D dose and form, dosing regimen, and age, with null findings from these subgroup analyses increasing the applicability of our conclusions for each of these groups. This is of particular note for the population with low baseline vitamin D, given that other studies postulated a potential relationship here (Janssens 2013; Martineau 2015a).

Nonetheless, this systematic review was limited to meta-analysis of aggregate data from published manuscripts, augmented by specific unpublished data and individual participant data from authors where it was possible to obtain this. Despite strenuous attempts to obtain further data, for instance, outcomes stratified by baseline vitamin D status, only certain authors were able to provide this information. Therefore, fewer studies contributed data to subgroup analyses, and this may have constrained power leading to type 2 error. In particular, there was a paucity of data on the effects of vitamin D administration on asthma exacerbation risk in those who were profoundly vitamin D deficient (serum 25(OH)D < 25 nmol/L), with only three studies contributing data to this subgroup (Castro 2014; Jat 2020; Martineau 2015). Further research to clarify whether baseline vitamin D status modifies effects of vitamin D on exacerbation risk, including further individual participant data meta-analysis, is needed before definitive clinical recommendations can be made regarding effects of vitamin D replacement in individuals with the lowest baseline vitamin D status. We were also limited to studies focused mainly on children and adults with mild to moderate asthma, defined as requiring GINA step 4 treatment or below. Thus, conclusions cannot reliably be drawn for people with severe asthma.

Quality of the evidence

This review followed rigorous prespecified selection criteria in a published protocol (Martineau 2021), restricted to double-blind, placebo-controlled trials. This gives confidence in the internal validity of our findings.

Following a GRADE approach, we first considered the primary outcome of asthma exacerbations requiring systemic corticosteroids. We assessed the risk of bias as low or unclear in all studies contributing data to this outcome, with sensitivity analyses showing that the null findings remain consistent when studies with unclear risk of bias were excluded. The results showed high precision, with a 95% CI of 0.81 to 1.34 for the core outcome of

the proportion of participants experiencing such an exacerbation. Results showed low heterogeneity for two of the three dimensions of this outcome, proportion experiencing one or more severe exacerbations (Analysis 1.1, I^2 = 0%) and time to first severe exacerbation (Analysis 1.3, I^2 = 22%).

The third dimension of this primary outcome, the rate ratio of asthma exacerbations (Analysis 1.2), showed less precision (RR 0.86, 95% CI 0.62 to 1.19) and higher heterogeneity, with I^2 = 60%. However, the null findings in this dimension of the primary outcome were consistent with other expressions of this outcome (OR (Analysis 1.1) versus RR (Analysis 1.2) versus HR (Analysis 1.3)), and when different definitions of exacerbation were used (exacerbations treated with systemic corticosteroids (Analysis 1.1) versus those defined according to study protocols (Analysis 1.17)). The consistency of null findings across the three dimensions of this outcome increases our confidence in rating evidence as consistent for the outcome as a whole. The null effect identified was also consistent with null findings across a range of different secondary outcomes, enhancing our confidence in a true null result. We also assessed this evidence as direct rather than indirect, as a wide range of patient populations were studied and subgroup analyses were consistent with the overall null finding.

We created funnel plots for the primary outcome as more than 10 studies contributed data. These showed no obvious asymmetry, suggesting no evidence of publication bias (Figure 3; Figure 4). Assessment for publication bias is discussed further under Potential biases in the review process. We classified the evidence for this primary outcome as high quality.

We downgraded the evidence for five secondary outcomes to moderate quality. The proportion of participants with one or more exacerbations precipitating an emergency department visit or requiring hospital admission, or both, showed less precision (OR 0.56, 95% CI 0.26 to 1.21) and included fewer studies than the primary outcome, so we downgraded by one level to moderate-quality evidence. Four further outcomes with null findings showed heterogeneity of evidence: end-study cACT score (MD 0.23, 95% CI -0.26 to 0.73; I^2 = 29%), end-study % lower airway eosinophils (MD -0.38, 95% CI -1.92 to 1.15; I^2 = 43%), end study % predicted FVC (MD 1.84, 95% CI -3.60 to 7.29; I^2 = 73%), and end-study PEFR (MD 4.84, 95% CI -8.95 to 18.62; I^2 = 79%). We downgraded the evidence in each case to moderate quality as a result. Finally, evidence regarding fatal exacerbations was downgraded two levels to 'low', as no such events occurred in any included study.

We classified all remaining secondary outcomes as high-quality evidence, with low risk of bias, high precision, direct evidence, consistency of findings, and no evidence of publication bias on funnel plots where analysed.

Potential biases in the review process

This review followed rigorous prespecified selection criteria, restricted to double-blind, placebo-controlled trials. We searched multiple databases for eligible studies using prespecified criteria, and this strategy led to identification of unpublished data which are included in this review. As outlined in the Methods, AW, AS, and CJG assessed the eligibility and risk of bias of the new study co-authored by ARM (Camargo 2021). As for any review of randomised controlled trials, publication bias may have favoured publication of trials reporting favourable results. However, we used funnel plots to screen for any such bias.

Following Section 10.4.3 and Chapter 13 of the *Cochrane Handbook for Systematic Reviews of Interventions,* Higgins 2022, we did not conduct formal statistical tests for funnel plot asymmetry due to risk of misleading results, especially for continuous outcomes. Instead, we followed the recommended approach and assessed for selective non-reporting amongst eligible studies and trial protocols.

The initial screening for eligible studies utilised a wide range of trials registers to identify any initiated, ongoing or completed but unpublished studies that met the eligibility criteria. We identified 11 ongoing eligible trials that had not yet published their findings (listed under Ongoing studies). We contacted the named authors in each case to request preliminary data, but either did not receive a response, or were informed that the data were not yet available. However, each trial protocol identified was only recently published (2016 or later), with a planned duration extending until the date of this systematic review or beyond. Thus, we have a low suspicion of selective non-publication of findings that differ from our review conclusions.

We also considered the seven studies identified as ongoing in the previous Cochrane Review on this topic (Martineau 2016). Of these, three have now been published and incorporated into the current systematic review (Aglipay 2019; Ducharme 2019; Kerley 2016). One study is still listed as ongoing in the current systematic review, with a prespecified five-year follow-up period (Gold 2016). One study (Patella 2013) has not been published further, though full results were presented in two published abstracts referenced in the previous Cochrane Review, mitigating concerns about publication bias (Martineau 2016). Lastly, two studies were terminated prior to publication (NCT02424552; UMIN000004160). NCT02424552 terminated due to recruitment issues, with an actual enrolment of 54 relative to an intended enrolment of 160 people. As this study terminated before results were obtained, there is a low risk of selective publication bias. UMIN000004160 does not state a reason for termination, but no results are reported.

Overall, numerous studies contributed data to the primary outcome of this systematic review, with consistent null findings, symmetrical funnel plots, and no strong indications of publication bias.

Agreements and disagreements with other studies or reviews

We are aware of 13 other systematic reviews and meta-analyses that have synthesised evidence from randomised controlled trials of vitamin D in people with asthma. Seven of these, including the previous Cochrane Review, found protective effects (Chen 2021; Jolliffe 2017; Liu 2021; Martineau 2016; Pojsupap 2015; Riverin 2015; Xiao 2015) whilst six did not (De Menezes Rios 2021; Fares 2015; Hao 2022; Kumar 2022; Luo 2015; Nitzan 2022), with a trend towards the earlier reviews identifying a protective effect and more recent studies obtaining null findings.

The null findings of this systematic review stand in contrast with the report of an overall effect of vitamin D identified in the previous Cochrane Review on this topic (Martineau 2016). A previous meta-analysis of individual participant data (IPDMA) on the same topic

was consistent with this previous Cochrane Review, identifying an overall protective effect of vitamin D on the rate ratio of asthma exacerbations requiring systemic corticosteroids (RR 0.74, 95% CI 0.56 to 0.97) (Jolliffe 2017). Baseline 25(OH)D level did not significantly modify this effect (P value for interaction = 0.25). However, this IPDMA did not find a protective effect of vitamin D on the proportion of participants experiencing one or more exacerbations requiring systemic corticosteroids (OR 0.75, 95% CI 0.51 to 1.09).

We acknowledge that the previous Cochrane Review assessed its core findings as being based on high-quality evidence, yet our updated review has now arrived at contrasting null results, also based on high-quality evidence. We identify two potential reasons for these differing findings, which together give confidence that the true effect lies close to that of the estimate of the effect in this current review.

First, the current review draws evidence from a far larger pool of studies than the previous Cochrane Review (20 versus 9) including all studies previously analysed. It analyses a greater number of participants, with more diversity in characteristics and the capacity to conduct subgroup analyses which concur with our primary null finding in every case, except for the aforementioned single study finding a positive effect of calcidiol. Thus, the null findings obtained are likely to be a better assessment of the true relationship between vitamin D supplementation and asthma. We also applied more rigorous exclusion criteria than some reviews identifying a protective effect. For instance, studies considered by Chen 2021 were excluded by our review because they were not placebo-controlled (Baris 2014), not blinded (Dodamani 2019), or because duration of follow-up was less than 12 weeks (De Groot 2015). The review by Liu 2021 also included Dodamani 2019 despite its open-label methodology.

A second potential explanation for the null findings in this updated review relates to a secular trend towards increasingly widespread population use of vitamin D supplementation (Kantor 2016). For instance, the growing popularity of vitamin D supplements in the general population (and particularly in the subset of people taking part in clinical trials) may have led to increased use of vitamin D supplements among participants randomised to placebo in more recent versus less recent trials. This could have attenuated potential benefits of vitamin D, and increased the probability of null findings in more recent trials.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review does not find evidence to support a role for vitamin D supplementation to reduce risk of asthma exacerbations or improve asthma control. The null findings of this review are based on the largest pool of evidence analysed to date, and are consistent for primary and secondary outcomes. We deemed this evidence to be high quality for the primary outcome of reductions in asthma exacerbations requiring systemic corticosteroids, and also for several of the secondary outcomes. Nonetheless, participants with severe asthma and those with baseline 25-hydroxyvitamin D (25(OH)D) concentrations < 25 nmol/L were poorly represented, and a protective effect of the intervention cannot be excluded in these groups. A single study investigating effects of calcidiol yielded positive results; further studies investigating effects of this metabolite are needed.

Implications for research

Further research is required to clarify potential effects of calcidiol on risk of asthma exacerbation, and to determine whether vitamin D supplementation may yet have an effect in people with severe asthma or those with the lowest levels of baseline vitamin D (25(OH)D < 25 nmol/L), in whom a significant protective effect cannot currently be excluded.

ACKNOWLEDGEMENTS

We thank Yuen Fun Alexis Lai and Shu Yui Chew for language translation and Emma Jackson for assistance with co-ordinating translation.

We are very grateful to Mary Aglipay and Jonathon Maguire (University of Toronto, Canada), John Sluyter (University of Auckland, New Zealand), Francine Ducharme and Anna Smyrnova (University of Montreal, Canada), Juan C Celedón (University of Pittsburgh, PA, USA), Kana Ram Jat (All India Institute of Medical Sciences, New Delhi, India), Megan Jensen (University of Newcastle, Australia), Joanna Jerzyńska (Medical University of Lodz, Poland), Conor Kerley (National Children's Hospital, Dublin, Ireland), Iwona Stelmach and Pawel Majak (Medical University of Lodz, Poland), Mario Castro (Washington University School of Medicine, St Louis, MO, USA), Tonya S King (Penn State University, Hershey, PA, USA), and Thomas B Casale (Creighton University Medical Center, Omaha, NE, USA) for providing unpublished data relating to their studies; and Emma Dennett and Elizabeth Stovold of the Cochrane Airways Group, who provided advice on protocol content and search structure, respectively.

The authors and Cochrane Airways' Editorial Team are grateful to the following peer reviewers for their time and comments: Augusto Litonjua, Brigham and Women's Hospital (USA) and Scott Weiss, Harvard School of Public Health (USA).

The Background and Methods sections of this review are based on a standard template used by Cochrane Airways.

This project was supported by the National Institute for Health and Care Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Airways Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS, or the Department of Health and Social Care.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aglipay 2019

Study characteristics	
Methods	Multicentre, double-blind, randomised, placebo-controlled trial of 4 to 8 months' duration. Concomitant vitamin D supplements were stopped, but asthma medication was continued during the trial. Analysis was by intention to treat (ITT). There was no run-in period.
Participants	Participants were recruited from 8 paediatric or family medicine group practices in Toronto, Canada. The overall trial recruited 703 children, of whom 27 had physician-diagnosed asthma. Participants were randomised to intervention (n = 15) vs control (n = 12) arms. **Inclusion criteria** Age 1 to 5 yrs Healthy children by parental report (review considers subset of participants with physician-diagnosed asthma) Present to a TARGet Kids! practice for routine primary healthcare prior to viral season (September through November) **Exclusion criteria** Children with gestational age < 32 weeks Children with chronic illness (except for asthma) on parental report which is known to interfere with vitamin D metabolism and increase the risk of respiratory infection

Aglipay 2019 *(Continued)*

	Children with a sibling participating in the study to reduce clustering effects
Interventions	Active intervention (n = 15): vitamin D_3 2000 IU, 1 drop orally daily Control intervention (n = 12): vitamin D_3 400 IU, 1 drop orally daily
Outcomes	**Primary outcome** Wheezing episode in children with asthma as obtained from parent completed symptom checklist based on the International Study of Asthma and Allergies in Childhood
Notes	Data were obtained from the published abstract, with further information on the asthma-only subset obtained from authors, including number of participants with study-defined exacerbations. Data were not available on the number of participants with exacerbations requiring systemic corticosteroids.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based random-number generator
Allocation concealment (selection bias)	Low risk	Study personnel, parents, attending physicians, laboratory personnel, investigators, and data analysts were all blinded to group allocation throughout the study period.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Parents, attending physicians, laboratory personnel, and study personnel conducting the outcome assessments, data analysts and investigators were blind to the group allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Parents, attending physicians, laboratory personnel, and study personnel conducting the outcome assessments, data analysts and investigators were blind to the group allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants contributed data to analysis of baseline outcomes. Of the asthma patient subset, no participants were lost to follow-up from either the treatment or control arms (correspondence with author).
Selective reporting (reporting bias)	Low risk	Prespecified secondary analysis of protocol NCT01419262
Other bias	Low risk	Nil

Andújar-Espinosa 2021

Study characteristics

Methods	Single-centre, triple-blinded, placebo-controlled randomised controlled trial of 6 months' duration. Concomitant medication was continued throughout. Analysis was of all participants with follow-up data available (3 lost to follow-up per group excluded from results), not stated as ITT. There was no run-in period. The power calculation was as follows: "accepting an alpha risk of 0.05 and a beta risk of 0.2 (80% power), a total of 100 participants (ie, 50 patients in each group) was required to detect an absolute difference of 3 points in the ACT, considering the mean of 19 and an SD of ± 5. A loss rate of 7% of patients was estimated."

Andújar-Espinosa 2021 *(Continued)*

Participants	112 participants were recruited from the Emergency Department, Hospital Morales Meseguer, Murcia, Spain. They were randomised to intervention or control in equal numbers. Three individuals per group were lost to follow-up, and thus were not analysed. **Inclusion criteria** People aged 18 or over who were hospitalised or seen in the emergency department in 2013 and 2014 with bronchial asthma as a primary or secondary diagnosis **Exclusion criteria** Smoking more than 10 pack years, current use of vitamin D supplements, the prevalence of kidney disease (defined as serum creatinine > 2 mg/dL), hypercalcaemia (defined as serum calcium corrected with proteins > 10.5 mg/ dL), history of recurrent kidney stones (3 or more episodes), presence of pathologies affecting the intestinal capacity to absorb vitamin D, pregnancy, breastfeeding or severe psychosocial problems (such as dementia, alcoholism or other drug addictions, psychiatric disorders such as major active depression or schizophrenia), baseline serum levels 25-hydroxyvitamin-D_3 (25-OH-D_3) > 30 ng/mL).
Interventions	Active intervention (n = 53 completing trial): 16 000 IU of oral calcifediol in one ampoule per week (Hidroferol 266 µg, 1.5 ml) Control intervention (n = 53 completing trial): the placebo, also presented as one ampoule per week, was designed with the same internal consistency, flavour and with the same external appearance as the supplements. Mean serum 25(OH)D concentration, intervention arm: 41.8 nmol/L (baseline), control: 43.7 nmol/L (baseline)
Outcomes	**Primary outcome** Changes in the asthma control scores (ACT) between baseline and 6 months **Secondary outcomes** 1. Changes in 6 months prior to study vs the study period in average quality of life, measured with the validated Spanish version of the Mini Asthma Quality of Life Questionnaire (AQLQ) 2. Dose of ICSs (classified as low, medium or high doses according to the Global Initiative for Asthma criteria) 3. Number of oral corticosteroid cycles 4. Number of asthma attacks 5. Number of unscheduled visits with the primary care physician for asthma-related causes 6. Number of emergency visits 7. Number of hospitalisations due to asthma Exacerbation: defined according to GEMA as requiring an increased treatment dose for at least 3 days Hospitalisations and study-defined asthma attacks were only presented as an event rate rather than proportion of participants, which was the outcome for this meta-analysis, so could not be included.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated

Andújar-Espinosa 2021 *(Continued)*

Allocation concealment (selection bias)	Low risk	Opaque numbered envelopes allocated to group A or B
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Triple-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rates of withdrawal overall, which were seen equally in treatment and control arms (3/56 lost to follow up in each arm).
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting, all prespecified primary and secondary outcomes from the protocol were reported in the main paper.
Other bias	Low risk	Nil

Camargo 2021

Study characteristics	
Methods	Multicentre, double-blind, placebo-controlled randomised controlled trial with an average of 3.3 years duration. Concomitant medication was continued. A run-in period was applied, with an initial questionnaire given alongside a masked placebo capsule. Participants were randomised on return of questionnaire within four weeks. Analysis was by ITT.
Participants	**Camargo 2021** Participants (n = 214) were individuals with asthma but not COPD, drawn from the ViDA trial (n = 5110) recruited from family practices and community groups across Auckland and then assessed at School of Population Health, Tamaki Campus, University of Auckland. Predominantly European with some Maori, South Asian and Pacific Islander participants. N = 214; 73 male, 141 female; mean age 63.4 yrs In this paper participants with both asthma and COPD (n = 205), and with COPD only (n = 356), were also analysed separately, but are not included in this systematic review. Baseline characteristics were similar between these groups. Participants were randomised equally to receive vitamin D or placebo treatment in the main study. **Sluyter 2017** 10% of the ViDA trial (n = 517) were randomly invited to participate in a one-year follow-up of respiratory outcomes. 442 agreed to participate and were included in the analysis. Of these, 14% (n = 20) had an asthma diagnosis, and their results are included in this systematic review. **Inclusion criteria (both papers)** 1. Doctor-diagnosed asthma identification, and had been dispensed a prescription for an ICS, a short-acting beta-agonist, or a long-acting beta-agonist at any time from 12 months before randomisation to 36 months after

Camargo 2021 *(Continued)*

2. Prior vitamin D supplementation ≤ 600 IU per day if aged 50 to 70 years; ≤ 800 IU per day if aged 71 to 84 years)

Exclusion criteria

1. Missing FEV1/FVC ratio
2. Not on inhaled asthma medication
3. Steroid dose insufficient with exacerbation
4. Other medical condition commonly treated by oral corticosteroids; inflammatory arthritis, inflammatory bowel disease or multiple sclerosis

Interventions	Active intervention (n = 106 in Camargo 2021, n = 7 in Sluyter 2017): initial bolus of 200,000 IU vitamin D_3, then 100,000 IU vitamin D_3 monthly. Control intervention (n = 108 in Camargo 2021, n = 13 in Sluyter 2017): identical placebo regimen. Mean serum 25(OH)D concentration, Camargo 2021: intervention arm: 64.5 nmol/L (baseline), control: 60.4 nmol/L (baseline)
Outcomes	**Camargo 2021** Primary outcome: exacerbations of asthma or COPD **Sluyter 2017** Primary outcome: FEV1 (ml) at baseline and follow-up Secondary outcome: FVC (ml) at baseline and follow-up
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Subsamples drawn from ViDA trial, in which 5110 participants were randomised by the study statistician—within random block sizes of 8, 10, or 12, and stratified by ethnic origin (Maori, Pacific Island, South Asian, European, or other) and 5-year age groups For Sluyter 2017, 256 of the vitamin D arm and 261 of the placebo arm were randomly invited for one-year follow-up
Allocation concealment (selection bias)	Low risk	Receive identical-looking softgel capsules containing either vitamin D_3 (100,000 IU) or placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	Camargo 2021: participant retention high at 77% for overall paper (asthma + COPD) No asthma-only participants withdrew from the trial in either arm. This is because the exclusion criteria included missing FEV1/FVC ratio, so excluded those lost to follow-up by construction.

Camargo 2021 *(Continued)*

		Sluyter 2017: no evidence of incomplete outcome data. 517 (10%) were randomly selected and invited to partake in the substudy. Of these, 74 declined and 1 withdrew consent (data analysis prohibited), and were thus not included in subsequent analyses. Out of the remaining 442, a complete set of both baseline and 1-year follow-up measurements was available in 366 participants (83%). Similar numbers were lost to follow-up across treatment and control arms.
Selective reporting (reporting bias)	Low risk	No suggestion of selective outcome reporting. The prepublished trial protocol applies to the overall ViDA study rather than to this paper alone, and includes a secondary outcome of 'Incidence rate of respiratory disease'. This paper then reports asthma exacerbations as its (only) outcome. Sluyter 2017: no suggestion of selective outcome reporting. Text states that this was a prespecified subgroup analysis.
Other bias	Unclear risk	Camargo 2021: defined exacerbation as “any prescription of oral corticosteroids more than 20 days apart for a short period (e.g. several days)”. However, these participants may have been prescribed oral corticosteroids for non-asthma reasons. Investigators excluded people with autoimmune conditions and other known reasons for oral corticosteroids, but there may still be residual non-asthma causes.

Castro 2014

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled, parallel-group trial Multicentre, 28 weeks long 4-week run-in period, prior asthma treatments discontinued 48 dropped out from study due to consent withdrawal, treatment failure, and asthma-related adverse event Analysed by ITT
Participants	9 academic medical centres in the USA, AsthmaNet network Predominantly white/black with some Hispanic and Asian N = 408; 130 male, 278 female; mean age 39.7 yrs **Inclusion criteria** 1. 18 years or older with asthma and a serum 25-hydroxyvitamin D level of less than 30 ng/mL **Asthma entry criteria** 1. Physician-diagnosed disease 2. Evidence of either bronchodilator reversibility (FEV1 ≥ 12% following 180 µg (4 puffs) of levalbuterol) or airway hyper-responsiveness (PC20 ≤ 8 mg/mL) **Exclusion criteria** 1. Taking vitamin D supplements containing > 1000 IU/day of vitamin D or supplements containing > 2500 mg/day calcium 2. Chronic oral corticosteroid therapy

Castro 2014 *(Continued)*

3. Chronic inhaled corticosteroid therapy > 1000 mcg of fluticasone daily or the equivalent
4. New allergen immunotherapy within the past 3 months
5. History of physician-diagnosed nephrolithiasis or ureterolithiasis
6. History of life-threatening asthma within the last 5 years
7. Use of concomitant medications that alter vitamin D metabolism
8. Impaired renal function (GFR < 30 ml/min) at visit 1
9. Asthma exacerbation within past 4 weeks requiring systemic corticosteroids
10. Respiratory tract infection within past 4 weeks
11. Chronic diseases (other than asthma) that would prevent participation in the trial
12. History of smoking in the past year
13. Use of investigative drugs or enrolment in intervention trials in the 30 days prior to screening
14. Serum calcium greater than 10.2 mg/dl on entry (at visit 1)
15. Urine calcium/creatinine ratio (mg) > 0.37 (at visit 1)
16. More than 8 weeks elapsed between visit 0 (screen) and visit 2 (evaluated at visit 2)

Interventions	Treatment (n = 201): oral vitamin D_3, 100,000 IU bolus once, then 4,000 IU/day for 28 weeks, added to inhaled ciclesonide (320 µg/d) Control (n = 207): placebo soft gelatin capsules matching in appearance, added to inhaled ciclesonide (320 µg/d) Median 25(OH)D concentration at baseline: 47 nmol/L. Mean serum 25(OH)D concentration, intervention arm: 105 nmol/L (12 weeks), 107 nmol/L (20 weeks), 105 nmol/L (28 weeks)
Outcomes	**Primary outcome** Time to first asthma treatment failure. Treatment failure defined as 1 or more of the following. 1. Peak expiratory flow of 65% or less of baseline measurement on 2 of 3 consecutive measurements 2. FEV1 of 80% or less of baseline measurement on 2 consecutive measurements 3. Increase in levalbuterol dose of 8puffs/d or more for 48 hours (vs baseline) 4. Additional use of inhaled corticosteroids or use of oral or parenteral corticosteroids for asthma; emergency department or hospitalisation for asthma with systemic corticosteroid use 5. Participant lack of satisfaction with treatment; and physician clinical judgement for safety reasons **Secondary outcomes** 1. Lung function measures. FEV1 (litres and % predicted) - extracted from graph manually using ruler, following Higgins 2022 2. Asthma symptoms (ASUI) 3. Exacerbations 4. Asthma-specific quality of life using Asthma Brother Profile 5. Impairment from asthma, in terms of productivity loss and activity 6. Impairment. Using Work Productivity and Activity Impairment questionnaire (WPAI: Asthma) 7. Pharmacogenetics. Potential genetic modifiers of response to corticosteroids and vitamin D 8. Vitamin D levels. Initial and postrandomisation vitamin D levels compared to asthma outcomes 9. Corticosteroid responsiveness. Change in lung function in corticosteroid unresponsive and responsive individuals evaluated. Corticosteroid-responsive airflow obstruction defined as a ≥ 5% improvement in FEV1 following systemic corticosteroids 10. Total inhaled corticosteroid dose
Notes	Grants awarded by the National Heart and Lung Institute. Ciclesonide and levalbuterol were provided without cost by Sunovion Pharmaceuticals Inc.

Castro 2014 *(Continued)*

	The National Institutes of Health (NIH) program officers participated in the design and conduct of the study, and did not participate in the collection, management, analysis, and interpretation of the data. The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Study was "double-masked" and active and placebo capsules were matched in appearance. Randomisation code was held by the Data Co-ordinating Centre; the Data Safety Monitoring Board oversaw the trial and reviewed data as the trial progressed in aggregate (group A and B) then unblinded at the end. Allocation was kept concealed until the last participant completed the trial (information from trial report and principal investigator).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rates of withdrawal overall, which were seen equally between study arms (17/201 in active arm vs 23/207 in control arm discontinued the study)
Selective reporting (reporting bias)	Low risk	No suggestion of selective outcome reporting; outcomes detailed in Methods were reported in Results. However, we did not have access to the original protocol.
Other bias	Low risk	Nil

Ducharme 2019

Study characteristics

Methods	Randomised, triple-blind, placebo-controlled, parallel-group trial Single centre, 7 months long No run-in period, all participants had asthma treated as per Canadian national recommendations 5 did not complete: 4 withdrew from the treatment arm and 1 from the control arm due to inconvenience or fear of blood tests Study analysed on an ITT basis
Participants	Recruited from the Sainte-Justine University Health Centre (SJUHC), Montreal Canada Participants were majority Caucasian N = 47; 30 male, 17 female; mean age 2.9 yrs **Inclusion criteria**

Ducharme 2019 *(Continued)*

1. Aged 1 to 5 years
2. Physician-diagnosed asthma, based on clinical signs of airflow obstruction and reversibility
3. URTI reported by parents as the main asthma trigger
4. ≥ 4 URTIs in the preceding year
5. ≥ 1 exacerbation requiring rescue oral corticosteroids (OCS) in the preceding 6 months (or ≥ 2 in the past 12 months), confirmed by pharmacy and/or medical records

Exclusion criteria

1. Intake of or intention to use > 400 IU/day of vitamin D supplement
2. Extreme prematurity (< 28 weeks' gestation)
3. High risk of vitamin D deficiency (e.g. vegan diet)
4. Condition(s) (e.g. rickets) or drug(s) altering calcium or vitamin D absorption or metabolism (e.g. anti-epileptic, diuretic, antacid, or anti-fungal medications)
5. Anticipated difficult follow-up

Interventions	Active intervention (n = 23): 2 mL of vitamin D_3 (100,000 IU of cholecalciferol) administered by the nurse at baseline and 3.5 months Control intervention (n = 24): 2 mL of placebo administered by the nurse at baseline and 3.5 months Baseline mean serum 25(OH)D concentration, intervention arm: 74.8 nmol/L, control arm: 77.0 nmol/L
Outcomes	**Primary outcome:** Overall change from baseline in total serum 25OHD and at 3.5 and 7 months **Secondary outcomes:** 1. Incidence of URTIs per child 2. Incidence of asthma exacerbations with URTIs per child 3. Intensity of asthma symptoms per episode, documented using the Asthma Flare-up Diary for Young Children (ADYC) 4. Duration of asthma exacerbations with URTIs, in days 5. Intensity of ß2-agonist use per episode (cumulative number of puffs) 6. Parental functional status during exacerbations ascertained using the Effect of a child's asthma flare-up on parents (ECAP) survey 7. Parental workdays missed per episode 8. Courses of oral steroids per child 9. Acute care visits for asthma per child 10. Number of subjects with ≥ 1 exacerbation requiring rescue OCS 11. Number of subjects with ≥ 1 exacerbation requiring acute care visit 12. Adverse health events 13. Number of children with hypercalciuria (Ca:Cr) > 1.25 (1 to 2 years) or > 1 (2 to 5 years) nmol/nmol at any point in time
Notes	Premature trial cessation due partial funding enabling only a 2-year single-centre pilot trial, rather than an adequately powered multicentre study of 865 children, the primary outcome was modified post hoc (from proportion of children with one or more exacerbations requiring OCS) to the overall change from baseline in total serum 25OHD and at 3.5 and 7 months, similar to our previous pilot study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated block randomisation

Ducharme 2019 *(Continued)*

Allocation concealment (selection bias)	Low risk	The Central Pharmacy (SJUHC) held the allocation codes, prepared the study supplements in sequentially coded syringes, and dispensed as per randomisation 2 mL of vitamin D3 (100,000 IU of cholecalciferol) or identical placebo, administered by the nurse at baseline and 3.5 months.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple-blind, placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Triple-blind, placebo-controlled study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants contributed data to analysis of baseline outcomes. Rates of withdrawal were low overall, though differed between arms (4/23 in intervention arm vs 1/24 control arm).
Selective reporting (reporting bias)	Unclear risk	There was no evidence of selective reporting. However, the prespecified primary and secondary outcomes were changed as a result of premature trial cessation due to partial funding.
Other bias	Low risk	Potential generalisability issues 1. Exclusion criteria included anticipated difficulty to follow-up. 2. Of 172 potentially eligible children, 125 declined participation, mainly because of the number of blood tests, lack of time to comply to other procedures, and lack of interest.

Forno 2020

Study characteristics	
Methods	Multicentre, double-blinded, placebo-controlled randomised controlled trial of 48 weeks' duration. Concomitant medication was discontinued, and replaced by inhaled fluticasone and as-needed inhaled albuterol. This was adjusted as follows: “following randomization, participants continued taking the same dose of fluticasone until the 24-week visit, when their fluticasone dose was reduced by 50%if their asthma was well controlled and if they had FEV1 and FEV1 to forced vital capacity (FEV1/FVC) greater than or equal to 80% of predicted, were using a rescue inhaler 4 or fewer times per week, and had asthma symptoms preventing full participation in daily activities no more than once per month." Analysis was by ITT. There was a four-week run-in period. "Based on prior studies, the trial was designed to have a sample size of 400 participants for 88% power to detect an absolute reduction in the rate of severe asthma exacerbations of 16% (from 40% in the placebo group to 24% in the intervention group), assuming an overall α of.05, a 2-sided test, and a withdrawal rate of 15%."
Participants	192 participants were recruited from seven children’s hospitals across the USA, and randomised to intervention or control arms in equal numbers. **Inclusion criteria** 1. Physician-diagnosed asthma for at least 1 year 2. At least 1 severe asthma exacerbation (systemic corticosteroids for at least 3 days, or a hospitalisation or emergency department visit requiring systemic corticosteroids) in the previous year 3. Use of asthma medications (daily controller medications, or inhaled β2-agonists at least thrice per week) for at least 6 months in the previous year

Forno 2020 *(Continued)*

4. FEV1 ≥ 70% of predicted
5. Either bronchodilator responsiveness (an increment in baseline FEV1 of 8% or more 15 minutes after inhalation of 180-µg albuterol) or, in those without bronchodilator response, increased airway responsiveness (a provocative concentration of methacholine at which FEV1 decreased by 20% (PC20) < 8 mg/mL if not receiving inhaled corticosteroids, or < 16 mg/mL if receiving inhaled corticosteroids)

Exclusion criteria

1. Vit D ≥ 30 ng/mL or < 14 ng/mL
2. Chronic respiratory disorders other than asthma
3. Chronic oral corticosteroid therapy
4. Severe asthma
5. Inability to perform adequate spirometry
6. Elevated serum calcium
7. Reported allergic to albuterol
8. Taking vit D supplements

Interventions	Active intervention (n = 96): oral vitamin D_3 4000 IU daily Control intervention (n = 96): oral placebo tablet daily Baseline mean serum 25(OH)D concentration, intervention arm: 56.25 nmol/L, control arm: 57.0 nmol/L
Outcomes	**Primary outcome** Hazard ratio (HR) for the time to a severe asthma exacerbation across the 48-week study period **Secondary outcomes** 1. The time to a viral-induced severe asthma exacerbation, defined by having both a severe exacerbation and a positive PCR result to a panel of common respiratory viruses 2. Difference in mean cumulative dose of inhaled steroids 3. Proportion of participants achieving a 50% reduction in inhaled corticosteroid dose at or after the 24-week visit **Han 2021 primary outcomes** 1. Change in ACT or cACT (presented as a composite cACT, with ACT scores transformed linearly to fit the cACT scale as outlined in manuscript) 2. End-study FEV1, % predicted 3. End-study FVC, % predicted 4. pAQLQ, multivariate coefficient **Rosser 2021 primary outcomes** 1. Total IgE 2. IgE to Dermatophagoides pteronyssinus 3. IgE to Blattella germanica Exacerbation defined as requiring use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or (2) a hospitalisation or emergency department visit because of asthma, requiring systemic corticosteroids The number of hospitalisations with an asthma exacerbation was reported as an event rate, but not as the proportion of participants experiencing one or more hospitalisations. Thus, this outcome could not be meta-analysed.
Notes	Details about discontinuation of concomitant medication is provided by Han (2021) report of same trial, not in core text.

Forno 2020 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation was stratified according to study site and race/ethnicity, with treatment assignments made in random permuted block sizes of 2 and 4.
Allocation concealment (selection bias)	Low risk	The soft gelatin placebo capsules were matched in appearance to those containing vitamin D_3.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rates of withdrawal overall, which were similar in treatment and control arms (8/96 lost to follow up in treatment arm, 3/96 in control arm). 10 participants had study medication stopped (4 in treatment arm, 6 in control) due to ≥ 3 exacerbations, or clinically low vitamin D levels in control group.
Selective reporting (reporting bias)	Low risk	All prespecified primary and secondary outcomes from the protocol were reported in the main paper.
Other bias	Low risk	Nil

Jat 2020

Study characteristics

Methods	Single-centre, double-blinded, placebo-controlled randomised controlled trial of 9 months' duration. All participants received asthma treatment as per standard GINA guidelines. No run-in period is described. Analysis was by ITT. "To detect a 15% difference in the proportion of children with controlled asthma with 80% power and a 5% level of significance, the required number of participants for each group was 113." 125 participants were enrolled in each group, allowing for 10% loss to follow up.
Participants	250 participants were recruited from the Department of Pediatrics, All India Institute of Medical Sciences, New Delhi from May 2017 to August 2019. They were randomised to intervention or control arms in equal numbers. **Inclusion criteria:** Children age 4 to 12 with persistent asthma receiving regular inhaled corticosteroids who had vitamin D deficiency. Vitamin D deficiency was defined as levels of serum 25(OH) D below 20 ng/mL (50 nmol/L) **Exclusion criteria:** 1. Clinical features of rickets 2. Chronic diseases like chronic renal failure, chronic liver disease or any bone disease 3. Mental retardation

Jat 2020 *(Continued)*

4. Receiving vitamin D supplementation
5. Received a mega-dose of vitamin D (≥ 300,000 units) in last 3 months

Interventions	Active intervention (n = 125): Vitamin D 1000 IU in liquid form (1 mL), daily for 9 months Control intervention (n = 125): oral placebo liquid (1 mL), daily for 9 months
Outcomes	**Primary outcome** 1. Proportion of children having Childhood Asthma Control Test (CACT) score of ≥ 20 at the end of the intervention 2. Any adverse effects including nausea, vomiting, pain in abdomen, constipation, headache, altered sensorium and seizures. This data was presented as the total number of events, rather than the number of participants experiencing one or more such events. Thus, it could not be meta-analysed, but was included narratively. **Secondary outcomes** 1. Change in FEV1, FEV1/FVC and PEFR from baseline to end of the treatment 2. Change in mean CACT score from baseline to end of the treatment; presented as a median, but with symmetric IQR so this data was converted to mean and standard deviation following Higgins 2022. 3. Number of emergency visits during study period; only presented as a median with asymmetric IQR, so this data could not be converted to a mean for meta-analysis. 4. Number of days requiring rescue medications and number of night awakenings 5. Height gain from enrolment to end of the study 6. Number of courses of oral steroids uses 7. Total dose of inhaled steroids 8. Change in 25(OH)D levels Exacerbation was defined as requiring use of oral corticosteroids. Supplementary data provided by authors on request, stating that 17/112 participants in the intervention arm and 8/108 participants in the control arm experienced one or more severe exacerbations (requiring corticosteroids). There were 25 total severe exacerbations in the intervention arm and 8 total in the control arm.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation in blocks of 10
Allocation concealment (selection bias)	Low risk	Research staff, not engaged in the conduct of this trial, labelled the vitamin D and placebo syrups into serial number as per randomisation list.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants and research staff enrolling subjects and assessing outcomes were blinded to the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The participants and research staff enrolling subjects and assessing outcomes were blinded to the intervention.

Jat 2020 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants contributed data to analysis of baseline outcomes. Rates of loss to follow-up were comparable between arms (13/125 in intervention arm vs 17/125 control arm).
Selective reporting (reporting bias)	Low risk	No suggestion of selective reporting, outcomes matched those prespecified in protocol
Other bias	Low risk	Nil

Jensen 2016

Study characteristics	
Methods	Single-centre, double-blind, randomised, placebo-controlled trial of 6 months' duration. Concomitant asthma medications were not discontinued during the trial, and analysis was by ITT. There was no run-in period. The trial was a pilot study, powered to compare the proportion of participants achieving serum 25(OH)D concentration ≥ 75 nmol/L. Target enrolment was 17 per arm, actual enrolment was 11 per arm; enrolment was discontinued on receipt of funding for the substantive trial for which this was the pilot.
Participants	Participants (n = 22) were recruited from the asthma clinic, hospital wards, and emergency department of the Sainte-Justine University Health Centre, Montreal, Canada, and randomised to intervention vs control arms of the study in equal numbers. Baseline characteristics were well-matched, other than an excess of eczema among participants randomised to vitamin D3 vs placebo. **Inclusion criteria** 1. Age 1 to 5 years 2. Physician-diagnosed asthma, based on clinical signs of airflow obstruction and reversibility 3. URTIs as the main exacerbation trigger, reported by parents 4. ≥ 4 parent-reported URTIs in the past 12 months 5. ≥ 1 exacerbation requiring oral corticosteroids in the past 6 months or ≥ 2 in the past 12 months **Exclusion criteria** 1. Extreme prematurity (< 28 weeks' gestation) 2. "High risk of vitamin D deficiency" 3. Other chronic respiratory disease 4. Disordered calcium or vitamin D metabolism 5. Oral medications interfering with vitamin D metabolism 6. Vitamin D supplementation greater than 1000 IU/day in the past 3 months
Interventions	Active intervention (n = 11): 100,000 IU vitamin D_3 oral bolus at baseline, followed by 400 IU vitamin D_3 IU orally daily Control intervention (n = 11): oral placebo at baseline, followed by 400 vitamin D_3 IU orally daily Mean serum 25(OH)D concentration, intervention arm: 62 nmol/L (baseline), 157 nmol/L (10 days)
Outcomes	**Primary outcome** The mean group change in total serum 25(OH)D from baseline to 3 months **Secondary outcomes** 1. The proportion of children with total 25(OH)D ≥ 75 nmol/L (30 ng/mL) at 3 months and in total 25(OH)D values over 6 months

Jensen 2016 *(Continued)*

2. The proportion of children with hypercalciuria (urinary calcium: creatinine ratio (Ca:Cr) > 1.25 (1 to 2 years) and > 1 (2 to 5 years) mmol/mmol) at any time point
3. Serum calcium, phosphorus, and alkaline phosphatase (ALP)
4. Event rates for exacerbations requiring rescue oral corticosteroids (documented in medical or pharmacy records or both)

Notes	Note that low-dose vitamin D was administered to participants in both intervention and control arms of this trial. Unpublished full text obtained from corresponding author. No conflict of interest identified. Funding: Thrasher Research Fund.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Group assignment, recorded on a sequentially numbered list, was allocated by the Sainte-Justine Hospital Research Pharmacy, which held the randomisation code. To maintain blinding, the intervention and placebo dose were identical in colour, appearance, volume, taste, and packaging. All research personnel, physicians, nurses, participants and their parents were blinded to group allocation. The code was not broken until the study trial was complete (information from principal investigator).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	21/22 participants were included in analysis of primary outcome.
Selective reporting (reporting bias)	Low risk	All prespecified primary and secondary outcomes were reported in the main paper. All exploratory/additional outcomes were also reported, with the exception of the duration of exacerbations and viral infections and the severity of exacerbations (due to poor questionnaire completion rate, as well as space restrictions for the manuscript). The additional outcome of cytokine profile is to be reported separately (information from principal investigator; original study protocol was not obtained).
Other bias	Low risk	Nil. Information on risk of bias for this trial relates to unpublished data.

Jerzynska 2016

Study characteristics

Methods	Randomised, double-blind, placebo-controlled, parallel-group trial Single centre, 5 months long No run-in period, all participants had asthma treated as per GINA guidelines 0 participants in the subgroup with asthma did not complete follow-up

Jerzynska 2016 *(Continued)*

	Study analysed on an ITT basis
Participants	Recruited from the Medical University of Lodz, Poland N = 8 with asthma (from an overall study cohort n = 50). 3 male, 5 female; mean age 9.7 years (for subgroup with asthma) **Inclusion criteria** 1. Ages 5 to 12 years 2. Living in the same geographic location (Lodz, Poland) 3. Sensitive only to grass pollen 4. Clinical diagnosis of grass-related moderate- to-severe rhinoconjunctivitis (according to Allergic Rhinitis and its Impact on Asthma 2014 recommendations) with a duration of at least 1 year before the first study visit Eight participants had concomitant asthma (intermittent or mild-to-moderate persistent, according to Global Initiative for Asthma 2014 criteria) **Exclusion criteria:** 1. Allergic to perennial allergens 2. Severe or unstable asthma 3. Active upper respiratory tract infection within 1 month before the first study visit 4. Known contraindications of sublingual immunotherapy according to the European Academy of Allergy and Clinical Immunology 5. Any previous immunotherapy 6. Clinically significant pulmonary, haematologic, hepatic, gastrointestinal, renal, endocrine, neuronal, cardiovascular, and/or psychiatric diseases or malignancies that could either put them at risk during their participation in the study or might have influenced the results of the study (as judged by the investigator) 7. Systemic corticosteroids or immune suppressive drugs within 6 months 8. Supplementary vitamin D (or any vitamin supplements) used within 6 months
Interventions	Active intervention (n = 5): vitamin D 1000 IU daily wafer (25 µg of cholecalciferol, Vigantoletten 1000; Merck KGaA) + Oralair 300 IR tablet as a standardised extract of 5 grass pollens Control intervention (n = 3): daily placebo wafer + Oralair 300 IR tablet as a standardised extract of 5 grass pollens
Outcomes	**Primary outcome** 1. Reduction in total symptom-medication score 2. Reduction in nasal symptoms 3. Reduction in ocular symptoms 4. Reduction in asthma symptoms: presented using own asthma symptom score, not possible to meta-analyse 5. Reduction in medication use **Secondary outcomes** 1. FEV1 2. FVC: only presented as denominator in FEV1/FVC 3. FeNO: only provided for whole sample, not for asthma-only subset 4. PD20 5. Serum level of 25(OH)D 6. Methacholine bronchial provocation test

Jerzynska 2016 *(Continued)*

	Additional data provided by authors on request: 3/5 asthma patients in the intervention arm and 2/3 in the control arm experienced one or more severe asthma exacerbations, end-study FEV1% was 106.4+/-3.2 for the intervention arm and 104.1 +/- 2.8 for the control arm, and there were no withdrawals amongst the asthma subgroup.
Notes	Assessment of asthma was conducted using authors' own score, with detail provided by author: "asthma symptoms were measured as follows: cough 0-3, wheeze 0-3, dyspnoea 0-3 (0 = no symptoms; 1 = mild symptoms - present but easily tolerated; 2 = moderate symptoms - definite awareness of bothersome but tolerable symptoms; 3 = severe symptoms - symptoms hard to tolerate and that cause interference with daily activities and/or sleeping); the minimum score for each day was 0, and the maximum was 9. Every use of medication was registered (one point for each allowed medication from: inhaled corticosteroids, bronchodilators, leukotriene modifiers, theophylline)." Very small subsample with asthma (n = 8).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Vitamin D and placebo were blinded (prepared in wafers with 0.3 mg of lactose) by the hospital pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants contributed data to analysis of baseline outcomes. Of the asthma patient subset, zero were lost to follow-up from both treatment and control arms.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting. Trial protocol not obtained.
Other bias	Low risk	Nil

Jiang 2017

Study characteristics

Methods	Randomised, double-blind, placebo-controlled trial Single centre, 6 months long No run-in period, all participants had asthma in accordance with GINA guidelines 9 did not complete: 3 lost to follow-up from the treatment arm and 6 from the control arm Study analysed on a per-protocol basis, considering only those who completed the study
Participants	Recruited from the Child Health Hospital, Haikou, Hainan, China N = 92 randomised (46 to each arm), 83 completed trial and analysed. 45 male, 38 female; mean age 9.9 yrs

Jiang 2017 *(Continued)*

	Baseline characteristics similar in both arms. **Inclusion criteria** Aged 6 to 14 years Diagnosed as having asthma by two different paediatricians **Exclusion criteria** Already taken vitamin D Suffering from urinary stones or other potential calcium and bone-related diseases Suffering from chronic diseases other than asthma, such as mental illness and dysphagia Suffering from a disease that is difficult for other paediatricians to manage
Interventions	Active intervention (n = 43): vitamin D_3, 800 IU tablet daily Control intervention (n = 40): daily placebo, similar tablet made of flour Baseline vit D: 71.25 nmol/L intervention arm, 72.5 nmol/L control arm
Outcomes	**Primary outcomes** 1. Asthma ACT score: change from baseline 2. Serum 25-hydroxy vitamin D_3 level 3. % with FEV1 < 80% predicted; could not be meta-analysed 4. % with FVC < 80% predicted; could not be meta-analysed 5. % with PEF < 80% predicted; could not be meta-analysed **Secondary outcomes** 1. Number of hospital admissions for asthma: stated in introduction but not reported in results. 2. Number of withdrawals
Notes	Paper published in Chinese, with two translations provided by Yuen Fun Alexis Lai and Chew Shu Yui, to whom we are extremely grateful.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	High risk	Investigators were divided into planning and dispensing, and the ones in charge of planning did not disclose the experimental and placebo medications to the dispenser and participants. However, this suggests that planning investigators were not blinded to allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Investigators were divided into planning and dispensing, and the ones in charge of planning did not disclose the experimental and placebo medications to the dispenser and participants. However, this suggests that planning investigators were not blinded to allocation.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Investigators were divided into planning and dispensing, and the ones in charge of planning did not disclose the experimental and placebo medications to the dispenser and participants. It is unclear whether outcome assessors were blinded or not.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Rates of loss to follow-up were low and comparable between arms (3/46 in intervention arm vs 6/46 control arm).

Jiang 2017 *(Continued)*

Selective reporting (reporting bias)	Low risk	Trial protocol not obtained.
Other bias	Unclear risk	Only participants who completed the trial were analysed in baseline outcomes. Baseline characteristics of participants lost to follow-up were not presented.

Kerley 2016

Study characteristics	
Methods	Single-centre, double-blind, randomised, placebo-controlled trial of 15 weeks' duration. Concomitant asthma medication was continued during the trial (with an inclusion criterion being that participants were already treated according to GINA guidelines). Analysis was per protocol, with patients who dropped out excluded from the analysis. There was no run-in period.
Participants	Participants (n = 44) were recruited from the National Children's Hospital Dublin between November 2013 and January 2014, and randomised to intervention (n = 19) vs control (n = 25) arms. There were 5 dropouts from this point (2 from intervention arm, 3 from control arm), who were excluded from analysis. Baseline characteristics were well-matched. **Inclusion criteria:** 1. Previous diagnosis of asthma 2. Caucasian 3. Aged 6–16 4. Established on anti-asthmatic pharmacotherapy with uncontrolled asthma at baseline according to the Global Initiative for Asthma 2011 guidelines **Exclusion criteria:** 1. Conditions/medications that influence vitamin D metabolism or absorption
Interventions	Active intervention (n = 17): daily 2000 IU vitamin D_3 softgel capsule Control intervention (n = 22): daily placebo softgel capsule Baseline mean serum 25(OH)D concentration, intervention arm: 58 nmol/L, control arm: 51 nmol/L
Outcomes	**Primary outcome:** 1. Spirometry measures 2. cACT 3. Global Initiative for Asthma score (GINA score) 4. Mini-Paediatric Asthma Quality of Life Questionnaire (mPAQLQ) **Secondary outcomes:** 1. Change in medications, school days missed, infection rate, and GP, pharmacist, and hospital visits 2. Biochemical markers: serum 25(OH)D, parathyroid hormone (PTH), albumin, total calcium, alkaline phosphatases (ALP), phosphate (PO4), total IgE, immunoglobulin A (IgA), and high-sensitivity C reactive protein (hsCRP), IL-10 and LL-37 The outcomes of ACT, FEV1 and FVC were only presented in the paper as a median and IQR with significant skew, so could not be meta-analysed. ACT and AQLQ are reported in narrative form.

Kerley 2016 *(Continued)*

Notes	Unpublished data sought from previous IPD (Joliffe 2019) on number of participants with one or more severe exacerbations, and rate ratio of severe exacerbations.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	Placebo was softgel capsule identical to treatment 2000 IU vitamin D_3 softgel capsule
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	High rate of loss to follow-up (12 of 51 participants, 7 prior to randomisation and 5 postrandomisation). However, there is no evidence to suggest differential rates of loss to follow-up between the intervention and control arms (7 of 24 participants vs 5 of 27). Authors compare baseline characteristics of the 12 participants in the combined lost-to-follow-up group to those who were analysed, and find similar baseline characteristics.
Selective reporting (reporting bias)	Unclear risk	The primary outcome prespecified in the trial protocol was reported. However, two secondary outcomes were not reported; height velocity and a parental diary of child asthma symptoms.
Other bias	Low risk	Nil

Lewis 2012

Study characteristics

Methods	Randomised, double-blind, placebo-controlled, parallel-group trial (pilot study) Single-centre, 12 months long Run-in period not described Concomitant medication: current daily controller asthma medication 10 dropped out of study (reasons not provided) Analysis by ITT not specified
Participants	Omaha, Nebraska, USA Majority black/Hispanic N = 30, sex distribution not described, age range 6 to 17 yrs **Inclusion criteria**

Lewis 2012 *(Continued)*

	1. Children < 18 years old 2. Physician diagnosis of chronic persistent asthma and current daily controller asthma medication **Exclusion criteria** Not described
Interventions	Treatment (n = 15): oral vitamin D_3, 1000 IU/d for 12 months Control (n = 15): placebo (specifications not given) daily for 12 months Study dates not described. Mean serum 25(OH)D concentration, intervention arm: 30 nmol/L (baseline), 68 nmol/L (6 months, summer), 70 nmol/L (12 months, winter). Control arm: 35nmol/L (baseline) All 25(OH)D concentrations above estimated from figure.
Outcomes	**Primary outcomes** 1. ACT score at baseline, 6 and 12 months 2. Spirometry (FEV1) at baseline, 6 and 12 months 3. Serum 25(OH)D levels were measured at baseline, 6 and 12 months **Secondary outcomes** Not given
Notes	Disclosures: authors have nothing to disclose. Funding sources: funding provided by LB595 State of Nebraska Tobacco Settlement funds to Creighton University

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled trial
Incomplete outcome data (attrition bias) All outcomes	High risk	High rates of loss to follow-up (10/30 participants)
Selective reporting (reporting bias)	Low risk	No suggestion of selective outcome reporting: results were reported for outcomes listed as having been investigated in the study report. However, we did not have access to the original protocol.
Other bias	Low risk	Nil

Majak 2009

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled, parallel-group trial Single-centre, 12 months long Concomitant medication was continued except: inhaled long-acting beta2-agonists, leukotriene modifiers, beta-blockers, multivitamin supplements, and systemic corticosteroids Run-in period: September 2005 to March 2006 Analysed on ITT basis
Participants	Lodz, Poland Polish nationals Total N = 54 N = 36 used for data extraction; 22 male, 14 female; age range 6 to 12 yrs **Inclusion criteria** 1. Children aged 6 to 12 yrs 2. IgE-dependent asthma with regular symptoms requiring long-term treatment with inhaled corticosteroids 3. A disease duration of at least 2 years 4. Sensitised only to house dust mites **Exclusion criteria** 1. Poor understanding of a diary used to record daily symptoms 2. Lack of ability to perform reproducible spirometry, exhibiting the resting FEV1 of at least 70% 3. No contraindications for SIT 4. Sensitisation to allergens other than house dust mites 5. Previously received immunotherapy
Interventions	Treatment (n = 18): SIT with prednisone 20 mg + oral vitamin D_3, 1000 IU/week for 3 months Control (n = 18): SIT with prednisone 20 mg + placebo for 3 months SIT with placebo only group (n = 18) was not included as did not allow direct comparison of effect of vitamin D. Study dates: April 2006 to April 2007 Mean serum 25(OH)D concentration, intervention arm: 80 nmol/L (baseline), control 78.5 nmol/L
Outcomes	**Primary outcomes** Inhaled steroid-sparing effect of SIT (dose reduction) **Secondary outcomes** 1. Clinical outcomes: Asthma symptom score and FEV1 2. Immunological outcomes: IL-10, TGF-b1, IL-13, IL-5 3. 25(OH)D
Notes	This study was funded by grant 502-12-760 and 503-2056-1 from the Medical University of Lodz, Poland.

Majak 2009 *(Continued)*

	No conflict of interest to declare. Authors confirmed that no exacerbations requiring oral corticosteroids occurred in either arm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Low risk	Active intervention drugs and placebo were blinded by the hospital pharmacy. The double-blind code was not revealed until the end of the study.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rates of loss to follow-up, equal between study arms (1/18 for D_3 + steroid arm vs 1/18 for steroid arm)
Selective reporting (reporting bias)	Low risk	No suggestion of selective outcome reporting: outcomes listed in Methods are reported in Results. However, we did not have access to the trial protocol.
Other bias	Low risk	Nil

Majak 2011

Study characteristics

Methods	Randomised, double-blind, placebo-controlled, parallel-group trial Single-centre, 6 months long Run-in period: 6 months, concomitant medication discontinued No drop-out, all participants completed follow-up
Participants	Lodz, Poland Mainly Polish nationals N = 48. 32 m, 16 f. Mean age 11.5 yrs, range 5 to 18 yrs **Inclusion criteria:** 1. Children (5 to 18 yrs) with newly diagnosed asthma. 2. Sensitive only to house dust mites. **Exclusion criteria:** 1. Treatment with an oral, inhaled, or intranasal corticosteroid. 2. Supplementation with vitamin D during the 6 months preceding the trial.

Majak 2011 *(Continued)*

	3. History of fractures in the last 2 years. 4. Previous immunotherapy. 5. Obesity (body mass index > 30 kg/m^2). 6. Other chronic diseases.
Interventions	Treatment (n = 24): budesonide 800 mcg daily administered as a dry inhaled powder and oral vitamin D_3 500 IU daily. Control (n = 24): budesonide 800 mcg daily administered as a dry inhaled powder and oral placebo daily. Mean serum 25(OH)D concentration, intervention arm: 90 nmol/L (baseline), 94 nmol/L (6 months) Control arm: 87.75nmol/L (baseline)
Outcomes	**Primary outcomes:** 1. ATAQ symptom score. 2. Lung function (FEV1). 3. Number of exacerbations. **Secondary outcome:** Serum vitamin D status at various time points.
Notes	Supported by grant nos. 502-12-760 and 503-2056-1 from the Medical University of Lodz, Poland. Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	100% follow-up
Selective reporting (reporting bias)	Low risk	Nothing to suggest selective reporting: results were reported for outcomes listed as having been investigated in the study report. However, we did not have access to the original protocol.
Other bias	Low risk	Nil

Martineau 2015

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled, parallel-group trial Multicentre, 12 months long Run-in period: at least 2 weeks, concomitant medication continued 31 did not complete: 17 withdrew consent, 13 lost to follow-up, and 1 died Study analysed on ITT basis
Participants	London, UK Majority (202/250) white British N = 250; 109 male, 141 female; mean age 47.9 yrs **Inclusion criteria** Medical-record diagnosis of asthma treated with ICS **Exclusion criteria** 1. Aged 80 years or above 2. Tobacco smoking history > 15 pack-years 3. Medical-record diagnosis of COPD 4. Failure to exhibit significant variability/reversibility in airway obstruction
Interventions	Treatment (n = 125): six 2-monthly oral doses of 6 mL Vigantol oil (Merck Serono, Darmstadt, Germany) containing 3 mg (120,000 IU) vitamin D_3. Control (n = 125): six 2-monthly oral doses of 6 mL organoleptically identical placebo (Miglyol oil, Caesar & Loretz, Hilden, Germany). Mean serum 25(OH)D concentration, intervention arm: 50 nmol/L (baseline), 61.2 nmol/L (2 months), 69.4 nmol/L (12 months)
Outcomes	**Primary outcomes** 1. Time to first severe asthma exacerbation 2. Time to first URTI **Secondary outcomes** 1. Peak values and areas under the curve for symptom scores during severe exacerbation/URTI 2. Proportion of days with poor asthma control 3. Proportion of nights with awakenings due to asthma symptoms 4. Time to unscheduled healthcare attendance and use of antibiotics for exacerbation/URTI 5. ACT and SGRQ scores 6. FeNO concentration 7. Daily ICS doses 8. % predicted FEV1, PEFR 9. Use of inhaled relief medication and induced sputum differential cell count and supernatant inflammatory profiles at 2, 6, and 12 months 10. Serum concentrations of 25(OH)D and parathyroid hormone (PTH) at 2 months and 12 months

Martineau 2015 *(Continued)*

	11.Health economic outcomes (costs of exacerbations and URTI, quality-adjusted life years, and incremental net benefit over 1 year)
Notes	Funded by the National Institute for Health Research's Programme Grants for Applied Research Programme (ref RP-PG-0407-10398). No competing interests to declare.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Randomisation was performed by manufacturer (Nova Laboratories). Manufacturer and independent data monitoring committee held copies of the randomisation code, which was not revealed to investigators until database lock at the end of the trial. All personnel involved in recruitment and medication delivery were blinded to randomisation (information from trial report and principal investigator).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants contributed data to analysis of co-primary outcomes. Rates of loss to follow-up were comparable between arms (8/125 in intervention arm vs 5/125 control arm).
Selective reporting (reporting bias)	Low risk	Results of all analyses specified in protocol and relating to asthma control are reported; results of analyses relating to symptoms of allergic rhinitis will be reported elsewhere. We had access to the study protocol.
Other bias	Low risk	Nil

Ramos-Martínez 2018

Study characteristics

Methods	Randomised, double-blind, placebo-controlled, parallel-group trial Single centre, 6 months long No run-in period, all patients had asthma treated in accordance with GINA guidelines 3 did not complete: 2 lost to follow-up from the treatment arm and 1 from the control arm Study analysed on an ITT basis
Participants	Recruited from the Department of Allergy and Immunology at the General Hospital of Mexico N = 86; 75 male, 11 female; mean age 41.5yrs. **Inclusion criteria**

Ramos-Martínez 2018 *(Continued)*

1. Confirmed diagnosis of asthma by a qualified allergist according to the clinical characteristics established by GINA
2. A clinical history of bacterial infections in the upper respiratory tract recurring for at least 42 days per year
3. High levels of IgE (above 90 IU/ml) (IV) and peripheral eosinophilia (greater than 0.3 x10^3/µl)

Exclusion criteria

1. Patients with parasitic infections
2. Current antibiotic treatment
3. Hypokalemia
4. Lithiasis
5. Autoimmune disease
6. Pregnancy
7. Immunodeficiency
8. Cancer
9. Immunosuppressive therapy

Interventions	Active intervention (n = 43): vitamin D (0.25 µg calcitriol) (1,25-(OH)2D_3) per day orally Control intervention (n = 43): organoleptically similar placebo daily
Outcomes	**Primary outcome** Skin prick tests Pharyngeal bacterial cultures Sputum cathelicidin LL-37 **Secondary outcomes** Serum levels of IgE, eosinophils, IL-5, IL-9, IL-10, IL-13, and IFNγ
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Low risk	Organoleptically similar placebo given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants contributed data to analysis of baseline outcomes. Rates of loss to follow-up were comparable between arms (2/43 in intervention arm vs 2/43 control arm).
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting. Trial protocol not obtained.

Ramos-Martínez 2018 *(Continued)*

Other bias	Low risk	Nil

Tachimoto 2016

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled, parallel-group trial Multicentre, 6 months long Run-in period: Not described, concomitant medication continued No drop-out, all participants completed follow-up Study analysed on ITT basis
Participants	Tokyo, Japan Predominantly Japanese N = 89; 50 male, 39 female; mean age 9.9 yrs **Inclusion criteria** 1. Children aged 6 to 15 years at entry 2. Diagnosed and treated for asthma by 3 collaborating paediatricians of this trial who were blinded to vitamin D or placebo treatment 3. Diagnosed according to Global Initiative for Asthma (GINA) **Exclusion criteria:** 1. Already taking a vitamin D supplement 2. History of hospital admission due to respiratory syncytial virus infection, respiratory treatment by intubation, or urinary tract stone or underlying disease related to calcium or bone 3. Underlying chronic disease other than asthma including fracture, mental retardation, or swallowing disturbance 4. Other difficulties judged by the paediatrician in charge
Interventions	Treatment (n = 54): vitamin D_3 800 IU/day orally for 2 months Control (n = 39): daily oral placebo for 2 months Mean serum 25(OH)D concentration, intervention arm: 71 nmol/L (baseline), 86 nmol/L (2 months), 77 nmol/L (6 months)
Outcomes	**Primary outcome** Changes in asthma control levels defined by GINA **Secondary outcomes** 1. Assessed changes in asthma control levels judged by the childhood ACT (C-ACT) for children aged 6 to 11 years or the ACT for children aged 12 to 15 years 2. Changes in Scoring Atopic Dermatitis (SCORAD) between the intervention groups 3. Subjective visual analog scales of pruritus and sleep loss for the last 3 days or nights, summed by the equation: (Extent/5 + Intensity*7/2 + Visual analog scale) 4. Improvement in pulmonary function: FVC % predicted, FEV1%, FEV1/FVC ratio (%), and PEFR % 5. Total IgE and allergen-specific IgE

Tachimoto 2016 *(Continued)*

	6. Serum levels of IL10, IL13, and IL17A
Notes	This study was supported by the Ministry of Education, Culture, Sports, Science and Technology in the Japan-Supported Program for the Strategic Research Foundation at Private Universities and the Jikei University School of Medicine as well by JSPH KAKENHI Grant Number: 23591553 KAKENHI. All the authors declare no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Person performing blinding had no clinical involvement in the trial. Randomisation code was kept by independent data management committee and was not revealed to staff or participants until the trial was complete (information from trial report and principal investigator).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Low risk	Nothing to suggest selective reporting: outcomes listed in Methods are reported in Results. However, the trial protocol was not accessed.
Other bias	Low risk	Nil. Information on risk of bias for this trial relates to unpublished data.

Thakur 2021

Study characteristics

Methods	Randomised, double-blind, placebo-controlled, parallel-group trial Single centre, 12 weeks long No run-in period; all participants had asthma treated as per GINA guidelines 4 did not complete: 1 withdrew consent, 3 lost to follow-up. Study analysed on ITT basis
Participants	Recruited from the All India Institute of Medical Sciences, a tertiary care hospital in Jodhpur, Rajasthan. Ethnic distribution not stated N = 60. 34 male, 26 female; mean age 9.0 yrs. **Inclusion criteria**

Thakur 2021 *(Continued)*

1. Aged 6 to 11 years
2. First time diagnosed asthma in clinic
3. Moderate persistent asthma (Step 3 GINA)
4. Willing to take prescribed medication and monthly follow-up for at least 3 months

Exclusion criteria

1. Rickets
2. Bronchopulmonary dysplasia
3. Coexisting primary parenchymal pulmonary disease (e.g. cystic fibrosis)
4. Congenital or acquired heart diseases
5. Renal or hepatic insufficiency
6. On antiepileptic drugs
7. Known case of vitamin-D deficiency or parathyroid disease
8. Received vitamin D or calcium supplements in past 3 months

Interventions	Active intervention (n = 30): vitamin D_3 2000 IU daily Control intervention (n = 30): oral placebo daily Mean serum 25(OH)D concentration, intervention arm: 39.5 nmol/L (baseline), 88.8 nmol/L (3 months)
Outcomes	**Primary outcome** Improvement in the C-ACT score from baseline to the end of the study period **Secondary outcomes** 1. Spirometry parameters: FEV1 and FeNO 2. Number of asthma exacerbations 3. Use of systemic steroids 4. Number of emergency visits 5. Number of hospitalizations 6. Vitamin D3 levels at 3 months 7. Adverse outcomes FeNO only included as median and IQR with significant skew, so could not be meta-analysed.
Notes	Baseline characteristics were similar except baseline cACT, for which the vitamin D group had a mean at baseline of 18, vs 15.5 in placebo (P < 0.001).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomisation
Allocation concealment (selection bias)	Low risk	Ensured concealment of allocation using serially numbered, opaque, sealed envelopes that contained a slip of paper with the allocation group.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled study
Blinding of outcome assessment (detection bias)	Low risk	Double-blind, placebo-controlled study

Thakur 2021 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants contributed data to analysis of baseline outcomes. Rates of loss to follow-up were comparable between arms (2/30 in intervention arm vs 2/30 control arm), for various reasons (3 did not attend, one withdrew consent).
Selective reporting (reporting bias)	Low risk	There was no evidence of selective reporting. All prespecified primary and secondary outcomes in the published protocol were reported in the final study.
Other bias	Unclear risk	Baseline cACT scores differ significantly between treatment and placebo groups. However, the current meta-analysis considers the change in cACT from baseline to end-study, minimising potential for bias to operate.

Urashima 2010

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled, parallel-group trial Multicentre, 24 weeks long Run-in period: not described, concomitant medication continued 96 were lost to follow-up, no reasons provided Study analysed on ITT basis
Participants	12 hospitals in Japan N = 430; 242 male, 188 female; mean age 10.2 yrs, range 6 to 15 yrs Number with diagnosed asthma: 110 **Inclusion criteria** 1. Schoolchildren aged 6 to 15 yrs 2. With or without underlying diseases **Exclusion criteria** 1. Had a history of stones in the urinary tract or diseases of calcium or bone metabolism. 2. Was already taking vitamin D3 or activated vitamin D as a treatment of an underlying disease. 3. Had a history of allergic reactions to ingredients in the tablets. 4. Had difficulties swallowing tablets. 5. Had been receiving immunosuppressive therapy including oral corticosteroids or chemotherapy within the past year. 6. Were considered incapable of taking part in the study by the paediatrician in charge.
Interventions	Treatment (n = 217): 3 tablets twice daily (total: 1200 IU vitamin D_3/day) Control (n = 213): 3 tablets twice daily (placebo tablets identical in appearance) Those with asthma on treatment n = 51 Those with asthma on placebo n = 59 Vitamin D status not assessed

Urashima 2010 *(Continued)*

Outcomes	**Primary outcome** Influenza A, diagnosed by influenza antigen testing **Secondary outcomes** 1. Influenza B diagnosed via nasopharyngeal swab. 2. Physician-diagnosed asthma attack that included wheezing improved by inhalation of a beta-stimulant in children who already had a diagnosis of asthma 3. Non-specific febrile infection in those who were not suspected to have influenza as well as other specific diseases 4. Gastroenteritis with 2 of 3 symptoms (nausea or vomiting, diarrhoea, or fever > 37°C) 5. Pneumonia diagnosed with chest X-ray 6. Admission to the hospital for any reason
Notes	Funded by the Jikei University School of Medicine. None of the authors had any conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Low risk	Allocation was concealed from staff and participants. Randomisation code was kept by independent data management committee and was not revealed to staff or participants until the trial was complete (information from trial report and principal investigator).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low withdrawals for asthma-only subgroup in data provided by author: 8/51 in vitamin D arm and 3/59 placebo
Selective reporting (reporting bias)	Low risk	Nothing to suggest selective reporting: outcomes listed in Methods are reported in Results. However, the trial protocol was not accessed.
Other bias	Low risk	Nil

Yadav 2014

Study characteristics

Methods	Randomised, double-blind, placebo-controlled, parallel-group trial Single-centre, 6 months long

Yadav 2014 *(Continued)*

	Run-in period: Not described, concomitant medication continued 18 were lost to follow-up, reasons not provided Study analysed by ITT
Participants	Rohtak, India Indian N = 100; 49 males, 51 females; mean age 9.6 yrs, range 5 to 13 yrs **Inclusion criteria** 1. Children aged between 3 and 14 yrs 2. With moderate to severe asthma as per Global Initiative for Asthma (GINA) guidelines, diagnosed by a physician **Exclusion criteria:** 1. Children on immunotherapy or anti-IgE 2. History of premature birth (< 36 weeks) 3. Home use of oxygen 4. Children with non-wheezy asthma and clinical features of vitamin D deficiency (bony deformities and hypocalcaemic symptoms)
Interventions	Treatment (n = 50): oral vitamin D_3 (cholecalciferol) 60,000 IU per month for 6 months. Control (n = 50): placebo powder in the form of glucose sachet Vitamin D status not assessed
Outcomes	**Primary outcome** Change in the level of asthma severity according to GINA guidelines **Secondary outcomes** 1. Number of exacerbations during treatment period 2. Change in the PEFR 3. Change in steroid dosage 4. Level of control 5. Emergency visits
Notes	No details on funding provided. Authors declare no conflict of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not reported.
Allocation concealment (selection bias)	Low risk	Allocation concealed in opaque envelopes.
Blinding of participants and personnel (performance bias)	Low risk	Double-blind, placebo-controlled trial

Yadav 2014 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled trial
Incomplete outcome data (attrition bias) All outcomes	High risk	10/50 children in control arm and 8/50 in active arm were lost to follow-up, but data for these 'lost' children are presented at the 6-month time point (end of study).
Selective reporting (reporting bias)	Low risk	Nothing to suggest selective reporting: outcomes listed in Methods are reported in Results. However, we did not have access to the trial protocol.
Other bias	High risk	Marked change in classification of asthma severity between 6-month time point and earlier time points suggests likelihood of misclassification bias operating at end-study time point.

25(OH)D, 25-hydroxyvitamin D; ACT, Asthma Control Test; ASUI, Asthma Symptom Utility Index; ATAQ, Asthma Therapy Assessment Questionnaire; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide concentration; FEV1, forced expiratory volume in one second; FVC: forced vital capacity; GEMA: Spanish Asthma Management Guidelines; GFR, glomerular filtration rate; ICS, inhaled corticosteroids; IgE, immunoglobulin E; ITT, intention to treat; IU, international unit (40 IU vitamin D = 1 microgram vitamin D); mPAQLQ, Mini-Paediatric Asthma Quality of Life Questionnaire; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; PC20, provocative concentration of methacholine at which FEV1 decreased by 20%; PEFR, peak expiratory flow rate; SCRG, St George's Respiratory Questionnaire; SIT, specific immunotherapy; URTI, upper respiratory tract infection.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alansari 2015	Not placebo controlled
Arshi 2014	Not placebo controlled
Babar 2017	Randomisation and blinding not stated, authors did not respond to efforts to clarify
Bantz 2015	Single-blind study
Baris 2014	Not placebo controlled
Bar Yoseph 2015	Duration < 12 weeks
Breitenbuecher 2012	Duration < 12 weeks
Darabi 2013	Not placebo controlled
De Groot 2015	Duration < 12 weeks
Dodamani 2019	Not blinded
Emami Ardestani 2020	Randomisation not stated, authors did not respond to efforts to clarify
EUCTR2016-004827-22-NL	Not yet published, authors confirmed via email that they did not focus on asthma.
Ganmaa 2020	Abstract focuses on tuberculosis, states will measure FEV1, FVC, and 'incident asthma' but final paper does not include asthma outcomes.

Study	Reason for exclusion
Goldring 2013	Primary prevention study
Huo 2019	Blinding not stated, authors did not respond to efforts to clarify
Lakatos 2000	Bone outcomes only
Litonjua 2014	Primary prevention study, protocol only
Liu 2018	Blinding not stated, abstract only, authors did not respond to efforts to clarify
Mansuroglu 2017	Randomisation and blinding not stated, authors did not respond to efforts to clarify
McDonald 2006	Bone outcomes only
Menon 2014	Not placebo controlled
Miraglia del Giudice 2016	Treatment arm received both L reuteri DSM 17938 (108 CFU) and vitamin D_3 (400 IU) whereas control arm received placebo only, so effect of vitamin D_3 could not be isolated.
Nanzer 2014	Duration < 12 weeks
Ozkars 2017	Blinding not stated, authors did not respond to efforts to clarify
Price 2015	Duration < 12 weeks
Rajanandh 2015	Not placebo controlled
Salas 2018	Primary prevention study
Schou 2003	Duration < 12 weeks
Swangtrakul 2022	Outcomes did not match our protocol: authors confirmed via email that the paediatric ACT score was only collected as categorical data (score > 20).
Thijs 2011	Duration < 12 weeks
Torres 2013	Duration < 12 weeks
Utz 1976	Duration < 12 weeks
Worth 1994	Bone outcomes only
Yemelyanov 2001	Bone outcomes only
Zhu 2022	No blinding stated in methodology. Sought to clarify with authors but unable to reach by email.

ACT: Asthma Control Test

Characteristics of ongoing studies *[ordered by study ID]*

Chiewchalermsri 2020

Study name	unknown

Chiewchalermsri 2020 *(Continued)*

Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	

Gold 2016

Study name	Lung VITAL
Methods	5-year U.S.-wide randomized, double-blind, placebo-controlled, 2 × 2 factorial trial
Participants	Subpopulation of 4314 randomized participants, adults age > 50
Interventions	Vitamin D_3 (2000 IU/day) and marine omega-3 fatty acids
Outcomes	Yearly follow-up questionnaires assess exacerbations of respiratory disease, asthma control and dyspnea
Starting date	2016
Contact information	diane.gold@channing.harvard.edu
Notes	

IRCT20190721044288N1

Study name	The effect of vitamin D on pulmonary function and serum level of interleukin 10 and antioxidant activity in patient with moderate to severe asthma
Methods	Double-blind RCT
Participants	Not stated in protocol
Interventions	Intervention group: vitamin D 2000 units daily for 3 months
Outcomes	Serum levels of interleukin 10 in the blood serum of patients
Starting date	2020
Contact information	G Mortazavi, gmortazavi@bums.ac.ir
Notes	Protocol now removed from WHO ICTRP Search Portal, reference number IRCT20190721044288N1

Jensen 2019

Study name	Vitamin D in the prevention of exacerbations of asthma in preschoolers (DIVA)
Methods	Phase III, randomised, triple-blind, placebo-controlled, parallel-group multicentre trial of vitamin D3 supplementation in children aged 1 to 5 years
Participants	n = 865
Interventions	Two oral boluses of 100,000 IU vitamin D_3 (3.5 months apart) with 400 IU vitamin D_3 daily; or (2) control: identical placebo boluses with daily placebo
Outcomes	Primary: number of exacerbations requiring oral corticosteroids per child Secondary: number of laboratory-confirmed viral upper respiratory tract infections, exacerbation duration and severity, parent functional status, healthcare use, treatment deintensification, cost and safety
Starting date	2019
Contact information	Francine M Ducharme; francine.m.ducharme@umontreal.ca
Notes	Email confirmation that trial is still ongoing

Lee 2018

Study name	Vitamin D for Sickle-cell Respiratory Complications
Methods	Phase 2 double-blind randomised clinical trial
Participants	n = 130 participants with sickle-cell disease
Interventions	Vitamin D_3 12,000 IU once a month for two years
Outcomes	Respiratory events (defined as respiratory infections, acute asthma exacerbation, and the acute chest syndrome)
Starting date	2011
Contact information	Gary Brittenham, Columbia University
Notes	Email confirmation: results not expected until late 2023.

NCT02424552

Study name	Effect of Vitamin D as add-on Therapy for Vitamin D Insufficient Patients With Severe Asthma
Methods	Double-blind, placebo-controlled RCT
Participants	Adults with physician-diagnosed severe asthma
Interventions	100,000 IU vitamin D_3 bolus, followed by 4000 IU daily, both orally

NCT02424552 *(Continued)*

Outcomes	Corticosteroid dose (primary), asthma exacerbations (secondary)
Starting date	June 2015
Contact information	Dr Stephanie Korn, Johannes Gutenberg University, Mainz, Germany
Notes	

NCT04117581

Study name	A Study to Investigate the Effect of Vitamin D3 Supplementation on Asthma Symptoms in Adults With Asthma (VITDAS) (VITDAS)
Methods	Double-blind RCT
Participants	n = 32
Interventions	Vitamin D_3 5000 IU daily for 12 weeks
Outcomes	Primary: FEV1 Secondary: ACT, 25(OH)D concentration, serum biomarkers
Starting date	2019
Contact information	S Mushtaq, University of Chester
Notes	

NCT05043116

Study name	High-dose Vitamin D Supplement for the Prevention of Acute Asthma-like Symptoms in Preschool Children (COPSACvitd)
Methods	Double-blind RCT
Participants	n = 320
Interventions	2000 IU vitamin D_3 daily dose (oral suspension) for 1 year
Outcomes	Primary: number of acute exacerbations Secondary: time to first exacerbation, duration of symptoms, need for medical treatment, daily symptom burden, step-down of preventative treatment, serum calcium and 25(OH)D, adverse events, gene expression, respiratory microbiome and immune profile, COVID-19 outcomes, daycare absence, missed days of work
Starting date	2021
Contact information	Hans Bisgaard, bisgaard@copsac.com
Notes	

Patella 2013

Study name	Vitamin D_3 associated to lactobacillus reuteri improves effects of allergen immunotherapy in asthmatic children
Methods	Double-blind, placebo-controlled RCT
Participants	Children with asthma and house dust mite allergy, age not stated
Interventions	Vitamin D, dose not stated
Outcomes	Asthma symptoms, FeNO, "medication scores"
Starting date	Not reported
Contact information	Prof Vincenzo Patella, Agropoli Hospital, Agropoli, Italy
Notes	Information from published abstract only

TCTR20210129003

Study name	Adjunctive vitamin A and vitamin D3 (Cholecalciferol) for enhancing efficacy of allergen-specific immunotherapy in allergic rhinitis, A randomized, double-blind, placebo-controlled trial
Methods	Randomized, double-blind, placebo-controlled trial
Participants	Not stated
Interventions	Vitamin A 25,000 IU/week and vitamin D_3 50,000 IU/week versus vitamin D_3 50,000 IU/week only versus placebo
Outcomes	Total nasal symptoms score, total nasal symptoms/medication score, dysfunctional T-reg
Starting date	2021
Contact information	Dr Mitthamsiri; watmitt@gmail.com
Notes	Since removed from Thai Clinical Trials Registry

UMIN000004160

Study name	A randomized, double blind, comparative study of vitamin D_3 versus placebo in small children with asthma to prevent asthma attack
Methods	Double-blind, placebo-controlled RCT
Participants	Children aged 2 to 5 years with physician-diagnosed asthma
Interventions	600 IU vitamin D_3 orally daily
Outcomes	Asthma exacerbations, C-ACT score

UMIN000004160 *(Continued)*

Starting date	October 2010
Contact information	Prof Mitsuyoshi Urashima, Jikei University School of Medicine, Tokyo, Japan
Notes	

ACT, Asthma Control Test; C-ACT, Childhood Asthma Control Test; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; IU, international unit (40 IU vitamin D = 1 microgram vitamin D); RCT, randomised controlled trial

DATA AND ANALYSES

Comparison 1. Vitamin D versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Proportion of participants with one or more exacerbations treated with systemic corticosteroids	14	1778	Odds Ratio (IV, Random, 95% CI)	1.04 [0.81, 1.34]
1.2 Rate of exacerbations treated with systemic corticosteroids	10	1599	Rate Ratio (IV, Random, 95% CI)	0.86 [0.62, 1.19]
1.3 Time to first exacerbation treated with systemic corticosteroids	3	850	Hazard Ratio (IV, Random, 95% CI)	0.82 [0.59, 1.15]
1.4 Proportion of participants with one or more exacerbations requiring systemic corticosteroids (stratified by baseline 25[OH]D)	8	1274	Odds Ratio (IV, Random, 95% CI)	0.99 [0.74, 1.33]
1.4.1 Baseline 25(OH)D < 25 nmol/L (10 ng/ml)	4	198	Odds Ratio (IV, Random, 95% CI)	0.78 [0.15, 3.96]
1.4.2 Baseline 25(OH)D 25 to 49.9 nmol/L (10 to 19.9 ng/ml)	8	515	Odds Ratio (IV, Random, 95% CI)	0.91 [0.57, 1.44]
1.4.3 Baseline 25(OH)D 50 to 74.9 nmol/L (20 to 29.9 ng/ml)	7	419	Odds Ratio (IV, Random, 95% CI)	1.16 [0.60, 2.25]
1.4.4 Baseline 25(OH)D ≥ 75nmol/L (30 ng/ml)	5	142	Odds Ratio (IV, Random, 95% CI)	0.98 [0.49, 1.95]
1.5 Proportion of participants with one or more exacerbations requiring systemic corticosteroids (stratified by daily dose equivalent)	11	1134	Odds Ratio (IV, Random, 95% CI)	1.13 [0.81, 1.58]
1.5.1 ≤ 2000	10	942	Odds Ratio (IV, Random, 95% CI)	1.13 [0.75, 1.69]
1.5.2 > 2000	1	192	Odds Ratio (IV, Random, 95% CI)	1.15 [0.63, 2.07]

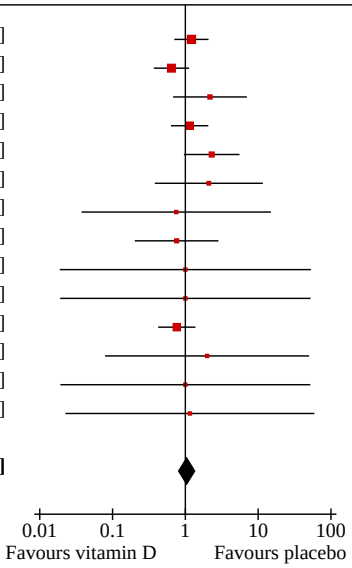
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6 Rate ratio, exacerbations requiring systemic corticosteroids (stratified by vitamin D type)	10	1599	Rate Ratio (IV, Random, 95% CI)	0.86 [0.62, 1.19]
1.6.1 Vitamin D3 (cholecalciferol) only	9	1487	Rate Ratio (IV, Random, 95% CI)	0.93 [0.68, 1.28]
1.6.2 Calcidiol only	1	112	Rate Ratio (IV, Random, 95% CI)	0.43 [0.22, 0.82]
1.7 Proportion of participants with one or more exacerbations treated with systemic corticosteroids (stratified by dosing regimen)	13	1712	Odds Ratio (IV, Random, 95% CI)	1.16 [0.92, 1.47]
1.7.1 Daily dosing	10	1201	Odds Ratio (IV, Random, 95% CI)	1.23 [0.91, 1.66]
1.7.2 Monthly or greater than monthly bolus dosing	3	511	Odds Ratio (IV, Random, 95% CI)	1.09 [0.68, 1.77]
1.8 Proportion of participants with one or more exacerbations requiring systemic corticosteroids (stratified by age)	14	1778	Odds Ratio (IV, Random, 95% CI)	1.04 [0.81, 1.34]
1.8.1 age < 5	2	69	Odds Ratio (IV, Random, 95% CI)	2.15 [0.82, 5.64]
1.8.2 age 5 to 16	9	837	Odds Ratio (IV, Random, 95% CI)	1.28 [0.83, 1.97]
1.8.3 Adults	3	872	Odds Ratio (IV, Random, 95% CI)	0.85 [0.58, 1.24]
1.9 Proportion of participants with one or more exacerbations treated with systemic corticosteroids (excluding trials at unclear risk of bias)	9	1365	Odds Ratio (IV, Random, 95% CI)	0.96 [0.71, 1.30]
1.10 Proportion of participants with one or more exacerbation as defined in primary trials (excluding trials at high risk of bias)	11	1439	Odds Ratio (IV, Random, 95% CI)	0.90 [0.62, 1.30]
1.11 Proportion of participants with one or more exacerbations treated with systemic corticosteroids (risk difference)	14	1778	Risk Difference (IV, Random, 95% CI)	0.00 [-0.02, 0.03]
1.12 Proportion of participants with one or more exacerbations requiring emergency department visit or hospitalisation, or both	9	1070	Odds Ratio (IV, Random, 95% CI)	0.56 [0.26, 1.21]
1.13 End-study C-ACT/ACT score	7	1271	Mean Difference (IV, Random, 95% CI)	0.23 [-0.26, 0.73]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.14 End-study FEV1, % predicted	11	1286	Mean Difference (IV, Random, 95% CI)	0.20 [-1.24, 1.63]
1.15 Proportion of participants with one or more serious adverse events due to any cause	12	1556	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.56, 1.41]
1.16 Proportion of participants with fatal asthma exacerbation	16	1976	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.01]
1.17 Proportion of participants with one or more exacerbation as defined in primary trials	12	1539	Odds Ratio (IV, Random, 95% CI)	0.77 [0.51, 1.17]
1.18 % eosinophils, lower airway	3	525	Mean Difference (IV, Random, 95% CI)	-0.38 [-1.92, 1.15]
1.19 End-study log 10 total IgE, IU/ml	3	366	Mean Difference (IV, Random, 95% CI)	0.07 [-0.13, 0.26]
1.20 End-study FVC, % predicted	4	476	Mean Difference (IV, Random, 95% CI)	1.84 [-3.60, 7.29]
1.21 End-study PEFR (L/min)	3	476	Mean Difference (IV, Random, 95% CI)	4.84 [-8.95, 18.62]
1.22 Withdrawals from trial	20	2225	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.77, 1.43]
1.23 Withdrawals from trial (excluding trials at high risk of bias)	17	2003	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.80, 1.53]

Analysis 1.1. Comparison 1: Vitamin D versus placebo, Outcome 1: Proportion of participants with one or more exacerbations treated with systemic corticosteroids

Study or Subgroup	log[OR]	SE	Vitamin D Total	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
Camargo 2021	0.192986	0.275259	106	108	21.7%	1.21 [0.71 , 2.08]
Castro 2014	-0.439951	0.284503	201	207	20.4%	0.64 [0.37 , 1.12]
Ducharme 2019	0.778305	0.594952	23	24	4.7%	2.18 [0.68 , 6.99]
Forno 2020	0.135802	0.301032	96	96	18.2%	1.15 [0.63 , 2.07]
Jat 2020	0.833815	0.449032	125	125	8.2%	2.30 [0.95 , 5.55]
Jensen 2016	0.741937	0.871507	11	11	2.2%	2.10 [0.38 , 11.59]
Jerzynska 2016	-0.287682	1.527525	5	3	0.7%	0.75 [0.04 , 14.97]
Kerley 2016	-0.275848	0.674724	19	25	3.6%	0.76 [0.20 , 2.85]
Majak 2009	0	2.026847	18	18	0.4%	1.00 [0.02 , 53.12]
Majak 2011	0	2.020305	24	24	0.4%	1.00 [0.02 , 52.44]
Martineau 2015	-0.27016	0.300941	125	125	18.2%	0.76 [0.42 , 1.38]
Tachimoto 2016	0.688463	1.647279	54	35	0.6%	1.99 [0.08 , 50.25]
Thakur 2021	0	2.016327	30	30	0.4%	1.00 [0.02 , 52.04]
Urashima 2010	0.144395	2.009036	51	59	0.4%	1.16 [0.02 , 59.27]
Total (95% CI)			**888**	**890**	**100.0%**	**1.04 [0.81 , 1.34]**

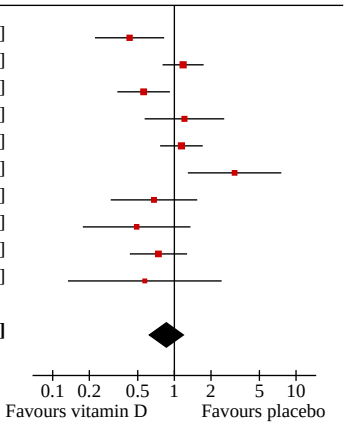
Heterogeneity: Tau² = 0.00; Chi² = 10.06, df = 13 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.32 (P = 0.75)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Vitamin D versus placebo, Outcome 2: Rate of exacerbations treated with systemic corticosteroids

Study or Subgroup	log[Rate Ratio]	SE	Vitamin D Total	Placebo Total	Weight	Rate Ratio IV, Random, 95% CI
Andújar-Espinosa 2021	-0.847231	0.333939	56	56	10.5%	0.43 [0.22 , 0.82]
Camargo 2021	0.165514	0.198225	106	108	14.6%	1.18 [0.80 , 1.74]
Castro 2014	-0.5816	0.2537	201	207	12.8%	0.56 [0.34 , 0.92]
Ducharme 2019	0.19062	0.384197	23	24	9.2%	1.21 [0.57 , 2.57]
Forno 2020	0.133569	0.205607	96	96	14.3%	1.14 [0.76 , 1.71]
Jat 2020	1.139434	0.451325	125	125	7.7%	3.12 [1.29 , 7.57]
Jensen 2016	-0.3857	0.4175	11	11	8.4%	0.68 [0.30 , 1.54]
Kerley 2016	-0.71335	0.519622	19	25	6.5%	0.49 [0.18 , 1.36]
Martineau 2015	-0.301105	0.276277	125	125	12.1%	0.74 [0.43 , 1.27]
Thakur 2021	-0.559666	0.741841	30	30	3.9%	0.57 [0.13 , 2.45]
Total (95% CI)			**792**	**807**	**100.0%**	**0.86 [0.62 , 1.19]**

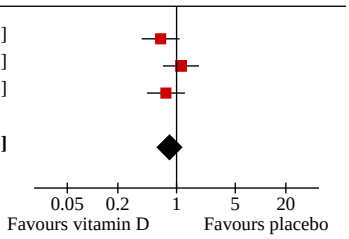
Heterogeneity: Tau² = 0.15; Chi² = 22.57, df = 9 (P = 0.007); I² = 60%
Test for overall effect: Z = 0.92 (P = 0.36)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Vitamin D versus placebo, Outcome 3: Time to first exacerbation treated with systemic corticosteroids

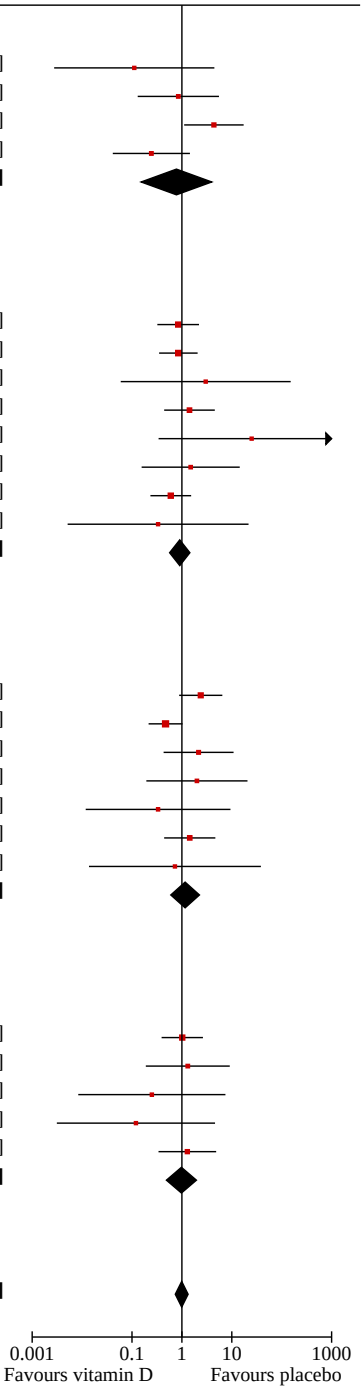
Study or Subgroup	log[Hazard Ratio]	SE	Vitamin D Total	Placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
Castro 2014	-0.437	0.2654	201	207	32.4%	0.65 [0.38 , 1.09]
Forno 2020	0.122218	0.251599	96	96	35.2%	1.13 [0.69 , 1.85]
Martineau 2015	-0.2925	0.265	125	125	32.4%	0.75 [0.44 , 1.25]
Total (95% CI)			**422**	**428**	**100.0%**	**0.82 [0.59 , 1.15]**

Heterogeneity: Tau² = 0.02; Chi² = 2.56, df = 2 (P = 0.28); I² = 22%
Test for overall effect: Z = 1.14 (P = 0.26)
Test for subgroup differences: Not applicable



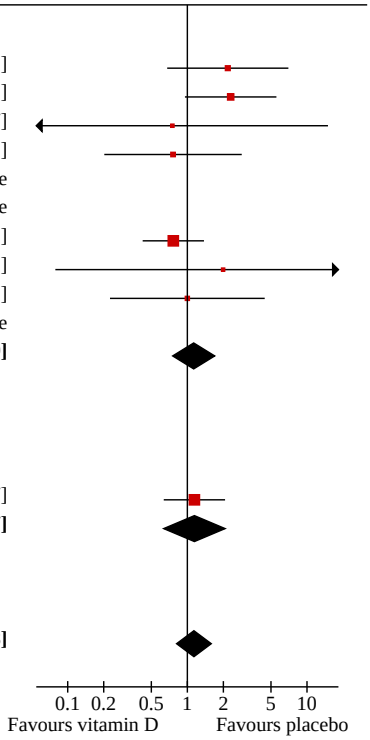
Analysis 1.4. Comparison 1: Vitamin D versus placebo, Outcome 4: Proportion of participants with one or more exacerbations requiring systemic corticosteroids (stratified by baseline 25[OH]D)

Study or Subgroup	log[OR]	SE	Vitamin D Total	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
1.4.1 Baseline 25(OH)D < 25 nmol/L (10 ng/ml)						
Camargo 2021	-2.197225	1.885618	2	4	0.6%	0.11 [0.00 , 4.48]
Castro 2014	-0.164303	0.956296	24	31	2.4%	0.85 [0.13 , 5.53]
Jat 2020	1.476678	0.699993	46	57	4.5%	4.38 [1.11 , 17.26]
Martineau 2015	-1.408767	0.907878	17	17	2.7%	0.24 [0.04 , 1.45]
Subtotal (95% CI)			**89**	**109**	**10.3%**	**0.78 [0.15 , 3.96]**
Heterogeneity: Tau² = 1.66; Chi² = 8.19, df = 3 (P = 0.04); I² = 63%						
Test for overall effect: Z = 0.30 (P = 0.76)						
1.4.2 Baseline 25(OH)D 25 to 49.9 nmol/L (10 to 19.9 ng/ml)						
Camargo 2021	-0.17185	0.490032	32	35	9.0%	0.84 [0.32 , 2.20]
Castro 2014	-0.162992	0.453169	77	87	10.4%	0.85 [0.35 , 2.07]
Ducharme 2019	1.098612	2	1	2	0.6%	3.00 [0.06 , 151.19]
Jat 2020	0.350458	0.595783	79	68	6.2%	1.42 [0.44 , 4.56]
Jensen 2016	3.218876	2.19089	2	2	0.5%	25.00 [0.34 , 1831.59]
Kerley 2016	0.405465	1.154701	5	8	1.7%	1.50 [0.16 , 14.42]
Martineau 2015	-0.51245	0.479226	53	55	9.4%	0.60 [0.23 , 1.53]
Tachimoto 2016	-1.098612	2.129163	7	2	0.5%	0.33 [0.01 , 21.64]
Subtotal (95% CI)			**256**	**259**	**38.2%**	**0.91 [0.57 , 1.44]**
Heterogeneity: Tau² = 0.00; Chi² = 4.42, df = 7 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.42 (P = 0.68)						
1.4.3 Baseline 25(OH)D 50 to 74.9 nmol/L (20 to 29.9 ng/ml)						
Camargo 2021	0.869771	0.508105	41	30	8.4%	2.39 [0.88 , 6.46]
Castro 2014	-0.754056	0.398986	100	89	13.2%	0.47 [0.22 , 1.03]
Ducharme 2019	0.770108	0.823273	14	11	3.3%	2.16 [0.43 , 10.84]
Jensen 2016	0.693147	1.190238	6	6	1.6%	2.00 [0.19 , 20.61]
Kerley 2016	-1.098612	1.703514	8	9	0.8%	0.33 [0.01 , 9.40]
Martineau 2015	0.362905	0.602431	33	29	6.0%	1.44 [0.44 , 4.68]
Tachimoto 2016	-0.320908	2.023183	25	18	0.6%	0.73 [0.01 , 38.26]
Subtotal (95% CI)			**227**	**192**	**33.9%**	**1.16 [0.60 , 2.25]**
Heterogeneity: Tau² = 0.21; Chi² = 8.48, df = 6 (P = 0.21); I² = 29%						
Test for overall effect: Z = 0.44 (P = 0.66)						
1.4.4 Baseline 25(OH)D ≥ 75nmol/L (30 ng/ml)						
Camargo 2021	0.017153	0.486513	31	38	9.1%	1.02 [0.39 , 2.64]
Ducharme 2019	0.271934	0.988024	7	11	2.3%	1.31 [0.19 , 9.10]
Jensen 2016	-1.386294	1.732051	3	3	0.8%	0.25 [0.01 , 7.45]
Kerley 2016	-2.120264	1.861899	3	2	0.7%	0.12 [0.00 , 4.61]
Martineau 2015	0.251314	0.678467	20	24	4.8%	1.29 [0.34 , 4.86]
Subtotal (95% CI)			**64**	**78**	**17.6%**	**0.98 [0.49 , 1.95]**
Heterogeneity: Tau² = 0.00; Chi² = 2.15, df = 4 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.06 (P = 0.95)						
Total (95% CI)			**636**	**638**	**100.0%**	**0.99 [0.74 , 1.33]**
Heterogeneity: Tau² = 0.01; Chi² = 23.50, df = 23 (P = 0.43); I² = 2%						
Test for overall effect: Z = 0.06 (P = 0.95)						
Test for subgroup differences: Chi² = 0.44, df = 3 (P = 0.93), I² = 0%						

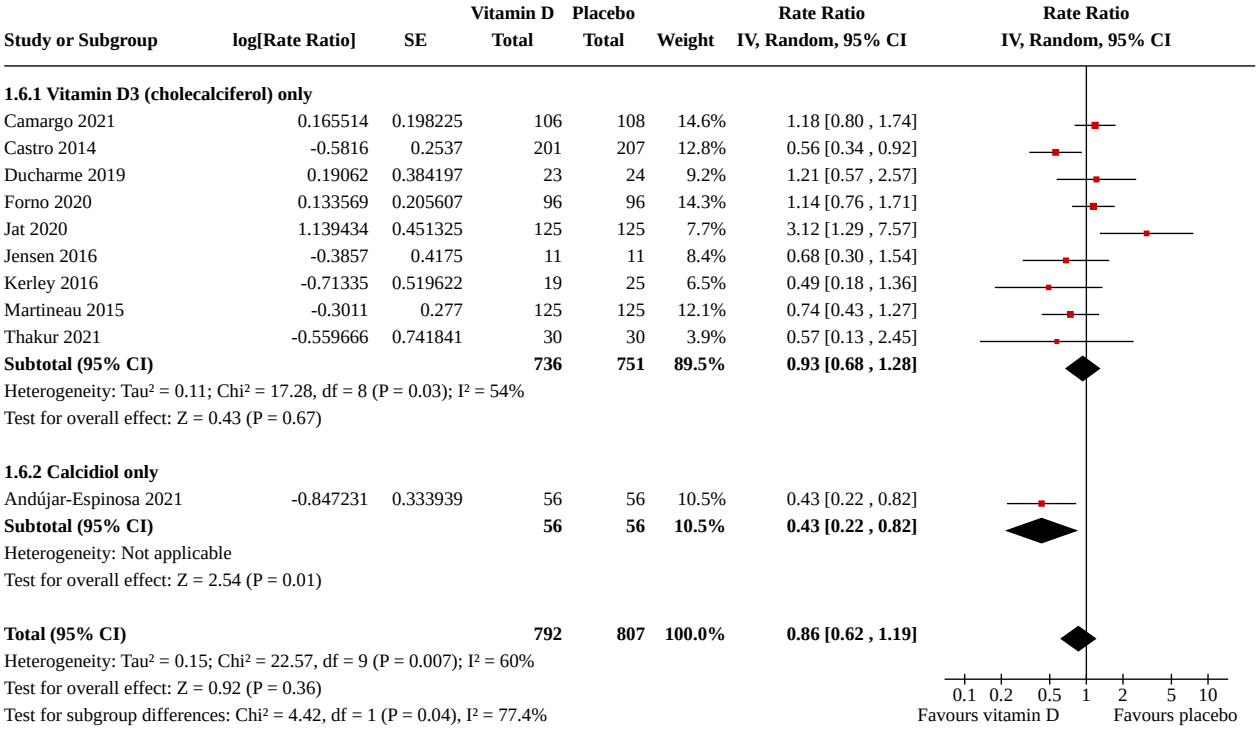


Analysis 1.5. Comparison 1: Vitamin D versus placebo, Outcome 5: Proportion of participants with one or more exacerbations requiring systemic corticosteroids (stratified by daily dose equivalent)

Study or Subgroup	log[OR]	SE	Vitamin D Total	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
1.5.1 ≤ 2000						
Ducharme 2019	0.778305	0.594952	23	24	8.2%	2.18 [0.68 , 6.99]
Jat 2020	0.833815	0.449032	125	125	14.3%	2.30 [0.95 , 5.55]
Jerzynska 2016	-0.287682	1.527525	5	3	1.2%	0.75 [0.04 , 14.97]
Kerley 2016	-0.275848	0.674724	19	25	6.4%	0.76 [0.20 , 2.85]
Majak 2009	0	0	18	18		Not estimable
Majak 2011	0	0	24	24		Not estimable
Martineau 2015	-0.27016	0.300941	125	125	31.9%	0.76 [0.42 , 1.38]
Tachimoto 2016	0.688463	1.647279	54	35	1.1%	1.99 [0.08 , 50.25]
Thakur 2021	0	0.759555	30	30	5.0%	1.00 [0.23 , 4.43]
Urashima 2010	0	0	51	59		Not estimable
Subtotal (95% CI)			**474**	**468**	**68.1%**	**1.13 [0.75 , 1.69]**
Heterogeneity: Tau² = 0.00; Chi² = 5.99, df = 6 (P = 0.42); I² = 0%						
Test for overall effect: Z = 0.59 (P = 0.55)						
1.5.2 > 2000						
Forno 2020	0.135802	0.301032	96	96	31.9%	1.15 [0.63 , 2.07]
Subtotal (95% CI)			**96**	**96**	**31.9%**	**1.15 [0.63 , 2.07]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						
Total (95% CI)			**570**	**564**	**100.0%**	**1.13 [0.81 , 1.58]**
Heterogeneity: Tau² = 0.00; Chi² = 5.99, df = 7 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.74 (P = 0.46)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%						

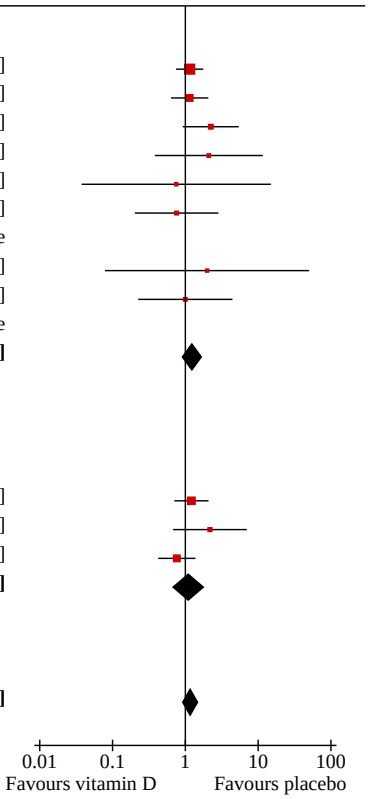


Analysis 1.6. Comparison 1: Vitamin D versus placebo, Outcome 6: Rate ratio, exacerbations requiring systemic corticosteroids (stratified by vitamin D type)



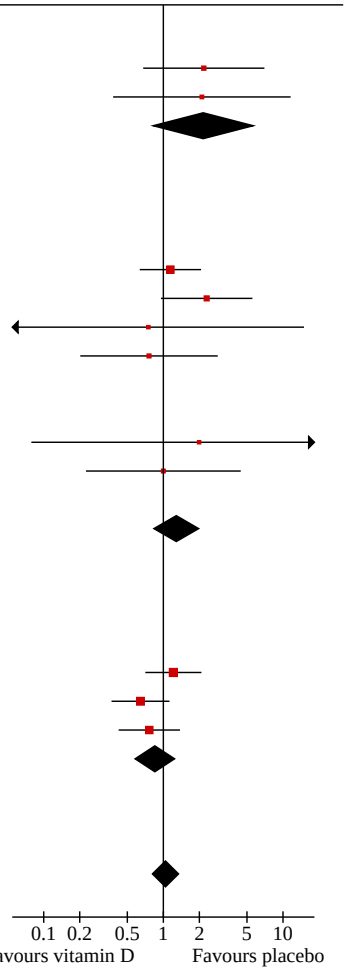
Analysis 1.7. Comparison 1: Vitamin D versus placebo, Outcome 7: Proportion of participants with one or more exacerbations treated with systemic corticosteroids (stratified by dosing regimen)

Study or Subgroup	log[OR]	SE	Vitamin D Total	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
1.7.1 Daily dosing						
Castro 2014	0.136815	0.21851	201	207	29.9%	1.15 [0.75 , 1.76]
Forno 2020	0.135802	0.301032	96	96	15.8%	1.15 [0.63 , 2.07]
Jat 2020	0.805065	0.452051	112	108	7.0%	2.24 [0.92 , 5.43]
Jensen 2016	0.741937	0.871507	11	11	1.9%	2.10 [0.38 , 11.59]
Jerzynska 2016	-0.287682	1.527525	5	3	0.6%	0.75 [0.04 , 14.97]
Kerley 2016	-0.275848	0.674724	19	25	3.1%	0.76 [0.20 , 2.85]
Majak 2011	0	0	24	24		Not estimable
Tachimoto 2016	0.688463	1.647279	54	35	0.5%	1.99 [0.08 , 50.25]
Thakur 2021	0	0.759555	30	30	2.5%	1.00 [0.23 , 4.43]
Urashima 2010	0	0	51	59		Not estimable
Subtotal (95% CI)			**603**	**598**	**61.3%**	**1.23 [0.91 , 1.66]**
Heterogeneity: Tau² = 0.00; Chi² = 3.06, df = 7 (P = 0.88); I² = 0%						
Test for overall effect: Z = 1.34 (P = 0.18)						
1.7.2 Monthly or greater than monthly bolus dosing						
Camargo 2021	0.192986	0.275259	106	108	18.9%	1.21 [0.71 , 2.08]
Ducharme 2019	0.778305	0.594952	23	24	4.0%	2.18 [0.68 , 6.99]
Martineau 2015	-0.27016	0.300941	125	125	15.8%	0.76 [0.42 , 1.38]
Subtotal (95% CI)			**254**	**257**	**38.7%**	**1.09 [0.68 , 1.77]**
Heterogeneity: Tau² = 0.06; Chi² = 2.89, df = 2 (P = 0.24); I² = 31%						
Test for overall effect: Z = 0.37 (P = 0.71)						
Total (95% CI)			**857**	**855**	**100.0%**	**1.16 [0.92 , 1.47]**
Heterogeneity: Tau² = 0.00; Chi² = 6.28, df = 10 (P = 0.79); I² = 0%						
Test for overall effect: Z = 1.26 (P = 0.21)						
Test for subgroup differences: Chi² = 0.16, df = 1 (P = 0.69), I² = 0%						



Analysis 1.8. Comparison 1: Vitamin D versus placebo, Outcome 8: Proportion of participants with one or more exacerbations requiring systemic corticosteroids (stratified by age)

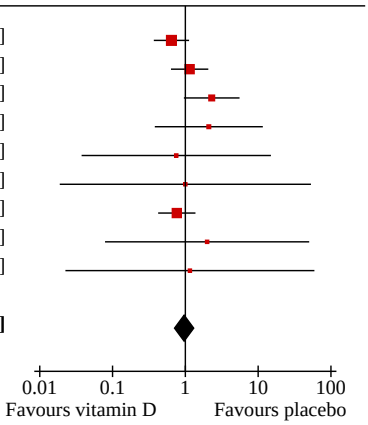
Study or Subgroup	log[OR]	SE	Vitamin D Total	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
1.8.1 age < 5						
Ducharme 2019	0.778305	0.594952	23	24	4.6%	2.18 [0.68 , 6.99]
Jensen 2016	0.741937	0.871507	11	11	2.2%	2.10 [0.38 , 11.59]
Subtotal (95% CI)			**34**	**35**	**6.8%**	**2.15 [0.82 , 5.64]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%						
Test for overall effect: Z = 1.56 (P = 0.12)						
1.8.2 age 5 to 16						
Forno 2020	0.135802	0.301032	96	96	17.9%	1.15 [0.63 , 2.07]
Jat 2020	0.833815	0.449032	125	125	8.1%	2.30 [0.95 , 5.55]
Jerzynska 2016	-0.287682	1.527525	5	3	0.7%	0.75 [0.04 , 14.97]
Kerley 2016	-0.275848	0.674724	19	25	3.6%	0.76 [0.20 , 2.85]
Majak 2009	0	0	18	18		Not estimable
Majak 2011	0	0	24	24		Not estimable
Tachimoto 2016	0.688463	1.647279	54	35	0.6%	1.99 [0.08 , 50.25]
Thakur 2021	0	0.759555	30	30	2.8%	1.00 [0.23 , 4.43]
Urashima 2010	0	0	51	59		Not estimable
Subtotal (95% CI)			**422**	**415**	**33.8%**	**1.28 [0.83 , 1.97]**
Heterogeneity: Tau² = 0.00; Chi² = 2.74, df = 5 (P = 0.74); I² = 0%						
Test for overall effect: Z = 1.13 (P = 0.26)						
1.8.3 Adults						
Camargo 2021	0.192986	0.275259	106	108	21.4%	1.21 [0.71 , 2.08]
Castro 2014	-0.439951	0.284503	201	207	20.1%	0.64 [0.37 , 1.12]
Martineau 2015	-0.27016	0.300941	125	125	17.9%	0.76 [0.42 , 1.38]
Subtotal (95% CI)			**432**	**440**	**59.4%**	**0.85 [0.58 , 1.24]**
Heterogeneity: Tau² = 0.03; Chi² = 2.75, df = 2 (P = 0.25); I² = 27%						
Test for overall effect: Z = 0.84 (P = 0.40)						
Total (95% CI)			**888**	**890**	**100.0%**	**1.04 [0.81 , 1.34]**
Heterogeneity: Tau² = 0.00; Chi² = 10.06, df = 10 (P = 0.44); I² = 1%						
Test for overall effect: Z = 0.32 (P = 0.75)						
Test for subgroup differences: Chi² = 4.13, df = 2 (P = 0.13), I² = 51.5%						



Analysis 1.9. Comparison 1: Vitamin D versus placebo, Outcome 9: Proportion of participants with one or more exacerbations treated with systemic corticosteroids (excluding trials at unclear risk of bias)

Study or Subgroup	log[OR]	SE	Vitamin D Total	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
Castro 2014	-0.439951	0.284503	201	207	29.4%	0.64 [0.37 , 1.12]
Forno 2020	0.135802	0.301032	96	96	26.3%	1.15 [0.63 , 2.07]
Jat 2020	0.833815	0.449032	125	125	11.8%	2.30 [0.95 , 5.55]
Jensen 2016	0.741937	0.871507	11	11	3.1%	2.10 [0.38 , 11.59]
Jerzynska 2016	-0.287682	1.527525	5	3	1.0%	0.75 [0.04 , 14.97]
Majak 2009	0	2.026847	18	18	0.6%	1.00 [0.02 , 53.12]
Martineau 2015	-0.27016	0.300941	125	125	26.3%	0.76 [0.42 , 1.38]
Tachimoto 2016	0.688463	1.647279	54	35	0.9%	1.99 [0.08 , 50.25]
Urashima 2010	0.144395	2.009036	51	59	0.6%	1.16 [0.02 , 59.27]
Total (95% CI)			**686**	**679**	**100.0%**	**0.96 [0.71 , 1.30]**

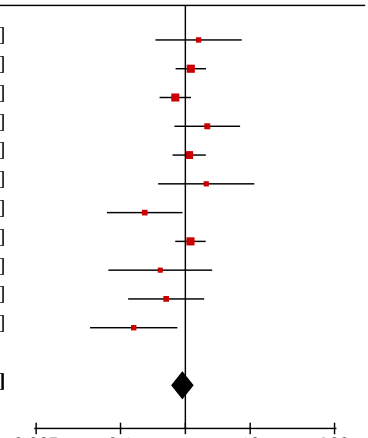
Heterogeneity: Tau² = 0.00; Chi² = 7.72, df = 8 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.25 (P = 0.80)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Vitamin D versus placebo, Outcome 10: Proportion of participants with one or more exacerbation as defined in primary trials (excluding trials at high risk of bias)

Study or Subgroup	log[OR]	SE	Vitamin D Total	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
Aglipay 2019	0.470004	0.781482	15	12	4.7%	1.60 [0.35 , 7.40]
Camargo 2021	0.192986	0.275259	106	108	16.5%	1.21 [0.71 , 2.08]
Castro 2014	-0.3567	0.2855	201	207	16.1%	0.70 [0.40 , 1.22]
Ducharme 2019	0.778305	0.594952	23	24	7.2%	2.18 [0.68 , 6.99]
Forno 2020	0.135802	0.301032	96	96	15.5%	1.15 [0.63 , 2.07]
Jensen 2016	0.7419	0.8715	11	11	3.9%	2.10 [0.38 , 11.59]
Majak 2011	-1.442384	0.683983	24	24	5.8%	0.24 [0.06 , 0.90]
Martineau 2015	0.182322	0.275357	108	114	16.5%	1.20 [0.70 , 2.06]
Tachimoto 2016	-0.891	0.9401	54	35	3.4%	0.41 [0.06 , 2.59]
Thakur 2021	-0.682218	0.689055	30	30	5.7%	0.51 [0.13 , 1.95]
Urashima 2010	-1.8334	0.7906	51	59	4.6%	0.16 [0.03 , 0.75]
Total (95% CI)			**719**	**720**	**100.0%**	**0.90 [0.62 , 1.30]**

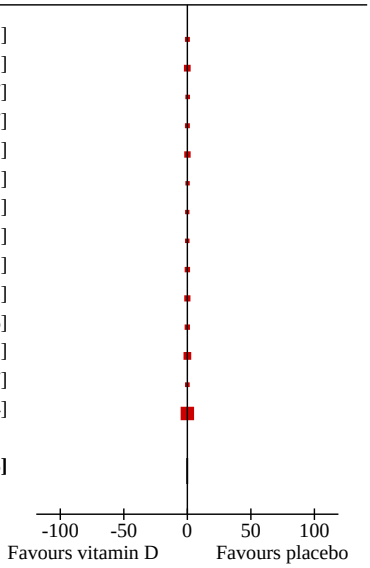
Heterogeneity: Tau² = 0.14; Chi² = 17.10, df = 10 (P = 0.07); I² = 42%
Test for overall effect: Z = 0.56 (P = 0.57)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Vitamin D versus placebo, Outcome 11: Proportion of participants with one or more exacerbations treated with systemic corticosteroids (risk difference)

Study or Subgroup	RD	SE	Vitamin D Total	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
Camargo 2021	0.047694	0.067915	106	108	2.8%	0.05 [-0.09 , 0.18]
Castro 2014	-0.05451	0.034888	201	207	10.5%	-0.05 [-0.12 , 0.01]
Ducharme 2019	0.192029	0.14312	23	24	0.6%	0.19 [-0.09 , 0.47]
Forno 2020	0.03125	0.069219	96	96	2.7%	0.03 [-0.10 , 0.17]
Jat 2020	0.072	0.037673	125	125	9.0%	0.07 [-0.00 , 0.15]
Jensen 2016	0.181818	0.208749	11	11	0.3%	0.18 [-0.23 , 0.59]
Jerzynska 2016	-0.066667	0.349391	5	3	0.1%	-0.07 [-0.75 , 0.62]
Kerley 2016	-0.056842	0.137512	19	25	0.7%	-0.06 [-0.33 , 0.21]
Majak 2009	0	0.051934	18	18	4.7%	0.00 [-0.10 , 0.10]
Majak 2011	0	0.039598	24	24	8.1%	0.00 [-0.08 , 0.08]
Martineau 2015	-0.048	0.053307	125	125	4.5%	-0.05 [-0.15 , 0.06]
Tachimoto 2016	0.018519	0.029373	54	35	14.8%	0.02 [-0.04 , 0.08]
Thakur 2021	0	0.087771	30	30	1.7%	0.00 [-0.17 , 0.17]
Urashima 2010	0	0.017913	51	59	39.7%	0.00 [-0.04 , 0.04]
Total (95% CI)			**888**	**890**	**100.0%**	**0.00 [-0.02 , 0.03]**

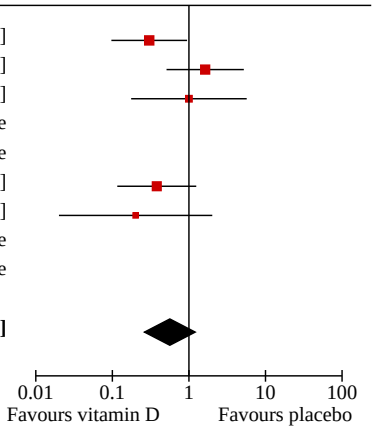
Heterogeneity: Tau² = 0.00; Chi² = 10.59, df = 13 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.42 (P = 0.67)
Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1: Vitamin D versus placebo, Outcome 12: Proportion of participants with one or more exacerbations requiring emergency department visit or hospitalisation, or both

Study or Subgroup	log[OR]	SE	Vitamin D Total	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
Castro 2014	-1.194	0.5806	201	207	26.0%	0.30 [0.10 , 0.95]
Ducharme 2019	0.48858	0.592849	23	24	25.4%	1.63 [0.51 , 5.21]
Jensen 2016	0	0.8864	11	11	14.7%	1.00 [0.18 , 5.68]
Majak 2009 (1)	0	0	18	18		Not estimable
Majak 2011 (1)	0	0	24	24		Not estimable
Martineau 2015	-0.9671	0.6058	125	125	24.7%	0.38 [0.12 , 1.25]
Tachimoto 2016	-1.6032	1.1762	54	35	9.3%	0.20 [0.02 , 2.02]
Thakur 2021	0	0	30	30		Not estimable
Urashima 2010 (1)	0	0	51	59		Not estimable
Total (95% CI)			**537**	**533**	**100.0%**	**0.56 [0.26 , 1.21]**

Heterogeneity: Tau² = 0.24; Chi² = 5.96, df = 4 (P = 0.20); I² = 33%
Test for overall effect: Z = 1.48 (P = 0.14)
Test for subgroup differences: Not applicable



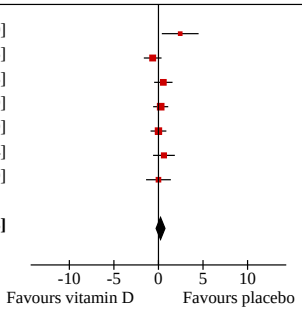
Footnotes

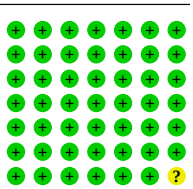
(1) No events in either arm

Analysis 1.13. Comparison 1: Vitamin D versus placebo, Outcome 13: End-study C-ACT/ACT score

Study or Subgroup	MD	SE	Vitamin D Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Andújar-Espinosa 2021	2.4408	1.05244	53	53	5.2%	2.44 [0.38 , 4.50]
Castro 2014	-0.648	0.5069	201	207	16.7%	-0.65 [-1.64 , 0.35]
Forno 2020	0.54623	0.526026	86	90	15.8%	0.55 [-0.48 , 1.58]
Jat 2020	0.25	0.4311	108	112	20.4%	0.25 [-0.59 , 1.09]
Martineau 2015	0	0.4518	108	111	19.3%	0.00 [-0.89 , 0.89]
Tachimoto 2016	0.6154	0.623	52	34	12.4%	0.62 [-0.61 , 1.84]
Thakur 2021	0	0.709376	28	28	10.2%	0.00 [-1.39 , 1.39]
Total (95% CI)			**636**	**635**	**100.0%**	**0.23 [-0.26 , 0.73]**

Heterogeneity: Tau² = 0.13; Chi² = 8.50, df = 6 (P = 0.20); I² = 29%
Test for overall effect: Z = 0.92 (P = 0.36)
Test for subgroup differences: Not applicable



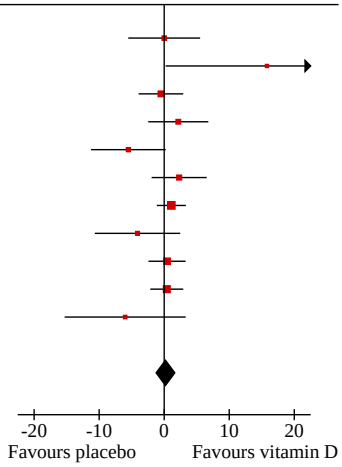


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.14. Comparison 1: Vitamin D versus placebo, Outcome 14: End-study FEV1, % predicted

Study or Subgroup	MD	SE	Vitamin D Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Andújar-Espinosa 2021	0	2.82	53	53	5.7%	0.00 [-5.53 , 5.53]
Camargo 2021	15.8	7.949843	7	13	0.8%	15.80 [0.22 , 31.38]
Castro 2014	-0.5	1.747424	178	181	12.1%	-0.50 [-3.92 , 2.92]
Forno 2020	2.169255	2.355761	86	90	7.7%	2.17 [-2.45 , 6.79]
Jat 2020	-5.5	2.929203	90	84	5.4%	-5.50 [-11.24 , 0.24]
Jerzynska 2016	2.3	2.159012	5	3	8.9%	2.30 [-1.93 , 6.53]
Majak 2009	1.1	1.1402	17	17	20.0%	1.10 [-1.13 , 3.33]
Majak 2011	-4.1	3.3517	24	24	4.2%	-4.10 [-10.67 , 2.47]
Martineau 2015	0.44	1.4592	108	111	15.3%	0.44 [-2.42 , 3.30]
Tachimoto 2016	0.4	1.2921	52	34	17.6%	0.40 [-2.13 , 2.93]
Thakur 2021	-6	4.749887	28	28	2.2%	-6.00 [-15.31 , 3.31]
Total (95% CI)			**648**	**638**	**100.0%**	**0.20 [-1.24 , 1.63]**

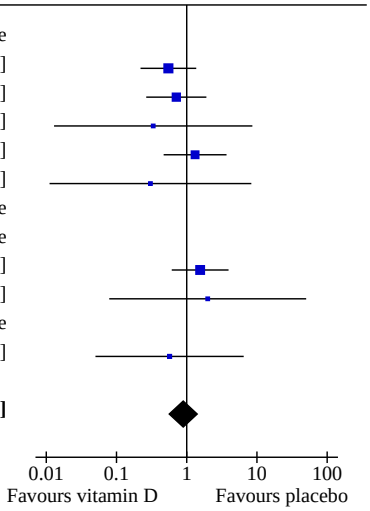
Heterogeneity: Tau² = 1.38; Chi² = 13.42, df = 10 (P = 0.20); I² = 25%
Test for overall effect: Z = 0.27 (P = 0.79)
Test for subgroup differences: Not applicable



Analysis 1.15. Comparison 1: Vitamin D versus placebo, Outcome 15: Proportion of participants with one or more serious adverse events due to any cause

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Andújar-Espinosa 2021	0	56	0	56		Not estimable
Camargo 2021	8	106	14	108	25.1%	0.55 [0.22 , 1.37]
Castro 2014	7	201	10	207	21.6%	0.71 [0.27 , 1.91]
Ducharme 2019	0	23	1	24	2.0%	0.33 [0.01 , 8.61]
Forno 2020	9	96	7	96	19.7%	1.32 [0.47 , 3.69]
Jensen 2016	0	11	1	11	1.9%	0.30 [0.01 , 8.32]
Jerzynska 2016	0	5	0	3		Not estimable
Kerley 2016	0	19	0	25		Not estimable
Martineau 2015	12	125	8	125	24.2%	1.55 [0.61 , 3.94]
Tachimoto 2016	1	54	0	35	2.0%	1.99 [0.08 , 50.25]
Thakur 2021	0	30	0	30		Not estimable
Urashima 2010	1	51	2	59	3.5%	0.57 [0.05 , 6.48]
Total (95% CI)		**777**		**779**	**100.0%**	**0.89 [0.56 , 1.41]**
Total events:	38		43			

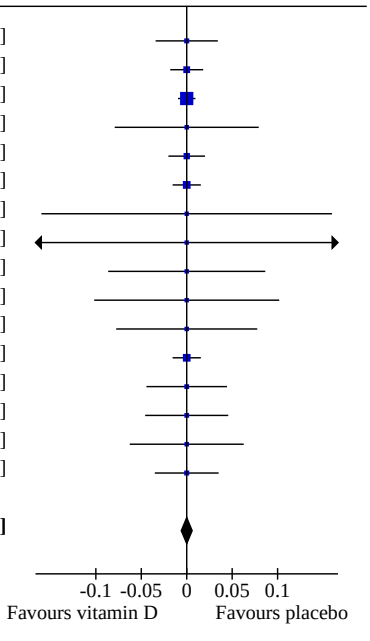
Heterogeneity: Tau² = 0.00; Chi² = 4.33, df = 7 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.49 (P = 0.62)
Test for subgroup differences: Not applicable



Analysis 1.16. Comparison 1: Vitamin D versus placebo, Outcome 16: Proportion of participants with fatal asthma exacerbation

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
Andújar-Espinosa 2021	0	56	0	56	3.0%	0.00 [-0.03 , 0.03]
Camargo 2021	0	106	0	108	10.8%	0.00 [-0.02 , 0.02]
Castro 2014	0	201	0	207	38.8%	0.00 [-0.01 , 0.01]
Ducharme 2019	0	23	0	24	0.6%	0.00 [-0.08 , 0.08]
Forno 2020	0	96	0	96	8.7%	0.00 [-0.02 , 0.02]
Jat 2020	0	125	0	125	14.7%	0.00 [-0.02 , 0.02]
Jensen 2016	0	11	0	11	0.1%	0.00 [-0.16 , 0.16]
Jerzynska 2016	0	5	0	3	0.0%	0.00 [-0.39 , 0.39]
Kerley 2016	0	19	0	25	0.5%	0.00 [-0.09 , 0.09]
Majak 2009	0	18	0	18	0.3%	0.00 [-0.10 , 0.10]
Majak 2011	0	24	0	24	0.6%	0.00 [-0.08 , 0.08]
Martineau 2015	0	125	0	125	14.7%	0.00 [-0.02 , 0.02]
Ramos-Martínez 2018	0	43	0	43	1.8%	0.00 [-0.04 , 0.04]
Tachimoto 2016	0	54	0	35	1.7%	0.00 [-0.05 , 0.05]
Thakur 2021	0	30	0	30	0.9%	0.00 [-0.06 , 0.06]
Urashima 2010	0	51	0	59	2.9%	0.00 [-0.04 , 0.04]
Total (95% CI)		**987**		**989**	**100.0%**	**0.00 [-0.01 , 0.01]**
Total events:	0		0			

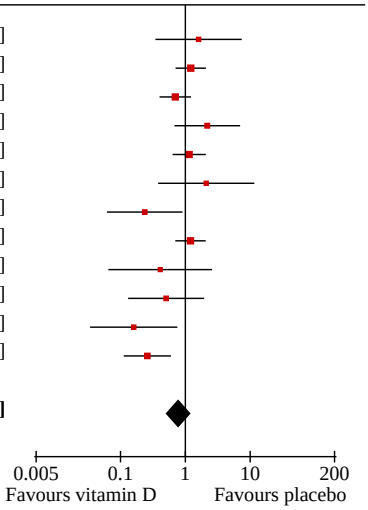
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 15 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Analysis 1.17. Comparison 1: Vitamin D versus placebo, Outcome 17: Proportion of participants with one or more exacerbation as defined in primary trials

Study or Subgroup	log[OR]	SE	Vitamin D Total	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
Aglipay 2019	0.470004	0.781482	15	12	5.1%	1.60 [0.35 , 7.40]
Camargo 2021	0.192986	0.275259	106	108	13.3%	1.21 [0.71 , 2.08]
Castro 2014	-0.3567	0.2855	201	207	13.1%	0.70 [0.40 , 1.22]
Ducharme 2019	0.778305	0.594952	23	24	7.2%	2.18 [0.68 , 6.99]
Forno 2020	0.135802	0.301032	96	96	12.7%	1.15 [0.63 , 2.07]
Jensen 2016	0.7419	0.8715	11	11	4.3%	2.10 [0.38 , 11.59]
Majak 2011	-1.442384	0.683983	24	24	6.1%	0.24 [0.06 , 0.90]
Martineau 2015	0.182322	0.275357	108	114	13.3%	1.20 [0.70 , 2.06]
Tachimoto 2016	-0.891	0.9401	54	35	3.9%	0.41 [0.06 , 2.59]
Thakur 2021	-0.682218	0.689055	30	30	6.0%	0.51 [0.13 , 1.95]
Urashima 2010	-1.8334	0.7906	51	59	5.0%	0.16 [0.03 , 0.75]
Yadav 2014	-1.3499	0.4272	50	50	10.0%	0.26 [0.11 , 0.60]
Total (95% CI)			**769**	**770**	**100.0%**	**0.77 [0.51 , 1.17]**

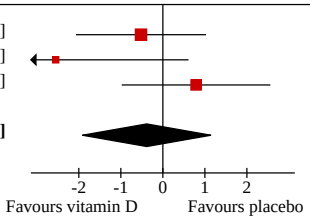
Heterogeneity: Tau² = 0.25; Chi² = 25.76, df = 11 (P = 0.007); I² = 57%
Test for overall effect: Z = 1.23 (P = 0.22)
Test for subgroup differences: Not applicable

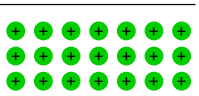


Analysis 1.18. Comparison 1: Vitamin D versus placebo, Outcome 18: % eosinophils, lower airway

Study or Subgroup	MD	SE	Vitamin D Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Castro 2014	-0.52	0.789	201	207	43.6%	-0.52 [-2.07 , 1.03]
Martineau 2015	-2.55	1.6128	17	14	18.1%	-2.55 [-5.71 , 0.61]
Tachimoto 2016	0.79	0.9022	52	34	38.3%	0.79 [-0.98 , 2.56]
Total (95% CI)			**270**	**255**	**100.0%**	**-0.38 [-1.92 , 1.15]**

Heterogeneity: Tau² = 0.78; Chi² = 3.48, df = 2 (P = 0.18); I² = 43%
Test for overall effect: Z = 0.49 (P = 0.62)
Test for subgroup differences: Not applicable



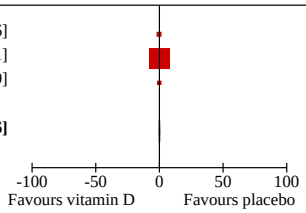


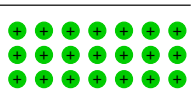
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.19. Comparison 1: Vitamin D versus placebo, Outcome 19: End-study log 10 total IgE, IU/ml

Study or Subgroup	MD	SE	Vitamin D Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Ramos-Martínez 2018	-0.2852	0.381549	43	43	7.0%	-0.29 [-1.03 , 0.46]
Forno 2020	0.1	0.106756	84	90	89.5%	0.10 [-0.11 , 0.31]
Andújar-Espinosa 2021	-0.07511	0.542293	53	53	3.5%	-0.08 [-1.14 , 0.99]
Total (95% CI)			**180**	**186**	**100.0%**	**0.07 [-0.13 , 0.26]**

Heterogeneity: Tau² = 0.00; Chi² = 1.02, df = 2 (P = 0.60); I² = 0%
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable



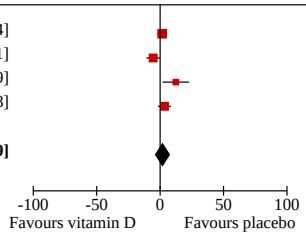


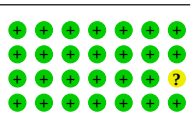
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.20. Comparison 1: Vitamin D versus placebo, Outcome 20: End-study FVC, % predicted

Study or Subgroup	MD	SE	Vitamin D Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Forno 2020	1.557343	1.981932	86	90	30.4%	1.56 [-2.33 , 5.44]
Jat 2020	-5.5	2.697016	90	84	26.9%	-5.50 [-10.79 , -0.21]
Camargo 2021	12.4	5.351348	7	13	15.4%	12.40 [1.91 , 22.89]
Andújar-Espinosa 2021	3.44	2.62	53	53	27.3%	3.44 [-1.70 , 8.58]
Total (95% CI)			**236**	**240**	**100.0%**	**1.84 [-3.60 , 7.29]**

Heterogeneity: Tau² = 21.41; Chi² = 11.29, df = 3 (P = 0.01); I² = 73%
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable



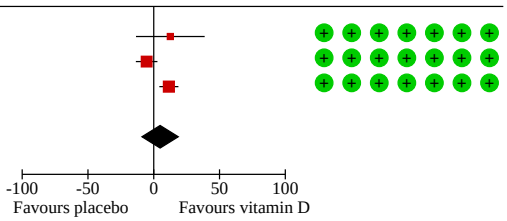


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.21. Comparison 1: Vitamin D versus placebo, Outcome 21: End-study PEFR (L/min)

Study or Subgroup	MD	SE	Vitamin D Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Jat 2020	12.6	13.316	90	84	17.6%	12.60 [-13.50 , 38.70]
Martineau 2015	-5.4	4.1838	106	110	40.6%	-5.40 [-13.60 , 2.80]
Tachimoto 2016	11.5	3.6956	52	34	41.9%	11.50 [4.26 , 18.74]
Total (95% CI)			**248**	**228**	**100.0%**	**4.84 [-8.95 , 18.62]**

Heterogeneity: Tau² = 104.47; Chi² = 9.56, df = 2 (P = 0.008); I² = 79%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable

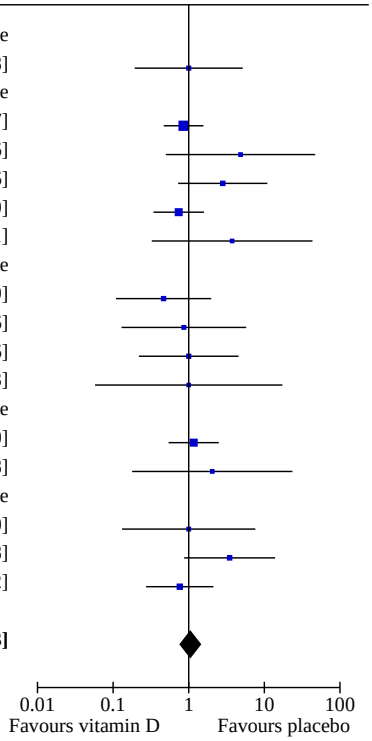


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.22. Comparison 1: Vitamin D versus placebo, Outcome 22: Withdrawals from trial

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Aglipay 2019	0	15	0	12		Not estimable
Andújar-Espinosa 2021	3	56	3	56	3.5%	1.00 [0.19 , 5.18]
Camargo 2021	0	106	0	108		Not estimable
Castro 2014	22	201	26	207	25.8%	0.86 [0.47 , 1.57]
Ducharme 2019	4	23	1	24	1.8%	4.84 [0.50 , 47.06]
Forno 2020	8	96	3	96	5.1%	2.82 [0.72 , 10.96]
Jat 2020	13	125	17	125	15.9%	0.74 [0.34 , 1.59]
Jensen 2016	3	11	1	11	1.6%	3.75 [0.32 , 43.31]
Jerzynska 2016	0	5	0	3		Not estimable
Jiang 2017	3	46	6	46	4.5%	0.47 [0.11 , 1.99]
Kerley 2016	2	19	3	25	2.6%	0.86 [0.13 , 5.76]
Lewis 2012	5	15	5	15	4.1%	1.00 [0.22 , 4.56]
Majak 2009	1	18	1	18	1.2%	1.00 [0.06 , 17.33]
Majak 2011	0	24	0	24		Not estimable
Martineau 2015	16	125	14	125	16.1%	1.16 [0.54 , 2.50]
Ramos-Martínez 2018	2	43	1	43	1.6%	2.05 [0.18 , 23.48]
Tachimoto 2016	0	54	0	35		Not estimable
Thakur 2021	2	30	2	30	2.3%	1.00 [0.13 , 7.60]
Urashima 2010	8	51	3	59	4.9%	3.47 [0.87 , 13.88]
Yadav 2014	8	50	10	50	9.0%	0.76 [0.27 , 2.12]
Total (95% CI)		**1113**		**1112**	**100.0%**	**1.05 [0.77 , 1.43]**
Total events:	100		96			

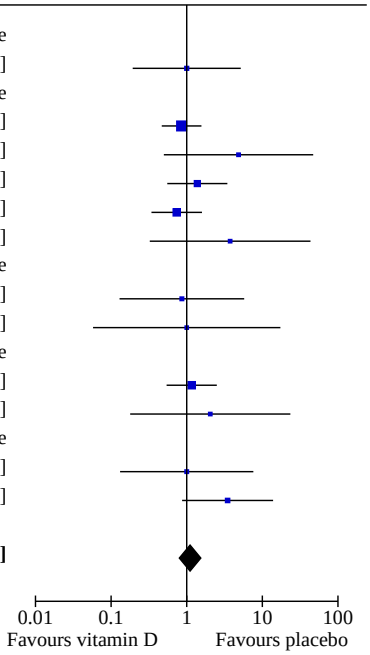
Heterogeneity: Tau² = 0.00; Chi² = 10.94, df = 14 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.76)
Test for subgroup differences: Not applicable



Analysis 1.23. Comparison 1: Vitamin D versus placebo, Outcome 23: Withdrawals from trial (excluding trials at high risk of bias)

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Aglipay 2019	0	15	0	12		Not estimable
Andújar-Espinosa 2021	3	56	3	56	3.9%	1.00 [0.19 , 5.18]
Camargo 2021	0	106	0	108		Not estimable
Castro 2014	22	201	26	207	29.1%	0.86 [0.47 , 1.57]
Ducharme 2019	4	23	1	24	2.1%	4.84 [0.50 , 47.06]
Forno 2020	12	96	9	96	12.7%	1.38 [0.55 , 3.45]
Jat 2020	13	125	17	125	18.0%	0.74 [0.34 , 1.59]
Jensen 2016	3	11	1	11	1.8%	3.75 [0.32 , 43.31]
Jerzynska 2016	0	5	0	3		Not estimable
Kerley 2016	2	19	3	25	3.0%	0.86 [0.13 , 5.76]
Majak 2009	1	18	1	18	1.3%	1.00 [0.06 , 17.33]
Majak 2011	0	24	0	24		Not estimable
Martineau 2015	16	125	14	125	18.2%	1.16 [0.54 , 2.50]
Ramos-Martínez 2018	2	43	1	43	1.8%	2.05 [0.18 , 23.48]
Tachimoto 2016	0	54	0	35		Not estimable
Thakur 2021	2	30	2	30	2.6%	1.00 [0.13 , 7.60]
Urashima 2010	8	51	3	59	5.5%	3.47 [0.87 , 13.88]
Total (95% CI)		**1002**		**1001**	**100.0%**	**1.11 [0.80 , 1.53]**
Total events:	88		81			

Heterogeneity: Tau² = 0.00; Chi² = 7.56, df = 11 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Sensitivity analysis: random-effects versus fixed-effect models

Analysis	Random-effects model	Fixed-effect model
People with one or more exacerbations requiring systemic corticosteroids	(OR 1.04, 95% CI 0.81 to 1.34)	(OR 1.04, 95% CI 0.81 to 1.34)
People with one or more exacerbations requiring systemic corticosteroids (risk difference)	(RD 0.00, 95% CI -0.02 to 0.03)	(RD 0.00, 95% CI -0.02 to 0.03)
FEV1, % predicted	(MD 0.20, 95% CI -1.24 to 1.63)	(MD 0.34, 95% CI -0.81 to 1.48)
End-study C-ACT/ACT score (0 to 27)	MD 0.23 (-0.26 to 0.73)	MD 0.20 (-0.21 to 0.60)
People with fatal asthma exacerbation	No events occurred (RD 0.00, 95% CI -0.01 to 0.01)	No events occurred (RD 0.00, 95% CI -0.01 to 0.01)
People with 1 or more serious adverse event due to any cause	(OR 0.89, 95% CI 0.56 to 1.41)	(OR 0.89, 95% CI 0.57 to 1.38)

Abbreviations: C-ACT/ACT, Childhood Asthma Control Test/ Asthma Control Test; CI, confidence interval; FEV1, forced expiratory volume in one second ; MD, mean difference; OR, odds ratio; RD, risk difference.

Table 2. Definitions of asthma exacerbation used in primary trials

Study	Definition
Aglipay 2019	Wheezing episode in children with asthma reported in parent completed symptom checklist, based on the International Study of Asthma and Allergies in Childhood
Camargo 2021	Any prescription of oral corticosteroids more than 20 days apart for a short period (e.g. several days)
Castro 2014	Meeting criteria for treatment failure and 1 or more of the following: • failure to respond to rescue algorithm within 48 hours; • FEV1 of less than 50% of baseline measurement on 2 consecutive measurements; • FEV1 of less than 40% of predicted level on 2 consecutive measurements; • use of 16 puffs/day or more of as-needed levalbuterol for 48 hours; • experiencing an exacerbation of asthma according to physician opinion; • use of oral or parenteral corticosteroids due to asthma.
Ducharme 2019	Exacerbation requiring rescue oral corticosteroids
Forno 2020	Either: • use of systemic corticosteroids for at least 3 days; or • hospitalisation or emergency department visit because of asthma, requiring systemic corticosteroids
Jensen 2016	Exacerbation requiring rescue oral corticosteroids, documented in medical or pharmacy records or both
Jerzynska 2016	Exacerbation not defined in study manuscript, individual participant data defined as requiring steroid course
Kerley 2016	Exacerbation not defined in study manuscript, individual participant data defined as requiring steroid course
Lewis 2012	Exacerbation not defined or reported in study manuscript
Majak 2009	Exacerbation not defined or reported in study manuscript; authors confirmed that no exacerbations requiring systemic corticosteroid treatment occurred in the study
Majak 2011	Reported but not defined in study manuscript; authors confirmed that no exacerbations requiring systemic corticosteroid treatment occurred in the study
Martineau 2015	Deterioration in asthma resulting in (A) treatment with oral corticosteroids, or (B) hospital admission or emergency department treatment, or (C) decrease in the morning PEFR to more than 25% below the mean run-in value on 2 or more consecutive days
Tachimoto 2016	Worsening of asthma symptoms prompting a need for a change in asthma treatment (from authors)
Thakur 2021	Reported but not defined in study manuscript
Urashima 2010	Asthma attack that included wheezing, improved by inhalation of a beta-stimulant in participants who already had a diagnosis of asthma; authors confirmed that no exacerbations requiring systemic corticosteroid treatment occurred in the study
Yadav 2014	Reported but not defined in study manuscript

FEV1, forced expiratory volume in one second; PEFR, peak expiratory flow rate.

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (the Cochrane Library)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)(Cumulative Index to Nursing and Allied Health Literature)	Monthly
AMED (EBSCO) (Allied and Complementary Medicine)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

Asthma search

1. exp Asthma/

2. asthma$.mp.

3. (antiasthma$ or anti-asthma$).mp.

4. Respiratory Sounds/

5. wheez$.mp.

6. Bronchial Spasm/

7. bronchospas$.mp.

8. (bronch$ adj3 spasm$).mp.

9. bronchoconstrict$.mp.

10. exp Bronchoconstriction/

11. (bronch$ adj3 constrict$).mp.

12. Bronchial Hyperreactivity/

13. Respiratory Hypersensitivity/

14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.

15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.

16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/

2. (randomised or randomised).ab,ti.

3. placebo.ab,ti.

4. dt.fs.

5. randomly.ab,ti.

6. trial.ab,ti.

7. groups.ab,ti.

8. or/1-7

9. Animals/

10. Humans/

11. 9 not (9 and 10)

12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Medline search strategy for update since 2016

1	exp *Asthma/
2	asthma$.ti,ab.
3	1 or 2
4	exp *Vitamin D/
5	exp Vitamin D Deficiency/

(Continued)

6	vitamin$ d$.ti,ab.
7	vitamin d$.ti,ab.
8	(calcitriol or cholecalciferol or alfacalcidol).ti,ab.
9	or/4-8
10	3 and 9
11	randomized controlled trial.pt.
12	controlled clinical trial.pt.
13	randomi?ed.ab,ti.
14	placebo.ab,ti.
15	dt.fs.
16	randomly.ab.
17	trial.ab,ti.
18	groups.ab.
19	or/11-17
20	exp animals/ not humans.sh.
21	19 not 20
22	10 and 21

Appendix 2. Search strategy to retrieve trials from the CAGR

Search strategy up to 2016

#1 AST:MISC1

#2 MeSH DESCRIPTOR Asthma Explode All

#3 asthma*:ti,ab

#4 #1 or #2 or #3

#5 MeSH DESCRIPTOR Vitamin D Explode All

#6 MeSH DESCRIPTOR Vitamin D Deficiency Explode All

#7 "vitamin d"

#8 #5 or #6 or #7

#9 #4 and #8

(in search line #1, MISC1 refers to the field in the record where the reference has been coded for condition, in this case, asthma)

Search strategy for update from 2016 onwards

1	AST:MISC1 AND INREGISTER
2	MeSH DESCRIPTOR Asthma Explode All AND INREGISTER
3	asthma*:ti,ab AND INREGISTER
4	#1 or #2 or #3
5	MeSH DESCRIPTOR Vitamin D Explode All AND INREGISTER
6	MeSH DESCRIPTOR Vitamin D Deficiency Explode All AND INREGISTER
7	vitamin* NEXT d* AND INREGISTER
8	Calcitriol or cholecalciferol AND INREGISTER
9	alfacalcidol AND INREGISTER
10	#5 or #6 or #7 OR #8 OR #9
11	#4 and #10
12	(2016 or 2017 or 2018 or 2019 or 2020 or 2021):yr AND INREGISTER
13	#11 AND #12

WHAT'S NEW

Date	Event	Description
6 February 2023	New search has been performed	Updated literature search prior to publication.
6 February 2023	New citation required and conclusions have changed	Since the previous Cochrane Review on this topic in 2016, debate has continued surrounding a potential role for vitamin D in reducing risk of asthma exacerbation and improving asthma control. We therefore conducted an updated meta-analysis to include data from new trials completed since this date.

HISTORY

Protocol first published: Issue 3, 2015
Review first published: Issue 9, 2016

Date	Event	Description
23 April 2019	Amended	An author added in error at the previous amendment was removed.

Date	Event	Description
13 September 2017	Amended	We discovered that two exacerbations requiring steroids had been misclassified in Martineau 2015, so the IRR for this study has been corrected from 0.70 (95% CI 0.41 to 1.21) to 0.74 (0.43 to 1.26). The pooled IRR has also been corrected from from 0.63 (0.45 to 0.88) to 0.64 (0.46 to 0.90).
15 November 2016	Amended	Two pieces of feedback received and authors have added two responses. No changes made to the review.

CONTRIBUTIONS OF AUTHORS

Anne Williamson (AW), Adrian R Martineau (ARM) and Christopher J Griffiths (CJG) assessed eligibility of trials for inclusion, extracted data, and performed risk of bias assessments. AW entered data into Review Manager 5.4 for statistical analysis, which ARM cross-checked. David Jolliffe (DJ) provided individual patient meta-data and contributed to statistical analysis. AW drafted the manuscript, and ARM, CJG, DJ, and Aziz Sheikh (AS) commented on it. All review authors critically evaluated it for important intellectual content and gave final approval of the version to be published.

Contributions of editorial team

Sally Spencer, Hayley Barnes and Kayleigh Kew (Editors) edited the review; advised on methodology, interpretation and content; approved the review prior to publication.

Emma Dennett (Deputy Co-ordinating Editor): advised on methodology, interpretation and content; edited the review.

Emma Jackson (Managing Editor): co-ordinated the editorial process; conducted peer review; obtained translations; edited references and other sections of the review.

Elizabeth Stovold and Vittoria Lutje (Information Specialists): designed the search strategy; ran the searches; edited the search methods section.

Andrea Takeda (Cochrane Central Productive Service): conducted copy-editing review.

DECLARATIONS OF INTEREST

Anne Williamson: none known.

Aziz Sheikh: none known.

David Jolliffe: none known.

Adrian R Martineau (ARM) and Christopher J Griffiths (CJG) acted as investigators in one or more clinical trials contributing data to this review. The risk of bias assessment for the study authored by ARM was performed independently by AW and CJG (Camargo 2021). The risk of bias assessment for the study authored by ARM and CJG was performed independently by UN and CJC in the previous systematic review (Martineau 2015). For all other studies, AW and ARM independently assessed the risk of bias for each study.

ARM declares receipt of funding in the last 36 months to support vitamin D research from the following companies who manufacture or sell vitamin D supplements: Pharma Nord Ltd, DSM Nutritional Products Ltd, Thornton & Ross Ltd and Hyphens Pharma Ltd. ARM also declares support for attending meetings from the following companies who manufacture or sell vitamin D supplements: Pharma Nord Ltd and Abiogen Pharma Ltd. ARM also declares participation on the Data and Safety Monitoring Boards for the VITALITY trial (Vitamin D for Adolescents with HIV to reduce musculoskeletal morbidity and immunopathology, NCT01784029) and the Trial of Vitamin D and Zinc Supplementation for Improving Treatment Outcomes Among COVID-19 Patients in India (NCT04641195). ARM also declares unpaid work as a Programme Committee member for the Vitamin D Workshop. ARM also declares receipt of vitamin D capsules for clinical trial use from Pharma Nord Ltd, Synergy Biologics Ltd and Cytoplan Ltd.

SOURCES OF SUPPORT

Internal sources

- Office for Students, UK

The salaries of ARM and CJG are supported by the Office for Students. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Office for Students, the Cochrane Systematic Reviews Programme, NIHR, NHS, or the Department of Health.

External sources

- National Institute for Health Research, UK

This project was supported by the National Institute for Health and Social Research (NIHR), via Cochrane Infrastructure, Cochrane Programme Grant, or Cochrane Incentive funding to Cochrane Airways. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS, or the Department of Health and Social Care.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The ordering of outcomes was changed from the published protocol, Martineau 2021, to the review, though all outcomes that met the prespecified criteria were reported on. The review protocol stated that where we identified substantial heterogeneity, specified as $I^2 > 40\%$, we would assess the value of exploring possible causes by using a prespecified subgroup analysis. Instead, we conducted all prespecified subgroup analyses that were possible given the available participant data.

It also stated that we would perform sensitivity analyses using fixed-effect models for outcomes where random-effects and fixed-effect models yielded different results. Instead, we pre-emptively conducted this sensitivity analysis for the primary outcome and all outcomes presented in the summary of findings table.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [adverse effects]; *Anti-Asthmatic Agents [adverse effects]; *Asthma [drug therapy]; Calcifediol; Cholecalciferol; Disease Progression; Hypercalciuria; Randomized Controlled Trials as Topic; Vitamin D [adverse effects]; Vitamins [adverse effects]

MeSH check words

Adolescent; Adult; Aged; Aged, 80 and over; Child; Child, Preschool; Female; Humans; Infant; Male; Middle Aged; Young Adult