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Vitamin D for the management of chronic obstructive pulmonary disease (Review)

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[Intervention Review]

Vitamin D for the management of chronic obstructive pulmonary disease

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ABSTRACT

Background

COPD is a common, preventable and treatable airway disease, and is currently the third leading cause of death worldwide. About one billion people worldwide are estimated to have vitamin D deficiency or insufficiency. Vitamin D deficiency is common among people with COPD, and has been reported to be associated with reduced lung function and increased risk of acute exacerbations of COPD. Several clinical trials of vitamin D to prevent acute exacerbations of chronic obstructive pulmonary disease (AECOPD) and improve COPD control have been conducted, but an up-to-date meta-analysis of all double-blind, randomised, placebo-controlled trials of this intervention is lacking.

Objectives

To assess the effects of vitamin D for the management of acute exacerbations and symptoms for people with COPD.

Search methods

We searched the Cochrane Airways Trials Register and reference lists of articles. We also searched trial registries directly, and contacted the authors of studies in order to identify additional trials. The date of the last search was 24 August 2022.

Selection criteria

We included double-blind, randomised, placebo-controlled trials of vitamin D or its hydroxylated metabolites, for adults with a clinical diagnosis of chronic obstructive pulmonary disease based on the presence of characteristic symptoms and irreversible airflow obstruction. We did not impose restrictions regarding disease severity or baseline vitamin D status, in order to maximise generalisability.

Data collection and analysis

We used standard Cochrane methods. The primary outcome was the rate of moderate or severe exacerbations (requiring systemic corticosteroids, antibiotics or both). We also performed subgroup analyses to determine whether the effect of vitamin D on the rate of moderate or severe exacerbations was modified by baseline vitamin D status, COPD severity or regular inhaled corticosteroid use.

The main secondary outcomes of interest were the proportion of participants experiencing one or more exacerbations (moderate or severe), the change in forced expiratory volume in one second (FEV1, % predicted) and the proportion of participants with one or more serious adverse events of any cause, mortality (all-cause) and quality of life. We used GRADE to assess the certainty of evidence for each outcome.

Main results

We included 10 double-blind, randomised, placebo-controlled trials in this review, involving a total of 1372 adults. Five studies contributed to the primary outcome analysis of the rate of moderate or severe exacerbations requiring systemic corticosteroids, antibiotics or both. The duration of studies ranged from six weeks to 40 months, and all investigated the effects of administering cholecalciferol (vitamin D_3). One study included two intervention arms, one where vitamin D_3 was given and one where calcitriol (1,25-dihydroxyvitamin D) was given. The majority of participants had mild to moderate COPD, and profound vitamin D deficiency (25-hydroxyvitamin D (25(OH)D) < 25 nmol/L) at baseline was rare (123 participants contributing data to subgroup analysis).

Administration of vitamin D or its hydroxylated metabolites results in little to no change in the overall rate of exacerbations requiring systemic corticosteroids, antibiotics or both (rate ratio (RR) 0.98, 95% CI 0.86 to 1.11; 5 studies, 980 participants; high-certainty evidence).

Vitamin D supplementation did not influence any meta-analysed secondary outcomes. These were all based on moderate- or high-certainty evidence aside from adverse events and quality of life, which were based on low-certainty evidence. We observed little to no change in the proportion of participants experiencing one or more moderate or severe exacerbations (odds ratio (OR) 0.94, 95% CI 0.72 to 1.24; 5 studies, 980 participants; high-certainty evidence). Additionally, vitamin D probably results in little to no difference in the inter-arm mean change in FEV1 (% predicted) (mean difference 2.82 higher in intervention arm, 95% CI -2.42 to 8.06; 7 studies, 1063 participants; moderate-certainty evidence).

There was also probably no effect of vitamin D on the incidence of serious adverse events due to any cause; although we identified an anticipated absolute effect of 36 additional adverse events per 1000 people, the confidence interval included the null hypothesis of no effect (OR 1.19, 95% CI 0.82 to 1.71; 5 studies, 663 participants; moderate-certainty evidence).

Vitamin D may have little to no effect on mortality (OR 1.13, 95% CI 0.57 to 2.21; 6 studies, 1019 participants; low-certainty evidence). It also may have little to no effect on quality of life as measured by validated instruments (narrative findings; 5 studies, 663 participants; low-certainty evidence).

We assessed one study as being at high risk of bias in at least one domain; this did not contribute data to the meta-analysis of the primary outcome reported above. Sensitivity analysis that excluded this study from the meta-analysed outcome to which it contributed, the inter-arm mean change in FEV1, did not change the findings.

Authors' conclusions

We found that administration of vitamin D results in little to no effect on the rate of moderate or severe exacerbations requiring systemic corticosteroids, antibiotics or both or the proportion of participants experiencing one or more exacerbations (moderate or severe) (both high-certainty evidence). Further, vitamin D probably has no effect on the inter-arm difference in change in lung volumes and the proportion of participants with one or more serious adverse event of any cause (both moderate-certainty evidence), and may make little to no difference to mortality or quality of life (both low-certainty evidence).

We recommend further research on the balance of benefits and harms of vitamin D supplements in COPD for those with very low or very high starting vitamin D levels, because we assessed the available evidence as low-certainty for these groups.

PLAIN LANGUAGE SUMMARY

Vitamin D to treat chronic obstructive pulmonary disease (chronic inflammatory lung disease)

Key messages

This Cochrane review does *not* find that vitamin D offers protection against acute flare-ups of chronic obstructive pulmonary disease (COPD), a chronic, inflammatory lung disease that causes breathing difficulties. It also does *not* find that vitamin D improves symptoms overall in people with COPD.

Why did we think that vitamin D might benefit people with COPD?

Low blood levels of vitamin D (the 'sunshine vitamin') have been linked to an increased risk of severe COPD flare-ups. In these flare-ups, patients experience breathing difficulty and increased cough - severe flare-ups are defined as those requiring steroid tablets or injections. Thus, we thought that supplementation to ensure good vitamin D levels might help to prevent flare-ups and improve control of symptoms.

What did we want to find out?

We wanted to find out if vitamin D supplementation:

• reduces the risk of COPD flare-ups;

• improves control of COPD symptoms;

• leads to any negative side effects.

What did we do?

We searched for research studies that compared the effect of vitamin D against matching placebo (dummy medication) on the risk of acute flare-ups of COPD and COPD symptom control. We did not place any limitations based on the dose of vitamin D given, the way it was delivered or the duration of the study. 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 the effects of vitamin D supplementation differed according to participants' vitamin D levels before taking supplements (baseline levels), how badly participants were affected by COPD initially and regular steroid medication use.

What did we find?

We included data from 10 studies in this review, which involved a total of 1372 people. Of these, five studies reported data on the rate of severe flare-ups. The studies lasted between six weeks and 40 months, and all investigated a particular form of vitamin D called cholecalciferol or vitamin D_3. This is the most common form of vitamin D tablet. One also investigated another form, called calcitriol. The majority of participants had mild/moderate COPD, and a minority had severe COPD.

• Overall, giving people vitamin D supplements makes little to no difference to the risk of COPD flare-ups compared to those given placebo (dummy medication).

• Vitamin D also makes little to no difference to the proportion of people who had one or more flare-ups during the study time period.

• Vitamin D supplementation probably makes little to no difference to lung capacity, or to the risk of serious harmful side effects.

• Vitamin D supplementation may have little to no effect on the risk of death, or on the quality of life of participants.

What are the limitations of the evidence?

• We are confident that vitamin D has no effect on COPD flare-ups, and moderately confident that it probably has little to no effect on lung capacity and the risk of serious harmful side effects.

• However, we have little confidence in the evidence for risk of death from COPD because it is based on studies with small numbers of participants. We also have little confidence in the evidence for quality of life because different studies used a range of measurements that could not be compared easily.

• We have little confidence in the results of one study, because it depended on participants remembering their day-to-day symptoms over the previous two months without use of a diary. This study contributed data to one of the main outcomes, lung function of people with COPD. However, when we repeated the analysis excluding this study, the overall result did not change - vitamin D supplementation had no effect in either case.

Future research

We recommend further research on the balance of the benefits and harms of vitamin D supplements in COPD for those with very low or very high starting vitamin D levels, because we found little evidence to help us answer our questions for these groups.

How up-to-date is this evidence?

The evidence is up-to-date to 24 August 2022.

Summary of findings 1. Summary of findings table - Vitamin D compared to placebo for the management of chronic obstructive pulmonary disease

Vitamin D compared to placebo for the management of chronic obstructive pulmonary disease

Patient or population: adults with a clinical diagnosis of chronic obstructive pulmonary disease
Setting: primary and secondary care, single-centre and multi-centre trials, across six countries (Belgium, Iran, the Netherlands, New Zealand, the UK and the USA)
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				
Rate of moderate or severe exacerbations	796 per 1000	**780 per 1000** (685 to 884)	**Rate ratio 0.98** (0.86 to 1.11)	980 (5 RCTs)	⊕⊕⊕⊕ High	Vitamin D results in little to no change in the rate of moderate or severe exacerbations, when compared to placebo.
Proportion of participants experiencing one or more exacerbations (moderate or severe)	459 per 1000	**443 per 1000** (379 to 512)	**OR 0.94** (0.72 to 1.24)	980 (5 RCTs)	⊕⊕⊕⊕ High	Vitamin D results in little to no change in the proportion of participants experiencing one or more moderate or severe exacerbations, when compared to placebo.
Mean difference in quality of life score	Lehouck 2012: used the Chronic Respiratory Questionnaire to assess emotional function on a scale of 1 (maximum impairment) to 7 (no impairment). No evidence of difference in end-study emotional score (MD -0.07 points lower in vitamin D arm, 95% CI -0.31 to 0.16). The minimum clinically important difference (MCID) for each dimension is 0.5 (Williams 2001). Two studies used the St George's Respiratory Questionnaire to measure effect on health and daily life, on a scale of 0 to 100 - higher scores showing worse quality of life. Neither found evidence of a difference between groups (Bjerk 2013: MD 2.3 points more in vitamin D arm, 95% CI -2.3 to 6.9 (change from baseline scores); and Martineau 2015: MD -2.26 less in vitamin D arm, 95% CI -2.85 to 7.37 (end scores)). The MCID for this questionnaire is estimated to be 7, for moderate to severe COPD patients (Alma 2006). Two studies used the EQ5D, with scores ranging from 0 to 1 where 1 represents full health. Neither found evidence of a difference between groups (Rafiq 2017: P = 0.08			663 (5 RCTs)	⊕⊕⊖⊖ Low[a]	Findings presented narratively as each study used a different form of outcome measure, so data were not suitable for meta-analysis. Studies reported mixed findings using different definitions and measures, but across these measures, all suggested that vitamin D may make little to no difference to quality of life.

	(change from baseline scores); and Rafiq 2022: 0.00 (-0.12 to 0.08) in the vitamin D arm versus 0.00 (-0.10 to 0.06) in the placebo arm (median change from baseline scores)). The MCID for this tool is estimated to be 0.028 (0.017 to 0.033) (Bae 2020).					
Difference in mean change in forced expiratory volume in 1 second (FEV1; % predicted)	The mean difference in mean change in forced expiratory volume in 1 second (FEV1; % predicted) was **-0.2** percentage points	MD **2.82 percentage points higher** (2.42 lower to 8.06 higher)	-	1063 (7 RCTs)	⊕⊕⊕⊖ Moderate[b]	Vitamin D probably results in little to no difference in mean change in FEV1 (% predicted), when compared to placebo. Baseline FEV1 was similar across arms.
Proportion of participants with one or more serious adverse event of any cause	275 per 1000	**311 per 1000** (237 to 393)	**OR 1.19** (0.82 to 1.71)	663 (5 RCTs)	⊕⊕⊕⊖ Moderate[c]	There was probably no effect of vitamin D on the incidence of serious adverse events due to any cause.
Mortality (all-cause)	43 per 1000	**48 per 1000** (25 to 90)	**OR 1.13** (0.57 to 2.21)	1019 (6 RCTs)	⊕⊕⊖⊖ Low[d]	Vitamin D may make little to no difference to all-cause mortality, but studies reported very few events in either arm.

*__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_440512744653831387.

[a] Downgraded two levels for very serious indirectness, as each study used different outcome measures and interventions.
[b] % predicted refers to the forced expiratory volume in 1 second as a percentage of the population average for someone of similar age, sex and body composition. Downgraded one level for imprecision, due to wide confidence intervals, which span no relative effect of vitamin D compared to placebo but also include appreciable benefit.
[c] Downgraded one level for imprecision, due to wide confidence intervals with anticipated proportions of 311/1000 participants (95% CI 237 to 393) in the vitamin D arm vs 275/1000 participants in the placebo arm.

[d] Downgraded two levels for very serious imprecision, due to wide confidence intervals with anticipated proportions of 48 participants per 1000 experiencing one or more events in the vitamin D arm and 95% CI 25 to 90, compared to 43 per 1000 in the placebo arm.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease, characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases (Vogelmeier 2017). In 2022, it was estimated to affect between 292 and 392 million people globally (Adeloye 2022). The condition was responsible for 3.23 million deaths in 2019, making it the third leading cause of death worldwide (WHO 2023). In the UK, an estimated 1.4 million people have a diagnosis of COPD, with a further 500,000 with undiagnosed disease (Stone 2023). COPD also causes significant functional impairment and reduced quality of life (Peruzza 2003).

Acute exacerbations of COPD (AECOPD) may be defined clinically as "an increase in dyspnea, cough, or sputum purulence with or without symptoms of upper respiratory infection", or pharmacologically as an acute worsening of a patient's respiratory symptoms beyond normal day-to-day variation that may warrant a change in medications (Anthonisen 1987; Celli 2019). Acute exacerbations are commonly classified as severe when they precipitate emergency department (ED) attendance and/or hospitalisation, and as moderate when they require treatment with antimicrobials and/or systemic corticosteroids without precipitating ED attendance and/or hospitalisation (Burge 2003). AECOPD are caused by complex interactions between the host, bacteria, viruses and environmental pollution (Sapey 2006). AECOPD are responsible for the majority of morbidity in people with COPD. They are common: cohort studies report that around 50% of people with COPD experience at least one such event over two to three years of follow-up (Dhamane 2015; Han 2017), with exacerbation rates varying from 0.85 per year in people with GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage 2 disease up to 2.00 exacerbations per year in people with GOLD stage 4 disease (Hurst 2010). The ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study identified a subgroup of participants with at least two exacerbations in the first year of follow-up, which were classified as the 'frequent exacerbator phenotype'; the prevalence of this phenotype increased with disease severity, affecting 22% of participants with stage 2 disease, 33% with stage 3 disease and 47% with stage 4 disease (Hurst 2010). Identification of this phenotype prompted efforts to aggressively treat these participants in an effort to reduce exacerbations and improve outcomes (Vogelmeier 2017). However, subsequent data from the SPIROMICS (SubPopulations and InteRmediate Outcome Measures In COPD Study) cohort indicate that the frequent exacerbator phenotype is not stable from year to year (Han 2017).

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, or both, 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 the active vitamin D metabolite 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 to 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 upregulated in response to infection and inflammation (Hansdottir 2008; Liu 2006).

How the intervention might work

About one billion people worldwide are estimated to have 25(OH)D concentrations of less than 75 nmol/L (Holick 2007). Vitamin D deficiency is common among people with COPD (Jolliffe 2018), in whom it is associated independently with worse lung function and increased risk of upper respiratory infections (Ginde 2009). Observational studies investigating associations between vitamin D deficiency and susceptibility to AECOPD have yielded conflicting results (Kunisaki 2012; Malinovschi 2014; Puhan 2014; Quint 2012). Administration of vitamin D3, vitamin D2 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 COPD, CYP27B1 expression in respiratory epithelium 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 to induce antimicrobial and antiviral activity (for example, by induction of antimicrobial peptide expression, apoptosis and generation of reactive oxygen and nitrogen intermediates) and exert anti-inflammatory activity (for example, by induction of the anti-inflammatory cytokine IL-10 and suppression of proinflammatory cytokines from type 1 helper T cells) (Greiller 2015; Heulens 2015). This combination of antimicrobial, antiviral and anti-inflammatory activity has the potential to decrease the risk of AECOPD, which are often precipitated by viral respiratory infections and which are characterised by dysregulated pulmonary inflammation.

Why it is important to do this review

There is considerable interest in the potential of administration of vitamin D to reduce the risk of AECOPD and to improve COPD symptom control. Evidence from two randomised controlled trials (RCTs) (one carried out by our group) shows that vitamin D supplementation reduces the risk of AECOPD in people with

baseline vitamin D deficiency (Lehouck 2012; Martineau 2015), and meta-analysis of data from RCTs shows that vitamin D supplementation reduces the risk of acute respiratory infections (which commonly precipitate AECOPD) (Jolliffe 2021). Uncertainty remains as to whether the benefits of vitamin D supplementation in people with COPD extend to those with vitamin D insufficiency; whether other clinical outcomes, for example, lung function, symptoms and quality of life, may be affected by vitamin D status; and whether vitamin D supplementation is a cost-effective intervention for people with COPD. Meta-analysis of intervention studies in the field has the potential to increase statistical power to detect effects of administering vitamin D on clinical outcomes in people with COPD, especially in subgroups who may be particularly responsive to this intervention.

OBJECTIVES

To assess the effects of vitamin D for the management of acute exacerbations and symptoms for people with COPD.

METHODS

Criteria for considering studies for this review

Types of studies

We included double-blind, randomised controlled trials (RCTs), which administered a comparison of either placebo (comparison #1), or vitamin D3 or vitamin D2 at a lower dose (comparison #2). Double-blind here refers to studies that were blinded to both the participants and personnel administering the study, and was a pre-specified criterion in our protocol to reduce risk of bias (Martineau 2019).

We did not exclude studies on the basis of cross-over or cluster design. We pre-specified that we would only meta-analyse data from cluster-RCTs if the available data had been adjusted (or can be adjusted), to account for the clustering (Martineau 2019). However, no such studies were identified.

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 results of the trial report. Studies in which vitamin D_3 or vitamin D_2 were administered only in combination with other micronutrients were excluded, as the specific effect of vitamin D could not be distinguished.

Types of participants

We included adults with a clinical diagnosis of COPD, based on the presence of characteristic symptoms and irreversible airflow obstruction. We did not impose restrictions regarding disease severity or baseline vitamin D status, in order to maximise generalisability.

Types of interventions

We included studies in which cholecalciferol (vitamin D_3), ergocalciferol (vitamin D_2) or their hydroxylated metabolites, such as calcidiol (25-hydroxyvitamin D) and calcitriol (1,25-dihydroxyvitamin D) were administered. We excluded studies in which vitamin D was given in combination with another intervention if the effects of vitamin D could not be isolated (e.g. by use of a factorial design). We did not place any limitations based on the dose of vitamin D given, the way it was delivered or the duration of the study.

We included RCTs that administered a comparison of placebo, and would also have included RCTs that administered a comparison of vitamin D_3 or vitamin D_2 at a lower dose had any been identified.

Types of outcome measures

Primary outcomes

- Rate of moderate or severe exacerbations (defined as requiring oral corticosteroids, antibiotics or both)

We selected this as the primary outcome on the grounds that avoidance of exacerbations is a key priority for people with COPD and physicians alike, and a key driver of COPD-related healthcare costs.

We selected event rate in preference to time from initiation of the intervention to first AECOPD and the proportion of people experiencing one or more AECOPD, as the event rate includes all events. For outcomes measured at different time points, we included the latest time point after randomisation to include all available data.

We also performed subgroup analyses to determine whether the effect of vitamin D on the rate of AECOPD was modified by:

- baseline 25(OH)D;
- COPD severity (by baseline FEV1, % predicted);
- baseline corticosteroid use.

Secondary outcomes

1. Effectiveness outcomes

- Proportion of participants experiencing one or more exacerbations (moderate or severe)
- Time to first exacerbation
- Rate of severe exacerbation, requiring emergency department (ED) attendance or hospitalisation
- Rate of moderate exacerbation
- Incidence of study-defined COPD exacerbation
- Mean difference in COPD symptom control, as judged by use of validated instruments (e.g. Chronic Respiratory Questionnaire; Guyatt 1987)
- Mean difference in days of work absence due to acute exacerbation of COPD
- Mean difference in self-reported short-acting bronchodilator use
- Mean difference in quality of life score, as judged by use of a variety of validated generic and disease-specific instruments (e.g. St George's Respiratory Questionnaire (SGRQ; Jones 1992))

2. Physiological/biochemical outcomes

- Inter-arm difference in mean change in FEV1 (% predicted)
- Inter-arm difference in mean change in forced vital capacity (FVC) (% predicted)
- Mean difference in exercise tolerance, using validated measures (e.g. six-minute walk distance)
- Mean difference in quadriceps strength/muscle strength, using validated measures (e.g. end-study handgrip strength)

- Biomarkers of inflammation in induced sputum/peripheral blood (lower airway/blood eosinophilia, other immunological parameters)

3. Health economic outcomes

- Mean difference in costs from the perspective of healthcare providers

4. Safety outcomes

- Proportion of participants with one or more serious adverse event of any cause
- Mortality (all-cause)
- Mortality (respiratory)

Search methods for identification of studies

Electronic searches

We first identified studies from the Cochrane Airways Trials Register, which was maintained by the Information Specialist for the Airways Group.

The Cochrane Airways Trials Register contains studies identified from several sources:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies (CRS) all years to date;
2. weekly searches of MEDLINE Ovid SP 1946 to date;
3. weekly searches of Embase Ovid SP 1974 to date;
4. monthly searches of PsycINFO Ovid SP 1967 to date;
5. monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature) 1937 to date;
6. monthly searches of AMED EBSCO (Allied and Complementary Medicine) all years to date; and
7. handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register were identified through search strategies based on the scope of Cochrane Airways. See Appendix 1 for search terms used to identify studies for this review. This full search of the Trials Register is up-to-date to 24 August 2022, and the authors also conducted a manual review of PubMed publications on 23 January 2024.

Details of the strategies for the other databases, as well as a list of handsearched conference proceedings are in Appendix 2.

We also searched the following trials registries:

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched January 2023).
2. World Health Organization (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch, searched January 2023).
3. ISRCTN registry (www.isrctn.com; searched December 2023).
4. Australian New Zealand Clinical Trials Registry (www.anzctr.org.au; searched December 2023).
5. UMIN Clinical Trials Registry (www.umin.ac.jp/ctr; searched December 2023).

We searched all sources from inception to present, with no restriction on language of publication, date of publication or publication status.

Searching other resources

We checked the reference lists of all primary studies and review articles for additional eligible studies. We considered the eligibility of all articles that could be located through the search registers above. We also searched relevant manufacturers' websites for information on studies in progress.

We also searched for errata or retractions from included studies published in full text on PubMed, with none identified, on 23 January 2024.

Data collection and analysis

Selection of studies

Two review authors (two of AW, AS, CJG, DJ and ARM) screened the titles and abstracts of the search results independently from one another, and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports of all potentially eligible studies and two review authors (two of AW, AS, CJG, DJ and ARM) screened these reports for inclusion independently of one another, recording the reasons for exclusion of ineligible studies. There were no disagreements regarding eligibility decisions.

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).

Data extraction and management

We used a data collection form for study characteristics and outcome data, which was piloted on at least one study in the review. Two review authors (two of AW, CJG, DJ, ARM and JS) extracted the study characteristics below from the included studies, independently from one another. There were no disagreements over extracted 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: N, mean age, age range, gender, 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 studies and notable conflicts of interest of trial authors.

We noted in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. One review author (AW) transferred data into the Review Manager file (RevMan 2020). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports.

A second review author (DJ, ARM or JS) conducted spot-checks of study characteristics for accuracy against the study report. Review authors were only involved in extraction and interpretation of studies for which they were not co-authors.

Assessment of risk of bias in included studies

Two review authors (two of AW, AS, CJG and ARM) assessed risk of bias independently for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). 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 bias.

Two authors from AW, AS, CJG and ARM judged each potential source of bias as low, high or unclear, and provided a quote from the study report together with a justification for our judgement in the risk of bias table. There were no disagreements regarding risk of bias. We summarised the risk of bias judgements across different studies for each of the domains listed. There were no cases where information on risk of bias related to unpublished data or correspondence with a trialist.

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome. AW, AS, CJG, JS and ARM performed assessments of the certainty of evidence.

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol (Martineau 2019), and justified any deviations from it in the Differences between protocol and review section.

For potentially eligible studies where a review author was involved, assessment of study eligibility, data extraction, interpretation/confirmation and risk of bias assessment were performed by two independent review authors, with no involvement from study authors. For Martineau 2015, this was performed by AW and AS. For Lehouck 2012, Rafiq 2017 and Rafiq 2022, this was performed by AW and ARM. For Camargo 2021, this was performed by AW and CJG. The assessment of certainty for outcomes that these studies contributed to was performed by AW and AS, who were independent of all contributing studies.

Measures of treatment effect

We analysed event rates as rate ratios (RR), dichotomous data as odds ratios (ORs) and time to first event as hazard ratios (HRs).

We used adjusted rate ratios where provided, as pre-specified in our protocol. This applied to Camargo 2021, which adjusted all ORs and HRs for age, sex and ethnicity. It also applied to Rafiq 2022, which adjusted for study centre, gender, age and smoking status. Where individual participant data were provided (Lehouck 2012; Martineau 2015; Rafiq 2017), we calculated adjusted ratios adjusting for age, sex and baseline COPD severity. Therefore, some adjusted ratios included in this meta-analysis differed slightly from the published ratios in the original articles. This adjustment approach was applied for all appropriate outcomes measured in terms of rate ratios or odds ratios (Analysis 1.1, subgroup analyses of this outcome; Analysis 1.2; Analysis 1.3; Analysis 1.4; Analysis 1.5; Analysis 1.7; Analysis 1.8). Where event rates but not rate ratios were published, we calculated ratios manually from the stated event rates and participant years of follow-up following Higgins 2022 (Section 9.4.8). Hazard ratios for time to first exacerbation were taken directly from published data, or unpublished data provided by authors (Analysis 1.6).

We analysed other continuous outcome measures as mean difference (MD). We used generic inverse variance meta-analysis where adjusted measures of treatment effect from individual trials are included, and for ORs, RRs and HRs. We entered data presented as a scale with a consistent direction of effect. For analyses of dichotomous outcomes for which no events occurred in some studies, we also calculated risk differences (RDs).

We undertook meta-analyses only where this was meaningful; that is, if the treatments, participants and the underlying clinical question were similar enough for pooling to make sense. Where multiple trial arms were reported in a single trial, we included only the relevant arms. If studies reported data over multiple time points, we used the time point furthest from the start in order to draw on all available data.

If two comparisons (for example, dose A versus placebo and dose B versus placebo) had been combined in the same meta-analysis, we would have halved the control group to avoid double-counting. However, the only study with two comparison arms did not report on outcomes eligible for meta-analysis, and was only presented narratively (Sanjari 2016). For outcomes measured at different time points, we included the latest time point after randomisation.

Unit of analysis issues

For dichotomous outcomes, we used participants, rather than events, as the unit of analysis (i.e. number of participants admitted to hospital, rather than number of admissions per person). However, if rate ratios were reported in a study or provided directly by study authors, we analysed them on this basis. No included studies were cross-over or cluster-RCTs, so we did not have to adjust to account for clustering.

Dealing with missing data

We assessed each study for risk of attrition bias based on data missing because trial participants dropped out, or were excluded (see Incomplete outcome data (attrition bias)). We did not impute any missing data, but contacted investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study was identified as an abstract only). If any data were missing, for instance due to patients lost to follow-up, we conducted an available case analysis.

We asked all investigators to provide data relating to the incidence of fatal COPD exacerbations and exacerbations requiring treatment with systemic corticosteroids and/or antibiotics and/or ED attendance and/or hospitalisation where these were not reported in the manuscript or abstract.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the studies in each analysis. If we identified substantial heterogeneity, we reported it and explored the possible causes by pre-specified subgroup analysis (Subgroup analysis and investigation of heterogeneity), where data were available.

Assessment of reporting biases

Following Section 10.4.3 and Chapter 13 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Page 2023), we did not conduct formal statistical tests for asymmetry due to the 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.

Data synthesis

All results that could not be included in a meta-analysis are reported narratively.

We used a random-effects model and performed a sensitivity analysis with a fixed-effect model where the two models yielded different results. We analysed all data by intention-to-treat, where available.

We synthesised event rates as rate ratios, dichotomous data as ORs and time to first event as HRs. We synthesised other continuous outcome measures as MD. We used means and standard deviations (SDs) when available. Where data were not reported, we approached the study authors.

Subgroup analysis and investigation of heterogeneity

We carried out the following subgroup analysis for the primary outcome of rate of AECOPD requiring systemic corticosteroids or antibiotics, or both:

1. baseline vitamin D status (< 25 nmol/L versus 25 nmol/L to 49.9 nmol/L versus 50 nmol/L to 74.9 nmol/L versus ≥ 75 nmol/L);
2. severity of COPD (< 50% predicted FEV1 versus ≥ 50% predicted FEV1); and
3. concomitant use of inhaled corticosteroids (yes versus no).

We used the formal test for subgroup interactions in Review Manager (RevMan 2020).

Sensitivity analysis

We carried out the following sensitivity analyses:

1. exclusion of 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; and
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 for the following comparison: vitamin D compared to placebo for the management of COPD. We included the outcomes listed below in the table.

1. Rate of moderate or severe AECOPD, defined as requiring oral corticosteroids, antibiotics or both
2. Proportion of participants experiencing one or more exacerbations (moderate or severe)
3. Mean difference in quality of life score
4. Inter-arm difference in mean change in FEV1 (% predicted)
5. Proportion of participants with one or more serious adverse event
6. Mortality (all-cause)

We used the five GRADE considerations (risk of bias, inconsistency, imprecision, indirectness and publication bias) to assess the certainty of the body of evidence as it related to the studies that contributed data for the prespecified outcomes. Working independently, two out of four review authors (AW, CJG, JS and ARM) assessed the certainty of the evidence. If there had been disagreements, a further review author (AS) would have arbitrated on this.

We used the methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2023), using GRADEpro software (GRADEpro GDT). We justified all decisions to downgrade the certainty of evidence using footnotes, and we made comments to aid the reader's understanding of the review where necessary.

RESULTS

Description of studies

Results of the search

We identified a total of 686 reports by searching the Cochrane Airways Trials Register and clinical trial registries, and handsearching major conference proceedings. After removing 210 duplicates, we screened 476 reports for eligibility. We excluded 453 reports on the basis of the titles or abstracts or both, as irrelevant. We assessed the remaining 23 reports for eligibility by consulting the full-text reports or contacting study authors or both; we then excluded five more studies that did not meet the eligibility criteria for inclusion, one study is awaiting classification and five studies are classified as ongoing. This resulted in 10 studies (12 reports) included in the final review, seven of which contributed quantitative data to meta-analyses (Figure 1). We have presented the reasons for excluding potentially relevant studies in the Characteristics of excluded studies table.

Figure 1. PRISMA Study Flow Diagram

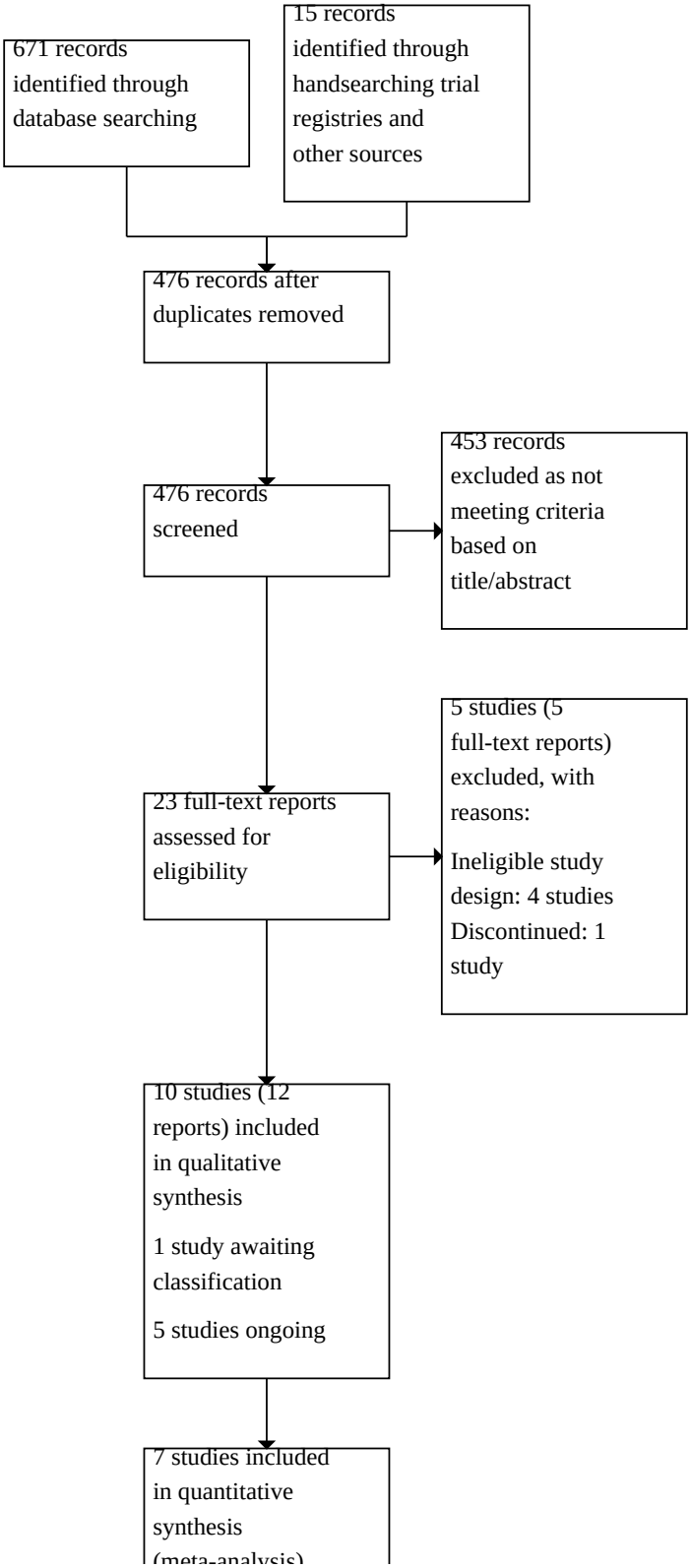


Figure 1. (Continued)

synthesis
(meta-analysis)

Included studies

Ten completed studies, including a total of 1372 participants with COPD, met the inclusion criteria for this review (Alavi Foumani 2019; Bjerk 2013; Camargo 2021; Dastan 2019; Lehouck 2012; Martineau 2015; Rafiq 2017; Rafiq 2022; Sanjari 2016; Zendedel 2015). See Characteristics of included studies for full details. Three of these studies provided additional information on outcomes not included in the original publication (Bjerk 2013; Camargo 2021; Rafiq 2022) and three provided full individual participant data for meta-analysis on request (Lehouck 2012; Martineau 2015; Rafiq 2017).

Included studies were published between 2012 and 2022, with data for the latest study collected up to July 2020 (Rafiq 2022).

Study design

All included studies were double-blind, randomised controlled trials with a parallel-group design, open to participants of any ethnic background; six were conducted at a single centre (Alavi Foumani 2019; Bjerk 2013; Dastan 2019; Lehouck 2012; Sanjari 2016; Zendedel 2015), and four were multi-centre studies (Camargo 2021; Martineau 2015; Rafiq 2017; Rafiq 2022). All were open to male and female participants; however, one only recruited male participants, as the study population was drawn from the Minneapolis Veterans Affairs Health Care System (Bjerk 2013). Eight studies recruited only in secondary care (Alavi Foumani 2019; Bjerk 2013; Dastan 2019; Lehouck 2012; Rafiq 2017; Rafiq 2022; Sanjari 2016; Zendedel 2015), one study recruited only in primary care (Camargo 2021) and one study recruited in both settings (Martineau 2015). Study duration of secondary prevention trials ranged from six weeks (Bjerk 2013), to an average of 40 months of follow-up (Camargo 2021). Eight studies were secondary prevention trials, which enrolled stable people with COPD to assess the effect of vitamin D on prevention of AECOPD or other disease control outcomes (Alavi Foumani 2019; Bjerk 2013; Camargo 2021; Lehouck 2012; Martineau 2015; Rafiq 2017; Rafiq 2022; Zendedel 2015). Two studies were treatment trials, where vitamin D was administered to people with ongoing AECOPD with a view to accelerating recovery or ameliorating long-term outcomes (Dastan 2019; Sanjari 2016). These studies were analysed separately, as additional exploratory outcomes.

All studies were restricted to individuals with a physician diagnosis of COPD. Of these, one study required a confirmed history of COPD exacerbation in the preceding year (Rafiq 2022). Five studies based eligibility on spirometry results, requiring FEV1 < 80% predicted (Lehouck 2012), FEV1 < 50% predicted (Zendedel 2015), FEV1/FVC < 70% (Camargo 2021), FEV1 ≤ 50% predicted and FEV1/FVC ≤ 70% (Bjerk 2013), or FEV1 < 80% predicted and FEV1/FVC < 70% (Rafiq 2017).

Three required a smoking history: over 100 cigarettes ever (Camargo 2021); history of being a current or former smoker (Lehouck 2012); or a smoking history ≥ 10 pack-years (Bjerk 2013). With the exception of two studies (Alavi Foumani 2019; Zendedel 2015), all also imposed age minimums of either over 40 years (Dastan 2019; Martineau 2015; Rafiq 2017; Rafiq 2022; Sanjari 2016) or over 50 years (Bjerk 2013; Camargo 2021; Lehouck 2012). One study also imposed an age maximum of 60 years (Sanjari 2016).

The two treatment trials required that participants be admitted with a diagnosis of AECOPD at the time of recruitment (Dastan 2019; Sanjari 2016). Sanjari and colleagues also required that participants have FEV1 < 88% predicted for men, or < 89% predicted for women (Sanjari 2016).

Four studies included baseline vitamin D status as an eligibility criterion. Two of these restricted eligibility to people with 25(OH)D concentration > 15 nmol/L but ≤ 50 nmol/L at screening (Rafiq 2017; Rafiq 2022). In both studies, a small number of participants were reported on with baseline 25(OH)D above 50 nmol, because participants underwent baseline sampling on a different visit within six weeks of screening. The third required baseline 25(OH)D ≤ 50 nmol/L only (Dastan 2019), and the fourth required baseline 25(OH)D to be > 25 nmol/L but ≤ 75 nmol/L (Alavi Foumani 2019). Six studies had exclusion criteria relating to maximum permitted pre-trial or concomitant supplemental vitamin D intake or both (Bjerk 2013; Camargo 2021; Dastan 2019; Lehouck 2012; Martineau 2015; Rafiq 2022).

Participants

The 10 studies involved 1372 adults in total.

Participants were ethnically diverse, across a range of geographic settings: Belgium (Lehouck 2012), Iran (Alavi Foumani 2019; Dastan 2019; Sanjari 2016; Zendedel 2015), the Netherlands (Rafiq 2017; Rafiq 2022), New Zealand (Camargo 2021), the UK (Martineau 2015) and the USA (Bjerk 2013).

The majority of participants had mild/moderate COPD, defined as GOLD stages 1 and 2, and a minority had severe COPD. Where measured, mean baseline serum 25(OH)D concentration ranged from 27 nmol/L (in Dastan 2019) to 58.75 nmol/L (in Bjerk 2013); a minority of participants had serum 25(OH)D concentrations in the profoundly deficient range, under 25 nmol/L (120, or 12%, of 972 participants contributing data to the primary outcome). Baseline FEV1 (% predicted) ranged from 34.5% (Zendedel 2015) to 76.8% (Camargo 2021). In each study, the baseline FEV1 (% predicted) was similar across arms.

Participation in the two treatment trials was limited to those experiencing an ongoing AECOPD (Dastan 2019; Sanjari 2016).

Intervention

All studies administered vitamin D_3 (cholecalciferol) to participants in the intervention arm. There was considerable heterogeneity

in vitamin D dosing regimens investigated. Of the preventative studies, two used a daily dosing regimen, one of 1200 IU/day (Rafiq 2017) and one of 2000 IU/day (Bjerk 2013). One study used weekly dosing (Rafiq 2022), two used monthly dosing (Lehouck 2012; Zendedel 2015), one gave doses every two months (Martineau 2015), one gave a bolus dose followed by monthly dosing (Camargo 2021) and one gave weekly dosing for eight weeks followed by monthly dosing (Alavi Foumani 2019).

Of the treatment trials, one used a dosing regimen of 30,000 IU vitamin D_3 daily for seven days, administered to one intervention arm (Sanjari 2016). This study also administered 0.25 µg calcitriol daily for seven days to participants randomised to a separate intervention arm, comparing both to a placebo regimen. The other treatment trial, Dastan 2019, compared a single dose of 300,000 IU vitamin D_3 administered intramuscularly to a single placebo injection. These studies were analysed separately from the secondary prevention trials.

Where follow-up vitamin D status was assessed, the intervention resulted in an inter-arm difference in follow-up serum 25(OH)D concentration on at least one follow-up time point in all studies except for one (Zendedel 2015).

Outcomes

Seven secondary prevention trials reported on COPD exacerbations requiring treatment with systemic corticosteroids as an outcome measure. Five reported on the primary outcome of the rate of AECOPD requiring systemic corticosteroids, antibiotics or both (moderate and severe AECOPD pooled). Definitions of AECOPD varied between studies; these definitions are summarised in Table 1.

Funding sources

Eight studies reported funding sources: Guilan University of Medical Sciences, Guilan, Iran (Alavi Foumani 2019), the Minnesota Veterans Medical Research and Education Foundation and the National Institutes of Health, Mayo Clinic Clinical and Translational Science award UL1 RR024150 (Bjerk 2013), the Health Research Council of New Zealand (grant 10/400), and the Accident Compensation Corporation of New Zealand (Camargo 2021), the School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran (Dastan 2019), the Applied Biomedical Research Program, Agency for Innovation by Science and Technology (IWT-TBM) (Lehouck 2012), the UK National Institute for Health Research (Martineau 2015), the Lung Foundation Netherlands (project number: 5.1.13.033) and Almirall grants (Rafiq 2022), and the vice chancellor and Physiology Research Center, Kerman University of Medical Sciences and Endocrine and Metabolism Research Center, Tehran University of Medical Sciences (Sanjari 2016). Each is summarised under Characteristics of included studies. The other two studies did not list any funding sources (Rafiq 2017; Zendedel 2015). There were no concerns about funding-associated bias in any case.

Excluded studies

Five studies were excluded: four due to ineligible study design and one that was discontinued due to COVID-19. See Characteristics of excluded studies for full details.

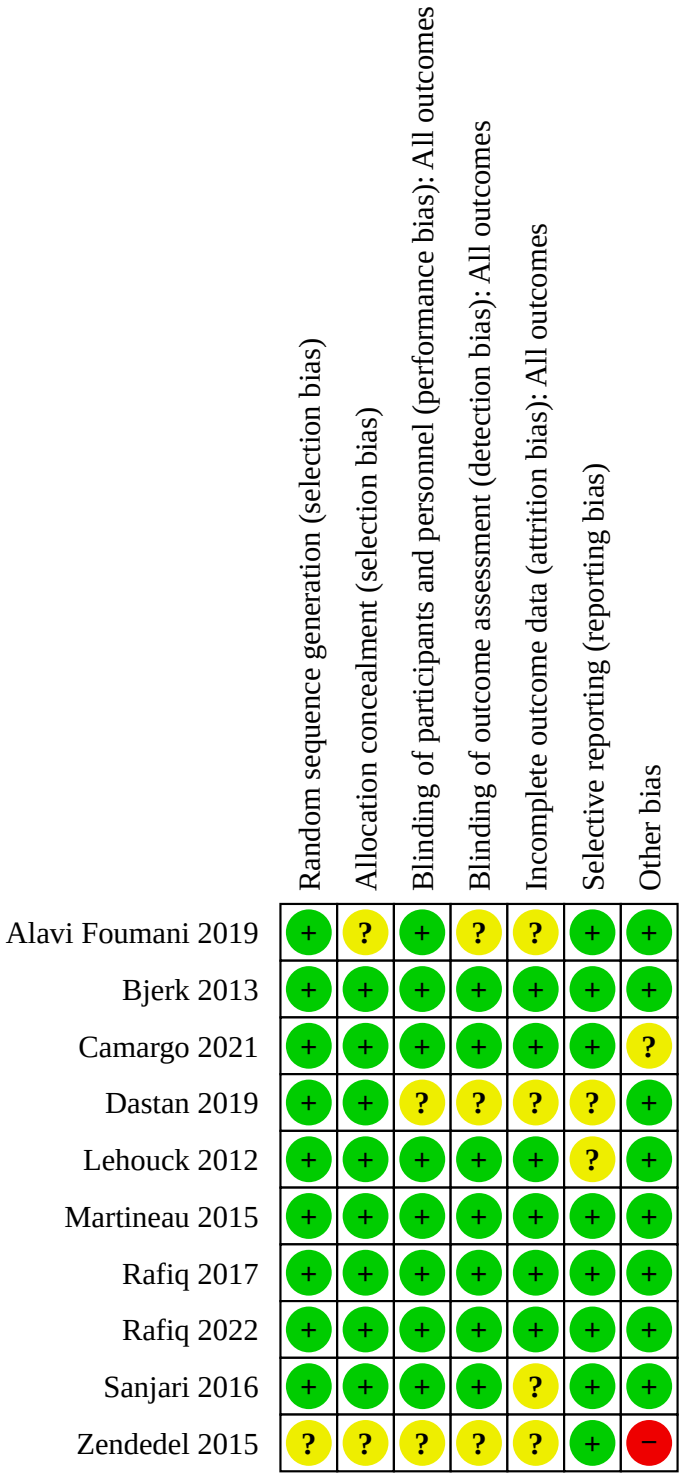
Ongoing studies

Five further studies were identified as ongoing, eligible trials that had not yet published their findings (listed under Ongoing studies). One of these studies lists COPD exacerbations as an outcome in its protocol (IRCT2016022826816N1), three studies list spirometry and exercise tolerance outcomes (Beijers 2022; IRCT201402029014N23; NCT03781895), and one is a five-year RCT commenced in 2016 focused on primary prevention of cardiovascular disease and cancer, with analysis of secondary respiratory outcomes ongoing (Gold 2016).

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.



We assessed one study as being at high risk of bias in one domain; this did not contribute data to the meta-analysis of the primary outcome. Sensitivity analysis that excluded this study from the meta-analysed outcome to which it contributed did not change the findings. We assessed this study, and five further studies, as being at unclear risk of bias in at least one domain, as outlined below. We assessed the remaining studies as being at low risk of bias in all domains.

Allocation

All studies reported the method of sequence generation and the method of allocation concealment, aside from two: Alavi Foumani 2019 did not provide details of placebo medication or envelope appearance, so was assessed as being at unclear risk of bias. Zendedel 2015 did not report either sequence generation or allocation concealment and was classified as being at unclear risk of bias for both. We classified the risk of selection bias for all other studies as low.

Blinding

Two studies did not report the method of blinding either participants or study personnel (Dastan 2019; Zendedel 2015), beyond stating that the study was blinded. We therefore classified the risk of bias as unclear. All other studies reported effective blinding of participants and study personnel, including those who administered the intervention. Thus, we assessed the overall risk of performance and detection bias as low, especially for the primary outcome, which these two studies assessed as unclear risk of bias did not contribute to.

Incomplete outcome data

Three studies only included participants who completed the trial in their baseline characteristics analysis (Alavi Foumani 2019; Dastan 2019; Sanjari 2016), precluding any assessment of attrition by characteristics. One further study, Zendedel 2015, did not state whether any participants withdrew or were lost to follow-up, and did not report on the number of participants contributing end-study data. We classified these studies as being at unclear risk of attrition bias.

Attrition rates of included studies ranged from 5% (Alavi Foumani 2019) to 22% (Martineau 2015). For each study, baseline characteristics and rates of attrition were similar between allocation arms, with no evidence of attrition bias. We therefore assessed the risk of attrition bias for the remaining studies as low.

Selective reporting

One study omitted two secondary outcomes pre-specified in the study protocol: days of antibiotics and oral steroids (Lehouck 2012). A second study listed the St George's Respiratory Questionnaire score as a secondary outcome in the study protocol, but did not publish these findings (Dastan 2019). 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 et al defined a COPD exacerbation as “any prescription of oral corticosteroids more than 20 days apart for a short period” (Camargo 2021), yet participants may have been prescribed oral corticosteroids for other reasons, including rescue packs to treat future exacerbations. Investigators sought to minimise contamination bias, by excluding participants with conditions other than COPD in which systemic corticosteroids may be indicated (e.g. autoimmune disease), but there still may have been residual non-COPD causes of steroid prescriptions. This risk, however, was unlikely to have differed between intervention and control arms in a way that systematically biased results. Therefore, we assessed this study as being at unclear risk of misclassification bias. A further study, Zendedel 2015, based its primary outcome on detailed recall of day-to-day symptoms without use of a diary at two-month intervals. We thus assessed this study as being at high risk of bias. We identified no other potential sources of bias for the remaining included studies.

Effects of interventions

See: **Summary of findings 1** Summary of findings table - Vitamin D compared to placebo for the management of chronic obstructive pulmonary disease

See Summary of findings 1.

Vitamin D versus placebo

Ten studies with a total of 1372 participants contributed to this comparison, six of which contributed quantitative data to one or more meta-analyses. For the primary outcome, Analysis 1.1 and subgroup Analysis 1.4 had 980 participants, whilst subgroup Analysis 1.2 had 975 participants and Analysis 1.3 had 978 participants. This is because a small number of participants did not have data available on either baseline 25(OH)D or baseline FEV1, so were excluded from subgroup analysis.

Primary outcome

Rate of moderate or severe exacerbations

Administration of vitamin D results in little to no change in the rate of moderate or severe COPD exacerbations, defined as requiring systemic corticosteroids or antibiotics or both, when compared to placebo (rate ratio 0.98, 95% confidence interval (CI) 0.86 to 1.11; 5 studies, 980 participants; I^2 = 0%; high-certainty evidence; Analysis 1.1).

Subgroup analyses

We conducted three pre-specified subgroup analyses for our primary outcome.

Baseline 25(OH)D

We stratified by participant 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). The formal RevMan test for subgroup differences found evidence to support the hypothesis that the effect of vitamin D compared to placebo was modified by baseline vitamin D status (Chi^2 = 8.79, P = 0.03).

Vitamin D administration reduced the rate of moderate or severe COPD exacerbations treated with systemic corticosteroids, compared to placebo, in people with severe vitamin D deficiency at baseline (25(OH)D < 25 nmol/L) (RR 0.68, 95% CI 0.47 to 0.99; 5 studies, 123 participants; I^2 = 0%; low-certainty evidence; Analysis 1.2).

However, there was no protective effect observed in any of the subgroups with higher baseline vitamin D status; 25 to 49.9 nmol/L (rate ratio 0.98, 95% CI 0.81 to 1.18; 5 studies, 380 participants; I^2 = 0%; low-certainty evidence), 50 to 74.9 nmol/L (rate ratio 0.96, 95% 0.73 to 1.26; 5 studies, 276 participants; I^2 = 0%; low-certainty evidence). In the subgroup of people with the highest baseline 25(OH)D concentrations ≥ 75 nmol/L, meta-analysis suggests an increased risk of exacerbation with administration of vitamin D (rate ratio 1.37, 95% 1.03 to 1.84; 5 studies, 196 participants; I^2 = 0%; low-certainty evidence). However, we note that most studies providing data stratified by baseline vitamin D status had only small participant numbers, particularly the subgroups with very low and very high baseline vitamin D. We also note that in each of the 25(OH)D < 25 nmol/L subgroup and the 25(OH)D ≥ 75 nmol/L subgroup, one study did not contribute estimable data as too few events occurred.

Baseline FEV1, % predicted

We stratified by COPD severity, categorised by baseline FEV1 (< 50% versus ≥ 50% predicted). The formal RevMan test for subgroup differences found no evidence to suggest that the effects of vitamin D compared to placebo were modified by baseline % predicted FEV1 (Chi^2 = 0.04, P = 0.83).

No within-subgroup effect of vitamin D was observed either for participants with baseline FEV1 < 50% predicted (rate ratio 1.00, 95% CI 0.84 to 1.20; 5 studies, 319 participants; I^2 = 0%; moderate-certainty evidence; Analysis 1.3) or for those with baseline FEV1 ≥ 50% predicted (RR 0.97, 95% CI 0.80 to 1.19; 5 studies, 659 participants; I^2 = 7%; moderate-certainty evidence).

Baseline corticosteroid use

We categorised participants according to whether or not they were prescribed concomitant regular inhaled corticosteroids. The formal RevMan test for subgroup differences again found no evidence of effect modification by this factor (Chi^2 = 0.10, P = 0.75).

Once again, no effect of the intervention was observed within either subgroup; with concomitant corticosteroids (rate ratio 0.92, 95% CI 0.80 to 1.06; 5 studies, 520 participants; I^2 = 0%; high-certainty evidence; Analysis 1.4) or without (rate ratio 0.97, 95% CI 0.72 to 1.29; 5 studies, 460 participants; I^2 = 0%; high-certainty evidence).

We converted study doses into their daily equivalent, but all studies administered doses in excess of the pre-specified threshold of 400 IU daily. All secondary prevention studies also administered the same form of 'parent' vitamin D, vitamin D_3 (one treatment trial administered vitamin D_3 to one intervention arm and calcitriol to another arm, but this study did not contribute to the primary outcome). Thus, we were unable to conduct a subgroup analysis by vitamin D dose or form. Further, every study included in this meta-analysis applied a different dosing frequency that could not be aggregated (Alavi Foumani 2019: weekly for eight weeks then monthly for four months; Lehouck 2012: monthly; Martineau 2015: every two months; Rafiq 2017: daily; Rafiq 2022: weekly), so we could not conduct a subgroup analysis by dosing frequency.

Secondary outcomes

Proportion of participants experiencing one or more exacerbations (moderate or severe)

Vitamin D administration makes little to no difference to the proportion of participants experiencing one or more moderate or severe AECOPD, defined as requiring systemic corticosteroids or antibiotics or both, when compared to placebo (OR 0.94, 95% CI 0.72 to 1.24; 5 studies, 980 participants; I^2 = 0%; high-certainty evidence; Analysis 1.5).

Time to first exacerbation

There was no evidence to suggest an influence of vitamin D on time to first moderate or severe AECOPD, defined as requiring systemic corticosteroids or antibiotics or both, when compared to placebo (HR 0.99, 95% CI 0.81 to 1.21; 4 studies, 624 participants; I^2 = 0%; high-certainty evidence; Analysis 1.6).

Rate of severe exacerbation, requiring ED attendance or hospitalisation

Administration of vitamin D did not influence the rate of severe AECOPD, defined as requiring ED attendance or hospitalisation or both, when compared to placebo (rate ratio 1.16, 95% CI 0.78 to 1.71; 4 studies, 622 participants; I^2 = 0%; moderate-certainty evidence; Analysis 1.7).

Rate of moderate exacerbation

We saw no effect of vitamin D compared to placebo on the rate of moderate AECOPD, defined as requiring systemic corticosteroids or antibiotics or both, but not ED attendance or hospitalisation (rate ratio 0.85, 95% CI 0.71 to 1.03; 3 studies, 467 participants; I^2 = 0%; high-certainty evidence; Analysis 1.8).

Incidence of study-defined exacerbation

The definitions of COPD exacerbations used in individual studies are summarised in Table 2. Administration of vitamin D did not affect the risk of experiencing at least one such exacerbation when compared to placebo (RR 0.96, 95% CI 0.85 to 1.10; 5 studies, 979 participants; I^2 = 0%; high-certainty evidence; Analysis 1.9).

Two further studies compared the mean number of study-defined COPD exacerbations over six months, but did not report the total number of incident events, so could not be included in meta-analysis (Alavi Foumani 2019; Zendedel 2015). Alavi Foumani 2019 observed similar mean events in intervention and control arms, with overlapping 95% confidence intervals (mean ± SD: intervention arm = 0.16 ± 0.45; control arm = 0.32 ± 0.6, P = 0.184). Zendedel 2015 did report a difference in the mean number of incident exacerbations during follow-up (mean ± SD: intervention arm = 9.7 ± 1.3; control arm = 18.8 ± 3.6; P < 0.001). However, the validity of this study depended on recall of day-to-day symptoms without use of a diary at two-month intervals, and thus we classified this study as being at high risk of bias.

Mean difference in COPD symptom control, as judged by use of validated instruments

Two studies investigated the effects of vitamin D compared to placebo on COPD symptom control. Data from these different instruments were unsuitable for pooling and were therefore not meta-analysed. This outcome is instead presented narratively.

Lehouck 2012 compared dyspnoea scores using the Chronic Respiratory Questionnaire, finding no evidence of a difference in end-study dyspnoea score with administration of vitamin D (MD -0.24 points lower in vitamin D arm, 95% CI -0.49 to 0.14). They also found no evidence of difference in end-study fatigue score (MD 0.15 points higher in vitamin D arm, 95% CI -0.12 to 0.42).

Martineau 2015 assessed the impact of vitamin D administration on peak symptom score for exacerbations, finding a reduced mean peak score per moderate or severe exacerbation in the vitamin D arm (MD -0.50 lower in vitamin D arm, 95% CI -0.97 to -0.02).

Mean difference in days of work absence due to AECOPD

One study conducted in adults investigated the outcome of work absence due to AECOPD (Martineau 2015). Allocation to vitamin D versus placebo 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 rate ratio 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).

Mean difference in self-reported short-acting bronchodilator use

One study conducted in adults investigated the effects of vitamin D compared to placebo on the number of uses of inhaled relief medication per 24 hours (Martineau 2015). Allocation to vitamin D versus placebo did not influence this outcome at 12 months (adjusted ratio of geometric means 1.00, 95% CI 0.77 to 1.28).

Mean difference in quality of life score, as judged by use of validated instruments

Five studies (663 participants) investigated quality of life outcomes, each using different instruments. These were unsuitable for pooling and are therefore presented narratively.

Lehouck 2012 compared quality of life outcomes using the Chronic Respiratory Questionnaire, which assesses quality of life over four dimensions, each on a scale of 1 (maximum impairment) to 7 (no impairment) aside from dyspnoea, on a scale of 0 to 7. The minimum clinically important difference (MCID) for each dimension is 0.5 (Williams 2001). They found no evidence of difference in end-study emotional score with administration of vitamin D compared to placebo (MD -0.07 points lower in vitamin D arm, 95% CI -0.31 to 0.16). Bjerk 2013 reported on the St George's Respiratory Questionnaire (SGRQ) (Jones 1992), a disease-specific instrument to measure effect on health and daily life, on a scale of 0 to 100 with higher scores showing worse quality of life. The MCID for this questionnaire is estimated to be 7, for moderate to severe COPD patients (Alma 2006). They found no evidence of an effect of vitamin D compared to placebo on inter-arm difference in change from baseline (MD 2.3 points more in vitamin D arm, 95% CI -2.3 to 6.9). Martineau 2015 also used the SGRQ, and found no evidence of an effect of vitamin D versus placebo on end-study scores (MD -2.26 less in vitamin D arm, 95% CI -2.85 to 7.37).

Rafiq 2017 considered the change in EQ5D, with scores ranging from 0 to 1, where 1 represents perfect health status. The MCID for this tool is estimated to be 0.028 (0.017 to 0.033) (Bae 2020). The study found no evidence of inter-arm difference in change from baseline (P = 0.08). In another study, Rafiq 2022 also considered the change in EQ5D, and found no evidence of difference between arms with a median change from baseline of 0.00 (interquartile range (IQR) -0.12 to 0.08) in the vitamin D arm and 0.00 (IQR -0.10 to 0.06) in the placebo arm, but no inter-arm analysis was conducted.

Overall, vitamin D supplementation may have little to no effect on quality of life (low-certainty evidence).

Inter-arm difference in mean change in FEV1 (% predicted)

Comparing secondary prevention studies, vitamin D versus placebo probably results in little to no effect on the inter-arm difference in mean change in FEV1 (% predicted) (MD 2.82 percentage points higher in intervention arm, 95% CI -2.42 to 8.06; 7 studies, 1063 participants; I^2 = 89%; moderate-certainty evidence; Analysis 1.10). These studies compared participants with very similar baseline FEV1%, with a mean FEV1 (% predicted) of 61.03% across all participants in the intervention arm of included studies (n = 529), and of 61.12% across all participants in the control arm (n = 490).

One treatment study, Sanjari 2016, also reported on the inter-arm difference in mean change in FEV1, comparing between admission to hospital with an AECOPD and follow-up seven days later. This study conducted a three-way comparison between vitamin D_3 versus calcitriol versus placebo, only reporting the P value of 0.44.

Inter-arm difference in mean change in FVC (% predicted)

There was no overall effect of vitamin D versus placebo on the inter-arm difference in mean change in FVC (% predicted) (MD -1.31 percentage points lower in intervention arm, 95% CI -4.44 to 1.82; 5 studies, 912 participants; I^2 = 0%; moderate-certainty evidence; Analysis 1.11).

Mean difference in exercise tolerance, using validated measures

Three studies reported on exercise tolerance, using slightly different measures taken from a six-minute walk test. None of these reported evidence of an effect of vitamin D, compared to placebo, on exercise tolerance. Lehouck 2012 reported no end-study inter-arm difference in six-minute walk distance (MD -7.9 m lower in vitamin D versus placebo arms, 95% CI -31.9 to 16.2), as did Rafiq 2022 (MD 34 m higher in vitamin D versus placebo arms, 95% CI -4 to 71). Rafiq 2017 recorded the mean change in six-minute walk for each arm without the end-study means, and also saw no evidence of inter-arm difference in change from baseline (P = 0.597).

Mean difference in quadriceps strength/muscle strength, using validated measures

Two studies reported no evidence of an effect of vitamin D, compared to placebo, on muscle strength as measured by end-study handgrip strength. The first, Rafiq 2022, provided unpublished quantitative data on this outcome (MD 1.15 kg higher in vitamin D arm, 95% CI -1.20 to 3.50). A further study, Rafiq 2017, narratively reported no effect of vitamin D supplementation on the change in this outcome, only providing a P value (P = 0.85).

Two other studies reported the effects of vitamin D supplementation on quadriceps strength. In both cases, the null hypothesis could not be rejected: Lehouck 2012 reported an end-study mean difference of 0.38 kg lower in the vitamin D arm (95% CI -0.43 to 1.18), whilst Martineau 2015 reported MD 1.23 kg lower in the vitamin D arm (95% CI -7.34 to 9.80).

One further study reported on Short Physical Performance Battery (SPPB) score, a pooled measure of lower body muscle strength (Bjerk 2013). This also found no effect of vitamin D supplementation

on mean within-arm change in SPPB score (MD 0.3 points higher in vitamin D versus placebo arms, 95% CI -0.80 to 1.50).

Biomarkers of inflammation in induced sputum/peripheral blood (lower airway/blood eosinophilia, other immunological parameters)

One secondary prevention study, Rafiq 2022, considered end-study serum concentrations of inflammatory markers. They did not find evidence that vitamin D administration influences end-study serum C-reactive protein (CRP) concentration when compared to placebo (MD 0.20 µg/mL higher in vitamin D arm, 95% CI -5.23 to 5.63), IL-6 (MD 0.5 µg/mL higher in vitamin D arm, 95% CI -4.93 to 5.93) or cathelicidin LL-37 (MD 1.15 µg/mL higher in vitamin D arm, 95% CI -4.33 to 6.53).

Both treatment studies measured the change in inflammatory markers (Dastan 2019; Sanjari 2016). Sanjari 2016 states narratively that vitamin D supplementation for AECOPD did not affect the change in CRP, though numerical data were not presented. Dastan 2019 reported that vitamin D supplementation led to a larger decrease in IL-6, with an inter-arm difference in change from baseline of 5.34 pg/mL (P = 0.02), but found no evidence of an effect on IL-8 (P = 0.15) or CRP (P = 0.24).

Mean difference in costs from the perspective of healthcare providers

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

Proportion of patients with one or more serious adverse event of any cause

Administration of vitamin D, compared with placebo, probably has no effect on the proportion of patients with one or more serious adverse events of any cause (OR 1.19, 95% CI 0.82 to 1.71; 5 studies, 663 participants; I^2 = 0%; moderate-certainty evidence; Analysis 1.12).

Mortality (all-cause)

Administration of vitamin D, compared with placebo, may have little to no effect on the incidence of deaths due to any cause (OR 1.13, 95% CI 0.57 to 2.21; 6 studies, 1019 participants; I^2 = 12%; low-certainty evidence; Analysis 1.13). There was also no effect when this variable was calculated as a risk difference (risk difference 0.00, 95% CI -0.02 to 0.03; 6 studies, 1019 participants; I^2 = 0%; Analysis 1.14).

Mortality (respiratory)

We saw no effect of vitamin D, compared with placebo, on the incidence of deaths due to AECOPD or respiratory failure (OR 1.26, 95% CI 0.33 to 4.87; 5 studies, 864 participants; I^2 = not applicable; low-certainty evidence; Analysis 1.15). However, deaths only occurred in Lehouck 2012, so this outcome is based on analysis of this study only. There was also no effect when this variable was calculated as a risk difference (risk difference 0.00, 95% CI -0.01 to 0.01; 5 studies, 864 participants; I^2 = 0%; Analysis 1.16).

Sensitivity analyses

Excluding studies at high risk of bias

The only study assessed as being at high risk of bias, Zendedel 2015, did not contribute data to the primary outcome of the rate of AECOPD requiring systemic corticosteroids or antibiotics or both.

It did contribute data to the inter-arm difference in mean change in FEV1, % predicted. A sensitivity analysis excluding this study did not change the null finding (MD 0.42 higher in intervention arm, 95% CI -0.33 to 1.17; 6 studies, 975 participants; I^2 = 0%; high-certainty evidence; Analysis 2.1).

Using a fixed-effect model

Random-effects and fixed-effect models yielded non-identical but similar results for six secondary outcomes.

For one outcome, inter-arm difference in mean change in FEV1 (% predicted), a fixed-effect model yielded an MD of 0.83 (95% CI 0.08 to 1.57), with the 95% confidence interval not including the null hypothesis, whereas the random-effects model yielded an MD with the 95% CI including the null (MD 2.82, 95% CI -2.42 to 8.06). However, the fixed-effect model estimate is still less than the minimal clinically important difference of a change exceeding 3% of baseline, as per established professional opinion (Cazzola 2008). Further, if the study deemed at high risk of bias is excluded, a null result is obtained with both the random-effects and fixed-effects model. Results of analyses performed using each model are presented in Table 2.

DISCUSSION

Summary of main results

This systematic review and meta-analysis incorporates evidence from 1372 adults with COPD who participated in 10 double-blind, randomised, placebo-controlled trials of vitamin D supplementation. We found that administration of vitamin D had no overall effect on primary or secondary outcomes considered, with key outcomes summarised in Summary of findings 1.

Five studies contributed data to analysis of the primary outcome of the rate of moderate or severe exacerbations. Administration of vitamin D had no effect on this outcome (high-certainty evidence). We note the lower bound of the 95% confidence interval of 0.86, such that we can state with 95% certainty that vitamin D supplementation leads to no more than a 14% reduction in exacerbation rate. There was no evidence of heterogeneity across studies for this primary outcome, with I^2 = 0%.

One of the pre-specified subgroup analyses for this primary outcome suggested that effects of the intervention may be modified by baseline 25(OH)D status: vitamin D supplementation reduced risk of moderate or severe exacerbation in participants with the lowest baseline 25(OH)D concentrations (< 25 nmol/L), but increased risk in those with the highest baseline 25(OH)D concentrations (≥ 75 nmol/L).

This could suggest that treatment of vitamin D deficiency is protective against exacerbations. However, the evidence underlying this subgroup analysis was assessed as being of low certainty due to imprecision, with small participant numbers in each group, especially those with very low or very high baseline

vitamin D. Accordingly, these findings should be interpreted with caution, and further research is warranted, focusing on the potential protective effects of vitamin D for those with significant baseline deficiency.

Pending results of such research, we highlight that the benefits of correcting profound vitamin D deficiency for maintaining calcium homeostasis and musculoskeletal health in the general population are well recognised. People with COPD are at heightened risk of osteoporosis due to a range of factors including regular corticosteroid use, smoking and reduced body mass (Inoue 2016). Our finding of a potentially protective effect against COPD exacerbations for individuals with severe baseline vitamin D deficiency provides an additional reason for vitamin D replacement. The effect identified in this subgroup was also sizeable, with a RR of 0.68 implying a 32% reduction in risk. This finding reinforces the current clinical justification for vitamin D supplementation in those who are deficient. We also found no evidence of any adverse events arising from vitamin D administration.

Secondly, at the other end of the baseline vitamin D spectrum amongst those with baseline 25(OH)D ≥ 75 nmol/L, we emphasise that the quality of subgroup evidence means uncertainty persists regarding any possible adverse effect of administration of vitamin D supplements to those with baseline 25(OH)D concentrations ≥ 75 nmol/L. Wider evidence finds no general health benefit in vitamin D supplementation amongst those with adequate concentrations, and the suggestion here is that this may be associated with adverse outcomes for people with COPD. Consequently, our findings are in concordance with the existing clinical recommendation that vitamin D supplementation is not justified for those with baseline 25(OH)D concentrations ≥ 75 nmol/L (Bouillon 2022).

Two further subgroup analyses of this primary outcome stratified by baseline COPD severity and baseline inhaled corticosteroid use found no modifying effect. These were also assessed as low-certainty evidence.

Vitamin D supplementation did not influence any meta-analysed secondary outcomes, which were all based on moderate- or high-certainty evidence, aside from mortality and quality of life outcomes (assessed as low-certainty due to small event numbers). We observed little to no effect on the proportion of participants experiencing one or more moderate or severe exacerbations (high-certainty evidence). We also observed little to no effect on the inter-arm difference in mean change in FEV1 (% predicted; moderate-certainty evidence), including or excluding the single study assessed as being at high risk of bias.

We observed no effect of the intervention on the proportion of participants experiencing one or more serious adverse events (SAEs; moderate-certainty evidence). The proportion experiencing one or more SAEs overall varied between studies, from < 5% in each arm in Bjerk 2013 to approximately 50% in each arm in Lehouck 2012. This is likely due to differences in the severity of participants' disease at baseline. For instance, Lehouck 2012 included a higher proportion of participants with severe COPD than other studies. We also observed little to no effect on the incidence of deaths due to any cause and on quality of life as measured by validated instruments (both low-certainty evidence).

Overall completeness and applicability of evidence

This review incorporated evidence from 10 studies (12 reports), across a range of populations in terms of age, country, baseline vitamin D status and vitamin D dosing regimens. This was a result of rigorous search criteria using a range of Cochrane and other databases to maximise completeness of evidence. This pool of studies is the largest analysed to date, with 980 participants contributing data to the primary outcome. Consistency of findings across these studies and across outcomes gives confidence in the completeness, external validity and applicability of the conclusions. Although only five of these 10 studies contributed data to the primary outcome (Analysis 1.1), the participant numbers were high (n = 980), and these five studies were varied in population, setting and intervention.

Given the focus of the review on vitamin D supplementation, it is of note that studies varied in their selection criteria regarding baseline vitamin D status. Four studies required low 25(OH)D levels as an inclusion criterion, of which two contributed data to meta-analysis of the primary outcome (Rafiq 2017; Rafiq 2022). This could be perceived as a limitation due to heterogenous study designs. However, the consistency of null findings across studies with different population baseline vitamin D levels further increases confidence in generalisability, and the pre-specified subgroup analysis by baseline 25(OH)D allowed us to explore evidence of differential subgroup-specific effects.

Included studies were published between 2012 and 2022, with data for the latest study collected up to July 2020 (Rafiq 2022). This means this study collected some follow-up data on participants during the early months of the COVID-19 pandemic - although this would only include a subset of overall study participants (n = 155). All other studies concluded data collection prior to the outbreak of COVID-19, with no ongoing studies offering unpublished data. This is important because COVID-19 viral infection is recognised as a new and important cause of AECOPD (Singh 2022). It is therefore notable that this study reported overall null findings for effects of vitamin D supplementation, consistent with all other studies that were conducted before the COVID-19 pandemic. Nonetheless, further research may be warranted to confirm the generalisability of results to SARS-CoV-2-triggered exacerbations of COPD.

Beyond external validity considerations, there is little reason to doubt the internal validity of our findings: these are based on double-blind, placebo-controlled trials and consistently maintained in sensitivity analyses excluding studies at high risk of bias. Moreover, we found effects of vitamin D on risk of exacerbation to be consistent when this outcome was expressed in different ways (RR (Analysis 1.1) versus OR (Analysis 1.5) versus HR (Analysis 1.6)), and when different definitions of exacerbation were used (exacerbations treated with systemic corticosteroids and/or antibiotics (Analysis 1.1) versus those defined according to study protocols (Analysis 1.9)). The null effect identified in aggregate outcomes was also consistent across a range of different secondary outcomes, enhancing our confidence in a true null result.

We also obtained individual participant data from authors, where possible (Lehouck 2012; Martineau 2015; Rafiq 2017), and supplementary unpublished data (Bjerk 2013; Rafiq 2022) as required, as pre-specified in our protocol. This allowed for subgroup analysis by baseline vitamin D status, COPD severity and concomitant inhaled steroid use, increasing the applicability

of our conclusions for each of these groups. However, we note that participant numbers in each subgroup were small, particularly those with severe baseline vitamin D deficiency (123 participants), and 95% CIs for effect estimates within these groups were correspondingly wide. Consequently, we downgraded our assessment of the evidence to low certainty for the subgroup analysis by baseline 25(OH)D concentration. We also downgraded our assessment of the evidence to moderate certainty for the subgroup analysis by % predicted baseline FEV1, due to relatively small participant numbers in the subgroup with baseline FEV1 < 50% (319 participants). These results should therefore be interpreted with caution. Small participant numbers in these subgroups also meant we could not assess whether there is any protective effect of vitamin D supplementation related to the severity of vitamin D deficit, not simply the presence of a deficit.

Finally, we also acknowledge that despite our efforts to obtain a wide pool of data and undertake pre-specified subgroup analyses for the primary outcome, there is heterogeneity in COPD presentations that we could not fully account for. Limitations of data availability were as follows. First, we lacked data on individual history of prior exacerbations, so we instead used FEV1 (% predicted) as a measure of COPD severity. More comprehensive individual participant data in future could allow for a subgroup analysis comparing the role of vitamin D supplementation for frequent versus infrequent exacerbators. Second, there were insufficient data on specific causes of COPD exacerbation across the included studies to carry out subgroup analysis of the primary outcome on this basis. We note that exacerbations are heterogenous in their causes, with triggers ranging from viral infection to eosinophilia to heart failure. More detailed participant data could allow for a future subgroup analysis based on cause of AECOPD. We also did not have sufficient individual patient data to fully explore any differential impacts of vitamin D supplementation for patients with renal failure, or those with malnutrition. However, the null findings were consistent across studies with a wide range of patient populations, ages and forms of vitamin D.

Quality of the evidence

This review followed rigorous pre-specified selection criteria, restricted to double-blind, placebo-controlled trials. Consequently, we assessed all included studies as being at low risk of performance bias and detection bias, aside from three, which did not explicitly detail the blinding process beyond stating that they were double-blinded – we classified these as being at unclear risk of bias for these categories, but they did not contribute to the primary outcome (Alavi Foumani 2019; Dastan 2019; Zendedel 2015). We also assessed Zendedel 2015 as being at high risk of 'other bias'. We included this study in one meta-analysis on the inter-arm difference in mean change in FEV1 (% predicted). However, sensitivity analysis showed no change in the null finding of this outcome once the study in question was excluded.

Following the GRADE approach, we first considered the primary outcome of the rate of moderate or severe exacerbations (requiring systemic corticosteroids, antibiotics or both). We assessed the risk of bias as low or unclear in all studies contributing data to this outcome. The results showed high precision, and very low heterogeneity.

We also assessed this evidence as direct rather than indirect, as a wide range of populations were studied. We followed the approaches specified in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess for publication bias (Higgins 2022), as outlined further under Methods and Potential biases in the review process. There was no evidence of publication bias. Therefore, the evidence for this primary outcome was classified as high certainty. Subgroup analyses for this outcome were classified as low certainty, due to serious imprecision as a result of small participant numbers in some subgroups.

We also followed the GRADE approach for secondary outcomes, as presented in Summary of findings 1. We assessed the proportion of participants experiencing one or more moderate or severe exacerbations as high-certainty evidence, as risk of bias was low or unclear in all contributing studies, the results showed high precision and very low heterogeneity, the evidence was assessed as direct (as above) and there was no evidence of publication bias.

We assessed the inter-arm difference in mean change in FEV1 (% predicted) as moderate-certainty evidence because of imprecision, due to wide confidence intervals that span no relative effect of vitamin D compared to placebo but also include appreciable benefit. However, this analysis included one study at high risk of bias - which was the only study to find that vitamin D affects mean change in FEV1 (% predicted). Sensitivity analysis excluding this study did not change this null finding, and found zero heterogeneity. However, we cannot be sure why the study at high risk of bias revealed a beneficial effect of vitamin D, so in order to be conservative, we have downgraded the overall certainty of this outcome to moderate certainty.

Mean difference in quality of life score was only presented narratively as each study used a different form of measuring quality of life. We downgraded this to low-certainty evidence due to indirectness, as each study used different outcome measures and interventions.

The proportion of participants with one or more serious adverse events of any cause showed less precision, with somewhat wide confidence intervals. Thus, we downgraded this by one level to moderate-certainty evidence.

We downgraded the final outcome included in the summary of findings table, the incidence of deaths due to any cause, to low-certainty evidence also due to imprecision, with very wide confidence intervals, as there were only a small number of events across the studies meta-analysed.

Potential biases in the review process

We searched multiple databases for eligible studies using prespecified criteria, and this strategy led to identification of the unpublished data included in this review. As outlined in the Methods, the eligibility and risk of bias of any studies authored by co-authors on this review (Camargo 2021; Lehouck 2012; Martineau 2015; Rafiq 2017; Rafiq 2022) were assessed by other co-authors (AW, ARM, CJG and AS as applicable, detailed in Methods). The assessment of certainty for outcomes that these studies contributed to was performed by AW and AS, independently of each other, who were both fully independent of all studies eligible for inclusion.

The search is up-to-date to 24 August 2022, which raises a potential limitation. However, the authors conducted a manual review of PubMed publications and major journals on 23 January 2024,

with no new randomised controlled trials identified. Thus, we are confident that this search date has no impact on the conclusions of the review. There were five studies identified as ongoing, which we have confirmed are still ongoing as of May 2024. One further study is listed as awaiting classification, due to inadequate information from the published abstract as to whether this study would meet the inclusion criteria (Khan 2017).

The protocol listed three additional databases to be searched: PsycINFO, CINAHL and AMED. These were previously included in the Cochrane Airways Group Register search. However, due to the closure of this group, we were unable to confirm whether these databases were included or to repeat a search. Thus, this raises a potential gap in the search. However, we carried out our search strategy across all other pre-specified databases, which also include psychology, allied health and nursing sources, and checked the references of existing studies and other systematic reviews. Thus, we feel confident in the comprehensiveness of our search.

As for any review of randomised controlled trials, publication bias may have favoured publication of trials reporting favourable results. If we had been able to pool more than 10 studies for any one outcome, we would have created and examined a funnel plot to contribute to this analysis. Instead, we followed the recommended approach in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022), including assessing for heterogeneity through analysing I^2, and assessing 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. Five studies were identified as ongoing, eligible trials that had not yet published their findings (listed under Ongoing studies). We assessed for preliminary data in each case, but either did not receive a response, or were informed that the data were not yet available. All trial protocols with a stated planned duration extended close to the date of this systematic review or beyond.

Overall, we have a low suspicion of selective non-publication of findings that differ from our review conclusions. Numerous studies contributed data to the primary outcome of this systematic review, with consistent findings and no strong indications of publication bias.

Agreements and disagreements with other studies or reviews

We are aware of six other systematic reviews and meta-analyses that have synthesised evidence from randomised controlled trials of the effects of vitamin D supplementation on COPD exacerbations (Chen 2019; Jolliffe 2019; Jolliffe 2021; Li 2020; Yang 2022; Zhu 2015).

The overall findings of this systematic review are consistent with four of these reviews, which did not find any overall effect of vitamin D administration in COPD, but found a reduced risk of AECOPD in participants with severe vitamin D deficiency at baseline. Two found no protective effects amongst aggregated participants with COPD (Chen 2019; Jolliffe 2021), aligning with the primary outcome of this systematic review. Two further analyses found protective effects amongst participant subgroups, including those with baseline vitamin D deficiency (Jolliffe 2019; Zhu 2015), also aligning with the subgroup analysis of this systematic review.

Conversely, two studies found overall protective effects (Li 2020; Yang 2022). However, these last two meta-analyses did not limit inclusion to double-blinded studies as an explicit inclusion criterion, and they combined prevention and treatment trials in a single meta-analysis with the potential for confounding results.

Our overall findings are also consistent with reviews not limited to populations with COPD, with two identifying a stronger protective effect of vitamin D against acute respiratory infections amongst individuals with severe vitamin D deficiency than those who are vitamin D replete (Jolliffe 2021; Martineau 2017).

AUTHORS' CONCLUSIONS

Implications for practice

We found that administration of vitamin D had no overall effect on the rate of moderate or severe exacerbations or the proportion of people experiencing one or more exacerbations (moderate or severe) of chronic obstructive pulmonary disease (COPD) (both high-certainty evidence). Vitamin D probably results in little to no difference in inter-arm difference in change in lung volumes, and in the proportion of participants with one or more serious adverse event of any cause (both moderate-certainty evidence). Vitamin D may also have little to no effect on all-cause mortality and quality of life (low-certainty evidence).

Implications for research

Further research is required to determine whether vitamin D supplementation has a protective effect against COPD exacerbation in people with the lowest baseline 25(OH)D concentrations (< 25 nmol/L), and also to investigate potential increases in exacerbation risk induced by vitamin D in people with baseline 25(OH)D concentrations ≥ 75 nmol/L.

There were insufficient data on specific causes of COPD exacerbation across the included studies to carry out subgroup analysis of the primary outcome on this basis. We note that exacerbations are heterogenous in their causes, with triggers ranging from viral infection to eosinophilia to heart failure. More detailed participant data could also allow for a future subgroup analysis based on cause of acute exacerbations of chronic obstructive pulmonary disease. Further research may also be warranted to confirm the generalisability of results to SARS-CoV-2-triggered exacerbations of COPD.

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Review protocol and search

- Emma Dennett and Elizabeth Stovold of Cochrane Airways provided advice on protocol content and search structure.
- Ian Yang was the Editor for the review protocol and commented critically on it.

Editorial and peer reviewer contributions

Cochrane Airways supported the authors in the development of this intervention review.

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Yuji Oba, Division of Pulmonary and Critical Care Medicine, University of Missouri, School of Medicine, Columbia Missouri, USA;
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Joanne Duffield, Central Editorial Service;
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported the editorial team): Sara Hales-Brittain, Central Editorial Service;
- Copy Editor (copy editing and production): Jenny Bellorini, Cochrane Central Production Service;
- Peer reviewers (provided comments and recommended an editorial decision): Raffaele Antonelli Incalzi, MD, Department of Internal Medicine University Campus Bio Medico Rome (clinical/content review); Munzer Naima (consumer review); Ina Monsef, Cochrane Haematology, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Faculty of Medicine and University Hospital Cologne, University of Cologne, Germany (search review). One additional peer reviewer provided clinical/content peer review but chose not to be publicly acknowledged.

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We are very grateful to Ken Kunisaki (Minneapolis Veterans Affairs Health Care System, USA) for providing unpublished data relating to his study.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Alavi Foumani 2019

Study characteristics	
Methods	Single-centre, double-blind, placebo-controlled randomised controlled trial of 6 months' duration Concomitant medication was continued. No run-in period was applied. Analysis was per protocol, excluding 3 lost to follow-up.
Participants	66 participants were recruited from Razi Hospital, Rasht, Iran. They were randomised to intervention or control in equal numbers. 3 individuals were lost to follow-up, and thus were not analysed. 60 m, 3 f Mean age: 68.2 years **Inclusion criteria:** Baseline vitamin D3 25 to 75 nmol/L Normal cell counts, liver-function tests, electrocardiograph, calcium, phosphorus and alkaline phosphatase Stable COPD in terms of physical and clinical health **Exclusion criteria:** Congestive heart failure, osteoporosis, acute myocardial infarction, glomerular filtration rate ≤ 45 mL/min/1.73 m^2, hypercalcaemia (> 10.3), malignancy, sarcoidosis, long-term azithromycin, taking antiepileptic drugs
Interventions	**Active intervention** (n = 32): 50,000 IU vitamin D3 once weekly for 8 weeks, then once monthly for 4 months **Control intervention** (n = 31): identical placebo Mean serum 25(OH)D concentration, intervention arm: 48.3 nmol/L (baseline), control: 46.4 nmol/L (baseline) Mean FEV1 (% predicted), intervention arm: 57.98% (baseline), control: 58.18% (baseline)
Outcomes	**Primary outcomes:** quality of life measured by COPD Assessment Test (CAT) score and lung function evaluated by spirometry, over 6 months' duration **Secondary outcomes:** mean number of exacerbations (study-defined), percentage at each GOLD level of severity, end-study 25(OH)D. Each over 6 months' duration. **Definition of exacerbation:** not defined in published text
Notes	Funded by Guilan University of Medical Sciences, Guilan, Iran. No declarations of interest reported.

Alavi Foumani 2019 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Classified according to random blocks
Allocation concealment (selection bias)	Unclear risk	Placebo (gelatin) and vitamin D3 were placed in 2 separate envelopes. However, the study does not state whether the tablets and/or envelopes were identical in appearance, or how it was decided which envelope was given to each participant.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinding was applied for both participants and care providers during the study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of study assessors was not specified.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Rates of loss to follow-up were low and comparable between arms (1/33 in intervention arm vs 2/33 in control arm). However, baseline characteristics were only reported for those who completed follow-up; thus, we could not assess for attrition bias based on characteristics.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting. Outcomes align with the published trial protocol from fa.irct.ir/trial/13784.
Other bias	Low risk	No other biases identified.

Bjerk 2013

Study characteristics

Methods	Single-centre, double-blind, placebo-controlled randomised controlled trial of 6 weeks' duration Concomitant medication was continued. No run-in period was applied. Analysis was by intention-to-treat.
Participants	36 participants were recruited from the Minneapolis Veterans Affairs Health Care System. They were randomised to vitamin D_3 (cholecalciferol) or placebo in equal numbers 36 m, 0 f Mean age 68 years **Inclusion criteria:** Age ≥ 50 years, FEV1/FVC ≤ 70%, FEV1 ≤ 50% of predicted, cigarette smoking history ≥ 10 pack-years and ability to ambulate independently or with the use of an ambulatory assist device, such as a cane or walker **Exclusion criteria:** use of > 500 IU/day of supplemental vitamin D, primary diagnosis of asthma, uncompensated congestive heart failure, acute myocardial infarction in the 6 months prior to enrolment, estimated glomerular filtration rate ≤ 45 mL/min/1.73 m^2, expected survival ≤ 6 months, malignancy treated with chemotherapy and/or radiation in the past 12 months, previously treated cancer now in

Bjerk 2013 *(Continued)*

	relapse, metastatic malignancy, "psychiatric disease interfering with the patient's judgment", inability to provide informed consent and any physical condition or diagnosis which the investigators felt would significantly interfere with assessment of muscle function. Participants with a baseline SPPB score of 12/12 were additionally excluded prior to randomisation, due to an inability to improve physical performance any further
Interventions	**Active intervention** (n = 19) 2000 IU oral capsule daily for 6 weeks **Control intervention** (n = 20) placebo capsule daily for 6 weeks Mean serum 25(OH)D concentration, intervention arm: 56.5 nmol/L (baseline), control: 61 nmol/L (baseline) Mean FEV1 (% predicted), intervention arm: 35% (baseline), control: 31% (baseline)
Outcomes	**Primary outcomes:** change in Short Physical Performance Battery (SPPB) score over 6 weeks **Secondary outcomes:** change in SGRQ, change in serum 25(OH)D, adverse events (unpublished data provided by authors). Each over 6 weeks. **Definition of exacerbation:** not defined
Notes	Funded by Minnesota Veterans Medical Research and Education Foundation and the National Institutes of Health, Mayo Clinic Clinical and Translational Science Award UL1 RR024150. No declarations of interest reported. Authors provided additional unpublished data on adverse effects and mortality rates.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, using variable block sizes of 2 or 4, to receive an oral capsule containing either vitamin D3 (cholecalciferol), or identical-appearing placebo, to be taken once daily for 6 weeks.
Allocation concealment (selection bias)	Low risk	Investigators, study co-ordinators and study participants were blinded to treatment allocation. Participants received an oral capsule containing either vitamin D3 (cholecalciferol), or identical-appearing placebo, to be taken once daily for 6 weeks.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Investigators, study co-ordinators and study participants were blinded to treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators, study co-ordinators and study participants were blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/20 participants withdrew from the placebo group (1 because of relocation out of the state, 1 as a result of family bereavement and unavailability for follow-up) and 1/19 participants withdrew from the intervention arm (due to prolonged hospitalisation and unavailability for follow-up).
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting. Trial protocol obtained at clinicaltrials.gov, NCT00914810. All pre-specified outcomes reported, and one secondary outcome added - St George's Respiratory Questionnaire.
Other bias	Low risk	No other biases identified.

Camargo 2021

Study characteristics	
Methods	The Vitamin D Assessment Study (ViDA) was a multi-centre, double-blind, placebo-controlled randomised controlled trial with an average of 3.3 years duration. The primary study, Scragg 2017, assessed the effect of monthly vitamin D on cardiovascular disease, with 2 secondary studies analysing the effects of this intervention on participants who had known COPD. This study was not used as a data source for the present review. Camargo 2021 analysed respiratory outcomes from the main ViDA study dataset, whilst Sluyter 2017 invited 10% of the participant cohort to participate in a further 1-year follow-up of respiratory outcomes. 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 the questionnaire within 4 weeks. Analysis was by intention-to-treat.
Participants	**Camargo 2021:** Participants (n = 356) were individuals with COPD but not asthma, 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 = 356 251 m, 105 f Age range: 50.6 to 84.9 years In this paper, participants with both asthma and COPD (n = 205), and with asthma only (n = 214), 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 1-year follow-up of respiratory outcomes. 442 agreed to participate and were included in the analysis. Of these, 17% (n = 77) had a COPD diagnosis, and their results are included in this systematic review. **Inclusion criteria (both reports):** COPD identification: a) FEV1/FVC ratio < 0.7; b) smoked 100 cigarettes ever in lifetime (i.e. obstructive pattern); 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. Missing smoking status or never smokers; 3. Steroid dose insufficient with exacerbation; 4. Other medical condition commonly treated by oral corticosteroids; inflammatory arthritis, inflammatory bowel disease, multiple sclerosis
Interventions	**Active intervention** (n = 200 in Camargo 2021, n = 40 in Sluyter 2017): initial bolus of 200,000 IU vitamin D3, then 100,000 IU vitamin D3 monthly **Control intervention** (n = 156 in Camargo 2021, n = 37 in Sluyter 2017): identical placebo regimen Mean serum 25(OH)D concentration, Camargo 2021: intervention arm: 66.1 nmol/L (baseline), control: 62.6 nmol/L (baseline) Mean FEV1 (% predicted), intervention arm: 74.3% (baseline), control: 80.1% (baseline)
Outcomes	*Camargo 2021:* **Primary outcomes:** exacerbations of asthma or COPD, over an average of 3.3 years duration *Sluyter 2017:* **Primary outcomes:** FEV1 (mL) at baseline and follow-up

Camargo 2021 *(Continued)*

	Secondary outcomes: FVC (mL) at baseline and follow-up
Notes	Funded by Health Research Council of New Zealand (grant 10/400), and the Accident Compensation Corporation of New Zealand. The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses or interpretation of data; in the writing of the manuscript; or in the decision to publish the results. Authors provided additional unpublished data on exacerbations by participant subgroup. This study was co-authored by 2 authors of this review. Neither of these authors were involved in assessment of eligibility, data extraction, risk of bias or certainty of evidence for outcomes to which this study contributed.

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 1-year follow-up.
Allocation concealment (selection bias)	Low risk	Randomised, double-blinded, placebo-controlled trial. Participants received identical-looking soft gel capsules containing either vitamin D3 (100,000 IU) or placebo. The capsules were provided by Tishcon Corporation (Westbury, NY, USA). The capsules were mailed monthly to the homes of the participants, with 2 capsules in the first letter (an initial bolus of 200,000 IU vitamin D3 or placebo) and, thereafter, 1 capsule monthly (100,000 IU vitamin D3 or placebo).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment was allocated automatically using computer generation by a study biostatistician, and all other staff and participants were masked. This is explained in Scragg 2017, the primary publication of the ViDA study, which reports on cardiovascular outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Treatment was allocated automatically using computer generation by a study biostatistician, and all other staff and participants were masked. This is explained in Scragg 2017, the primary publication of the ViDA study, which reports on cardiovascular outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Baseline characteristics were similar by allocation for both studies, with similar rates of attrition across arms and no evidence of attrition bias. **Camargo 2021:** participant retention 77% for overall paper (asthma + COPD). Exclusion criteria included missing FEV1/FVC ratio, so excluded those lost to follow-up by construction. **Sluyter 2017:** no evidence of incomplete outcome data. Of the 442 participants who were willing to participate in this sub-study, a complete set of both baseline and 1-year follow-up measurements was available in 366 participants (83%).
Selective reporting (reporting bias)	Low risk	No suggestion of selective outcome reporting. The pre-published 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 exacerbations as its (only) outcome.

Camargo 2021 *(Continued)*

		Sluyter 2017: no suggestion of selective outcome reporting. Text states that this was a pre-specified subgroup analysis.
Other bias	Unclear risk	This study defines an exacerbation as "any prescription of oral corticosteroids more than 20 days apart for a short period (e.g., several days)". These participants may have been prescribed oral corticosteroids for non-COPD reasons, though investigators excluded participants if they had medical conditions commonly treated by oral corticosteroids. This definition was applied equally to participants randomised to either arm of the trial, so it should not have introduced a systematic bias. This may have introduced a lack of precision, however, so in order to be conservative, we assessed the study as being at unclear risk of bias.

Dastan 2019

Study characteristics	
Methods	Single-centre, double-blind, placebo-controlled randomised controlled trial of 7 days' duration, investigating effects of vitamin D in treating current COPD exacerbations Concomitant medication was continued. No run-in period was applied. Analysis was per protocol, excluding those lost to follow-up..
Participants	70 participants were recruited from Shahid Beheshti University of Medical Sciences, Tehran, Iran. They were randomised to vitamin D3 or placebo in equal numbers. 57 m, 10 f Mean age 63.8 years **Inclusion criteria:** acute exacerbation of COPD diagnosis and vitamin D deficiency (serum 25(OH) vitamin D level of < 20 ng/mL) and an age of 40 years **Exclusion criteria:** using a maintenance dose of oral corticosteroids in the last 3 months and having a serum 25(OH) vitamin D level of < 5 ng/mL, 3 months of vitamin D supplementation before admission, a history of asthma, osteoporosis, renal failure (serum creatinine level of 2.5), nephrolithiasis, uncompensated liver failure (Child-Pugh classes of B and C), hypercalcaemia (ionised calcium level of > 1.3 mmol/L), conditions associated with pathological 1-alpha hydroxylase activity, such as sarcoidosis, lymphoma, multiple myeloma, pregnancy and lactation, immuno-compromised states and coagulopathy
Interventions	**Active intervention** (n = 33) 300,000 IU single IM injection of vitamin D3 **Control intervention** (n = 34) single IM injection placebo Mean serum 25(OH)D concentration, intervention arm: 26.5 nmol/L (baseline), control: 28.1 nmol/L (baseline) Mean FEV1 (% predicted), intervention arm: 46% of participants GOLD II, 36% GOLD III, 18% GOLD IV (baseline), control: 47% of participants GOLD II, 38% GOLD III, 15% GOLD IV (baseline)
Outcomes	**Primary outcomes:** change in interleukin 6, interleukin 8, high-sensitivity C-reactive protein (hsCRP) over 6 days **Secondary outcomes:** change in mMRC (Modified Medical Research Council) Dyspnea Scale over 6 days; length of stay **Definition of exacerbation:** "dramatic degradation of COPD symptoms (for example, the quantity and the color of phlegm or shortness of breath) that lasts for a couple of days"

Dastan 2019 *(Continued)*

Notes	Treatment trial rather than prevention trial, included as separate exploratory analysis Funded by the School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran. The authors declare that they do not have conflicts of interest related to the content of the manuscript.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A permuted (balanced)-block randomisation design was utilised for the treatment allocations in this trial.
Allocation concealment (selection bias)	Low risk	The participants were randomly allocated to receive 300,000 IU of vitamin D (25-hydroxycholecalciferol) or placebo as a single intramuscular injection.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated - unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated - unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were 3 withdrawals: 2/35 participants allocated to the intervention arm and 1/35 participants from the control arm. Only participants who completed the trial were analysed for baseline outcomes. Baseline characteristics of participants lost to follow-up were not presented, thus we assessed this risk of bias as unclear.
Selective reporting (reporting bias)	Unclear risk	One outcome was included in the trial protocol IRCT 2016031425726N4 but not published: St George's Respiratory Questionnaire.
Other bias	Low risk	No other biases identified.

Lehouck 2012

Study characteristics

Methods	Single-centre, double-blind, placebo-controlled randomised controlled trial of 1 year duration Concomitant medication was continued. No run-in period was applied. Analysis was by intention-to-treat.
Participants	182 participants were recruited from University Hospitals Leuven, Leuven, Belgium. They were randomised to intervention or control in equal numbers. 17 individuals were lost to follow-up, 10 in the intervention arm and 7 in the placebo arm, and thus were not analysed. 145 m, 37 f Mean age 68 years (standard deviation 9 years) **Inclusion criteria:** current/former smoker, age > 50, diagnosis of COPD according to GOLD, FEV1 < 80% **Exclusion criteria:** hypercalcaemia, sarcoidosis, active cancer, treatment with vitamin D supplements for new symptomatic osteoporosis, long-term azithromycin treatment
Interventions	**Active intervention** (n = 91) 100,000 IU monthly

Lehouck 2012 *(Continued)*

	Control intervention (n = 91) placebo monthly Mean serum 25(OH)D concentration, intervention arm: 50 nmol/L (baseline), control: 50 nmol/L (baseline) Mean FEV1 (% predicted), intervention arm: 44.18% (baseline), control: 42.24% (baseline)
Outcomes	**Primary outcomes:** time to first exacerbation, over 1 year **Secondary outcomes:** exacerbation rate, time to first hospitalisation, time to second exacerbation, FEV1, quality of life and death **Definition of exacerbation:** "Sustained worsening of respiratory symptoms during 48 hours and requiring oral corticosteroid, antibiotic, or combination treatment"
Notes	Funded by the Applied Biomedical Research Program, Agency for Innovation by Science and Technology (IWT-TBM). No declarations of interest reported. Study authors provided individual participant data for meta-analysis. This study was co-authored by an author of this review. This author was not involved in assessment of eligibility, data extraction, risk of bias or certainty of evidence for outcomes to which this study contributed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned participants in blocks of 20 to overcome seasonal influences on baseline characteristics. In each consecutive block, participants were allocated in a 1:1 ratio.
Allocation concealment (selection bias)	Low risk	Vitamin D and placebo were prepared in oral syringe dispensers, were identical in appearance and taste, and were numbered according to the randomisation schedule.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded randomised controlled trial. Pharmacists of the University Hospitals Leuven, who were independent of the clinical study team, randomly assigned participants using a computer-generated randomisation list and prepared the study medication.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	After the last participant completed the trial, masking continued until all data were entered in a database, which was verified and locked before unblinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 17 withdrawals: 10/91 participants allocated to the intervention arm and 7/91 participants from the control arm. There were also 15 deaths, 9/91 in the intervention arm and 6/91 in the control arm. Baseline characteristics were similar by allocation. There is no evidence of attrition bias.
Selective reporting (reporting bias)	Unclear risk	One outcome was included in the trial protocol NCT00666367 but not published: days of antibiotics and oral steroids. Unclear risk of bias.
Other bias	Low risk	No other biases identified.

Martineau 2015

Study characteristics	
Methods	Multi-centre, double-blind, placebo-controlled randomised controlled trial of 1 year duration Concomitant medication was continued. A run-in period of at least 2 weeks was applied, during which they completed a daily study diary, recording details of respiratory symptoms, medication use, health care use, time off work, and out-of- pocket expenses incurred as a result of COPD exacerbations or upper respiratory infections. Analysis was by intention-to-treat.
Participants	240 participants were recruited from 60 general practices and 4 Acute National Health Service Trust clinics across London, UK. They were randomised to intervention or control in equal numbers. 24/122 participants in the intervention arm, and 29/118 participants in the control arm, did not complete follow-up. 144 m, 96 f Mean age: 64.6 years **Inclusion criteria:** medical record diagnosis of COPD, emphysema or chronic bronchitis **Exclusion criteria:** age < 40, FEV1:FVC or slow vital capacity of > 70% after inhalation of 400 µg salbutamol, and medical record diagnosis of asthma Vitamin D supplements taken at doses of up to 10 µg (400 IU) per day were permitted during the trial
Interventions	**Active intervention** (n = 122): 3 mg (120,000 IU) vitamin D3 2-monthly **Control intervention** (n = 118): identical placebo Mean serum 25(OH)D concentration, intervention arm: 45.4 nmol/L (baseline), control: 46.7 nmol/L (baseline) Mean FEV1 (% predicted), intervention arm: 63.74% (baseline), control: 64.52% (baseline)
Outcomes	**Primary outcomes:** time to first moderate or severe COPD exacerbation and time to first upper respiratory infection, over 1 year duration **Secondary outcomes:** proportion of participants who had at least 1 moderate or severe exacerbation or upper respiratory infection; the rate of moderate or severe exacerbation or upper respiratory infection; peak values and areas under the curve for symptom scores during exacerbation or upper respiratory infections; the proportion of moderate or severe exacerbations associated with upper respiratory infections; incidence of unreported exacerbations; FEV1 and FVC; body mass index; differential white cell counts, presence of lower airway bacterial colonisation and concentrations of inflammatory mediators in induced sputum; use of respiratory medications; unscheduled health care attendance for exacerbation or upper respiratory infections; quality of life, as indicated by the St George's Respiratory Questionnaire (SGRQ) and EQ5D health questionnaire scores; work absence; health economic outcomes (costs of exacerbations and upper respiratory infections, quality-adjusted life-years and incremental net benefit over 1 year); serum concentrations of 25-hydroxyvitamin D, parathyroid hormone and corrected calcium; and incidence of adverse events **Definition of exacerbation:** the occurrence of at least 2 major COPD symptoms (dyspnoea, sputum volume or sputum purulence), or 1 major COPD symptom and at least 1 minor COPD symptom (increase in nasal congestion or discharge, wheeze, sore throat or cough), during at least 2 days consecutively
Notes	Funded by the UK National Institute for Health Research. The authors declare no competing interests. Study authors provided individual participant data for meta-analysis. This study was co-authored by 3 authors of this review. None of these authors were involved in assessment of eligibility, data extraction, risk of bias or certainty of evidence for outcomes that this study contributed to.

Martineau 2015 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation sequence using a computer program that assigned the term active or placebo to the numbers 1 to 300 with permuted blocks of 10. Each pack was then assigned a number according to this computer-generated randomisation sequence.
Allocation concealment (selection bias)	Low risk	3 mg (120 000 IU) vitamin D3 or 6 mL organoleptically identical placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment allocation was concealed from participants and study staff.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Treatment allocation was concealed from participants and study staff.
Incomplete outcome data (attrition bias) All outcomes	Low risk	24/122 in the intervention arm and 29/118 in the control arm did not complete follow-up, of whom 6 were lost to follow-up in the intervention arm and 14 lost in the control arm (others withdrew consent). A further 4 in each arm missed at least one dose of medication, so were classified as incomplete. Baseline characteristics were similar by allocation. There is no evidence of attrition bias.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting. Trial protocol obtained at ClinicalTrials.gov NCT00977873.
Other bias	Low risk	No other biases identified.

Rafiq 2017

Study characteristics

Methods	Multi-centre, double-blind, placebo-controlled randomised controlled trial of 6 months' duration Concomitant medication was continued. No run-in period was applied. Analysis was by intention-to-treat.
Participants	50 participants were recruited from Vrije Universiteit Medical Center, Amsterdam, Netherlands, and randomised to intervention or control. 7 individuals were lost to follow-up, 5 in the intervention arm and 2 in the control arm. 26 m, 24 f Age range: 58 to 66 years **Inclusion criteria:** serum 25(OH)D 15 to 50 nmol/L at screening, post-bronchodilator FEV1/FVC < 0.70, FEV1 < 80% predicted, COPD diagnosis confirmed by a physician, age 40 to 70 years After screening, participants were included within 6 weeks, and a sample was taken at the first study visit. These samples were analysed at the end of the study using the LC MS/MS assay, considered the gold standard for vitamin D deficiency. A small number of participants demonstrated 25(OH)D levels > 50 nmol at this baseline visit, despite being below this threshold at initial screening. They were included and analysed in the study and this meta-analysis.

Rafiq 2017 *(Continued)*

	Exclusion criteria: clinical suspicion of osteoporosis, malignant disease, life expectancy < 6 months, pregnant or lactating women, unable to consent
Interventions	**Active intervention** (n = 24): 1200 IU vitamin D3 daily **Control intervention** (n = 26): placebo daily Mean serum 25(OH)D concentration, intervention arm: 42.3 nmol/L (baseline), control: 40.6 nmol/L (baseline) Mean FEV1 (% predicted), intervention arm: 58.46% (baseline), control: 58.96% (baseline)
Outcomes	**Primary outcomes:** respiratory muscle strength was assessed by measuring maximal inspiratory and expiratory pressure. Physical performance score was assessed by the tandem test, chair stands test, 3-m walking test, and 6-minute walking test. **Secondary outcomes:** forced expiratory volume in 1 second, forced vital capacity, handgrip strength, exacerbation rate, scores on physical activity measured by LASA Physical Activity Questionnaire and quality of life (EQ5D) **Definition of exacerbation:** the presence, for at least 2 consecutive days, of an increase in any 2 major symptoms (dyspnoea, sputum purulence, sputum amount) or an increase in 1 major and 1 minor symptom (wheeze, sore throat, cough, symptoms of a common cold)
Notes	The authors declare that there is no conflict of interest. No funding sources declared. Study authors provided individual participant data for meta-analysis on request, and our assessment revealed no evidence of selective reporting. This study was co-authored by 2 authors of this review. Neither of these authors were involved in assessment of eligibility, data extraction, risk of bias or certainty of evidence for outcomes that this study contributed to.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomisation (blocks of 4 participants) to receive either vitamin D or placebo with stratification by gender and institution. Pharmacists of the Vrije Universiteit Medical Center, who were independent of the clinical study team, performed the allocation.
Allocation concealment (selection bias)	Low risk	Participants received either 1200 IU colecalciferol or a matching placebo according to randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Pharmacists of the Vrije Universiteit Medical Center, who were independent of the clinical study team, performed the allocation. After the last participant completed the study, masking continued until all analyses were performed.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	After the last participant completed the study, masking continued until all analyses were performed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 withdrawals; 5/24 participants allocated to the intervention arm (4 withdrew consent, 1 unable to comply with follow-up) and 2/26 participants from the control arm. Baseline characteristics similar by allocation. There is no evidence of attrition bias.

Rafiq 2017 *(Continued)*

Selective reporting (reporting bias)	Low risk	Trial protocol not obtained. No evidence of selective reporting, with full individual participant data provided for analysis.
Other bias	Low risk	No other biases identified.

Rafiq 2022

Study characteristics	
Methods	Multi-centre, double-blind, placebo-controlled randomised controlled trial of 1 year duration Analysis was by intention-to-treat. It was not stated whether concomitant medication continued. No run-in period was applied. Participants were randomised on return of the questionnaire within 4 weeks.
Participants	155 participants were recruited from 13 hospitals across the Netherlands. N = 155 101 m, 54 f Mean age 66 years 91% European descent **Inclusion criteria:** 1. 40 years or older; 2. Confirmed COPD diagnosis by pulmonologist; 3. Vitamin D deficiency (25(OH)D < 50nmol/L) at screening; 4. Confirmed history of COPD exacerbation in last 12 months After screening, participants were included within 6 weeks, and a sample was taken at the first study visit. These samples were analysed at the end of the study using the LC MS/MS assay, considered the gold standard for vitamin D deficiency. A small number of participants demonstrated 25(OH)D levels > 50 nmol at this baseline visit, despite being below this threshold at initial screening. They were included and analysed in the study and this meta-analysis. **Exclusion criteria:** 1. Severe vitamin D deficiency < 15 nmol/L; 2. Use of supplements containing > 400 IU vitamin D per day
Interventions	**Active intervention** (n = 74): 16,800 IU tablet weekly **Control intervention** (n = 81): identical placebo regimen Mean serum 25(OH)D concentration: intervention arm: 38 nmol/L (baseline), control: 40 nmol/L (baseline) Mean FEV1 (% predicted), intervention arm: 50% (baseline), control: 50.3% (baseline)
Outcomes	**Primary outcome:** COPD exacerbation rate in 1 year **Secondary outcomes:** time to first and second exacerbation, time to first and second hospitalisation, use of antibiotics, use of oral corticosteroids, first and final visit FEV1, first and final visit FVC, absolute lung volume, residual volume, functional residual capacity, total lung capacity, maximal inspiratory and expiratory mouth pressure, 6-minute walking test, 3-metre walking test, chair-stands test, tandem test, hand grip strength, quality of life (stated, not reported), physical activity, plasma CRP, IL-6, LL37, nasal microbiome **Definition of exacerbation:** sustained worsening of respiratory symptoms (Antonisen criteria) during 48 hours requiring oral corticosteroid and/or antibiotic treatment that was initiated by a physician
Notes	Grant funding from the Lung Foundation Netherlands (project number: 5.1.13.033) and Almirall. Neither had any role in study design or analysis, with the grant received after the start of the trial. The authors declare that there is no conflict of interest.

Rafiq 2022 *(Continued)*

Authors provided additional unpublished data on outcomes included in the systematic review.

This study was co-authored by 2 authors of this review. None of these authors were involved in assessment of eligibility, data extraction, risk of bias or certainty of evidence for outcomes to which this study contributed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible participants were allocated in a 1:1 ratio. For randomisation, a sequential balancing method was used, with study centre as the first step in the balancing algorithm, followed by gender, age and current smoking status.
Allocation concealment (selection bias)	Low risk	Matching placebo used. Randomisation and preparation of study medication was performed by the pharmacy of Amsterdam University Medical Center.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, randomised, placebo-controlled trial. Blinding was continued until after the data analysis.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, randomised, placebo-controlled trial. Blinding was continued until after the data analysis.
Incomplete outcome data (attrition bias) All outcomes	Low risk	20/155 were lost to follow-up. Analysis was carried out by intention-to-treat, and then repeated per-protocol for the 135 participants who completed the study – results were consistent across both.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting. Quality of life measure was not presented in the results, but was provided on request. Trial protocol obtained at ClinicalTrials.gov NCT02122627.
Other bias	Low risk	No other biases identified.

Sanjari 2016

Study characteristics

Methods	Single-centre, double-blind, placebo-controlled randomised controlled trial of 7 days' duration, investigating effects of vitamin D in treating current COPD exacerbations Concomitant medication was continued. No run-in period was applied. Analysis was by intention-to-treat.
Participants	135 participants were recruited from the Emergency Department of Kerman Afzalipour University Hospital. They were randomised to 3 arms: vitamin D3, calcitriol or placebo in equal numbers. 91 m, 44 f Mean age 56.6 years **Inclusion criteria:** ex-smokers with a history of chronic cough and expectoration who also had exertional dyspnoea and were admitted with the diagnosis of COPD exacerbation and FEV1 < 88% predicted for men, or < 89% predicted for women

Sanjari 2016 *(Continued)*

	Exclusion criteria: unwillingness to participate in the study, unable to perform spirometry, a history of asthma symptoms, existence of other respiratory disorders including bronchial carcinoma, a history of hospitalisation (within 4 weeks) for COPD, any medical condition that needed more invasive respiratory support, symptoms of lower respiratory tract infection or other kinds of simultaneous systemic disease such as hypercalcaemia, renal failure, hyperparathyroidism, malignancy, history of renal stone, cardiac arrhythmia or participants who were using lithium
Interventions	**Active intervention** (n = 45) 50,000 IU daily for 7 days Calcitriol intervention (n = 45) 0.25 µg calcitriol daily for 7 days **Control intervention** (n = 45) placebo daily for 7 days Mean serum 25(OH)D concentration, vitamin D3 arm: 58.9 nmol/L (baseline), calcitriol: 54.9 nmol/L (baseline), control: 59.9 nmol/L (baseline) Mean FEV1 (% predicted), vitamin D3 arm: 46.3% (baseline), calcitriol: 45.3% (baseline), control: 46.7% (baseline)
Outcomes	**Primary outcomes:** expiratory flow volume (FEV1) and forced volume capacity curves (FVC) and Modified Medical Research Council (MMRC) dyspnoea scale, over 7 days **Secondary outcomes:** change in albumin, calcium, 25(OH)D, CRP **Definition of exacerbation:** "dramatic degradation of COPD symptoms (for example, the quantity and the color of phlegm or shortness of breath) that lasts for a couple of days"
Notes	Treatment trial rather than prevention trial, included as separate exploratory analysis. The authors declare that they have no competing interests. Funded by the vice chancellor and Physiology Research Center, Kerman University of Medical Sciences and Endocrine and Metabolism Research Center, Tehran University of Medical Sciences

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised by a computer-generated list to 3 equal groups. Participants were divided into 3 groups according to the balance blocked randomisation.
Allocation concealment (selection bias)	Low risk	Placebo-controlled; participants in each group received the same envelopes containing different drugs. The trial medications and placebo were prepared at a separate site, and then taken to the clinic every week.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and the physicians and epidemiologist were blinded to the treatment received.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial medications and placebo were prepared at a separate site, and then taken to the clinic every week. The randomisation schedule was thus concealed from all care providers, ward physicians and other research personnel.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3, 6 and 6 participants "were eliminated in groups A (placebo), B (vitamin D3) and C (calcitriol), respectively. In phone recall, all of eliminated patients were alive and improved clinically after one week but they did not participate in the last part of the study (Second PFT and Lab Tests) due to personal problems." Only included participants who completed the trial were included in their baseline characteristics analysis, thus we assessed this as unclear risk of bias.

Sanjari 2016 *(Continued)*

Selective reporting (reporting bias)	Low risk	No evidence of selective reporting. Trial protocol obtained at IRCT138712271774N1.
Other bias	Low risk	No other biases identified.

Zendedel 2015

Study characteristics	
Methods	Single-centre, double-blind, placebo-controlled randomised controlled trial of 6 months' duration Concomitant medication was continued. No run-in period was applied. Study does not state whether analysed by intention-to-treat or per protocol.
Participants	88 participants were recruited from Ashayer University Hospital, Khorramabad, Iran. They were randomised to 'oral vitamin D' or placebo in equal numbers. 60 m, 28 f 3 participants were under 45 years old, 31 were aged 45 to 60, and 54 were over 60 years old **Inclusion criteria:** severe or very severe COPD as defined by Global Initiative for Chronic Obstructive Lung Disease guidelines **Exclusion criteria:** none stated
Interventions	**Active intervention** (n = 44) 100,000 IU oral monthly for 6 months **Control intervention** (n = 44) placebo monthly for 6 months Mean serum 25(OH)D concentration not stated Mean FEV1 (% predicted), intervention arm: 34.6% (baseline), control: 34.4% (baseline)
Outcomes	**Primary outcome:** change in FEV1, over 6 months Number of COPD exacerbations in preceding 3 months as defined by Anthoniesen criteria: presence of 2 or more of the major symptoms (increase in sputum purulence, sputum volume or dyspnoea) or any of the major symptoms accompanied by any of the minor symptoms (increase in nasal discharge, wheeze, sore throat, cough or fever) for at least 2 consecutive days
Notes	No funding sources declared. Declarations of interest: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Simple random sampling method" stated, with no further detail provided.
Allocation concealment (selection bias)	Unclear risk	The participants were randomly allocated to receive 100,000 IU of vitamin D orally per month, or oral placebo monthly for 6 months. No detail on allocation concealment provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blinded, detail not stated

Zendedel 2015 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blinded, detail not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The published data on this study does not state whether any participants withdrew or were lost to follow-up. They also do not state the number of participants in each arm contributing to end-study data.
Selective reporting (reporting bias)	Low risk	Trial protocol obtained; no evidence of selective reporting. IRCT registration number: IRCT2012071810332N1 (irct.behdasht.gov.ir/trial/10842).
Other bias	High risk	The validity of the primary outcome depended on detailed recall of day-to-day symptoms without use of a diary at 2-month intervals.

5(OH)D: 25-hydroxy vitamin D; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; EQ5D: EuroQol- 5 Dimension quality of life measure; f: female; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: global initiative of chronic obstructive lung disease; IM: intramuscular; IU: international units; LASA: Longitudinal Ageing Study Amsterdam; LC MS/MS: liquid chromatography with tandem mass spectrometry; m: male; n: number; nmol: nanomol; SGRQ: St George's Respiratory Questionnaire; SPPB: Short Physical Performance Battery; µg: microgram.

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

Study	Reason for exclusion
EudraCT2014-001250-41	Ineligible study design, as intervention and control cohorts participated in resistance training programme alongside vitamin D supplementation.
IRCT20190810044500N12	Trial discontinued due to COVID-19 pandemic.
Mølmen 2021	Ineligible study design, as intervention and control cohorts participated in resistance training programme alongside vitamin D supplementation, meaning the effects of vitamin D could not be isolated.
NCT03679325	Ineligible study design, as intervention and control cohorts participated in whole body vibration programme alongside vitamin D supplementation.
Rutten 2015	Ineligible study design: conference abstract presenting observational data only, i.e. non-interventional study.

COVID-19: coronavirus disease 2019

Characteristics of studies awaiting classification *[ordered by study ID]*

Khan 2017

Methods	Abstract for a randomised controlled trial conducted at East Medical Ward Mayo Hospital Lahore from January to December 2015. Did not state whether this was a double-blind RCT, which was one of the inclusion criteria for studies. Authors did not respond to efforts to clarify.
Participants	120 patients
Interventions	**Intervention:** oral vitamin D intake of 2000 IU daily for 6 months **Control:** not stated

Khan 2017 *(Continued)*

Outcomes	FVC at baseline and at 6 months, exacerbation at baseline and at 6 months. Authors did not report data disaggregated between intervention and control arms that would be necessary for inclusion in meta-analysis, or provide this on request.
Notes	Not possible to assess eligibility as authors did not respond to our requests for more information.

FVC: forced vital capacity; IU: international units; RCT: randomised controlled trial.

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

Beijers 2022

Study name	Effect of targeted nutrient supplementation on physical activity and health-related quality of life in COPD: study protocol for the randomised controlled NUTRECOVER trial
Methods	Double-blinded randomised controlled trial of 12 months' duration **Location:** Maastricht University, Netherlands
Participants	166 participants with COPD from multiple hospitals in the Netherlands
Interventions	**Intervention**: daily multinutrient supplement, including vitamin D, tryptophan, long-chain polyunsaturated fatty acids and prebiotic dietary fibres **Control:** identical placebo
Outcomes	**Primary outcomes:** physical activity assessed by triaxial accelerometry, over 12 months; health-related quality of life measured by the EuroQol-5 dimensions questionnaire, over 12 months **Secondary outcomes:** cognitive function, psychological well-being, physical performance, participant-reported outcomes and the metabolic profile assessed by body composition, systemic inflammation, plasma nutrient levels, intestinal integrity and microbiome composition
Starting date	2022
Contact information	r.beijers@maastrichtuniversity.nl
Notes	No funders stated. No declarations of interest.

Gold 2016

Study name	Lung VITAL
Methods	Double-blind, randomised, placebo-controlled trial of 5 years duration, with an ancillary study of lung function over 2 years **Location:** United States (US)
Participants	1973 participants from 11 urban US centres
Interventions	2 × 2 factorial trial of supplementation with vitamin D3 2000 IU/day and marine omega-3 fatty acids (Omacor® fish oil, eicosapentaenoic acid +docosahexaenoic acid, 1 g/day)
Outcomes	**Primary outcomes:** primary prevention of cardiovascular disease and cancer

Gold 2016 *(Continued)*

	Secondary outcomes: pneumonia risk, respiratory exacerbation episodes, asthma control and lung function in adults
Starting date	2016
Contact information	Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, United States
Notes	5 year study duration, analysis ongoing. No declarations of interest reported. Funded by grants: • R01 CA138962/CA/NCI NIH HHS/United States • R01 HL101932/HL/NHLBI NIH HHS/United States • U01 CA138962/CA/NCI NIH HHS/United States • U01 CA13962/CA/NCI NIH HHS/United States

IRCT201402029014N23

Study name	IRCT201402029014N23
Methods	Double-blinded randomised controlled trial **Location:** Hamadan University of Medical Sciences, Iran
Participants	Target sample n = 136
Interventions	**Intervention:** oral vitamin D 50,000 IU weekly for 8 weeks **Control:** oral placebo weekly
Outcomes	FEV1, over 8 weeks; FVC, over 8 weeks
Starting date	2014
Contact information	Department of Epidemiology & Biostatistics Hamadan University of Medical Sciences
Notes	Ongoing, authors did not respond to efforts to obtain data. Funded by the vice-chancellor for Research and Technology, Hamadan University of Medical Sciences. No declarations of interest reported.

IRCT2016022826816N1

Study name	IRCT2016
Methods	Double-blind, placebo-controlled trial **Location:** Iran University of Medical Sciences
Participants	Target n = 66 COPD participants, including those with emphysema and chronic bronchitis with serum vitamin D-25 level less than 75 nmol/L
Interventions	**Intervention:** oral vitamin D supplementation weekly for 12 weeks

IRCT20160228826816N1 *(Continued)*

	Control: placebo supplementation weekly for 12 weeks
Outcomes	**Primary outcomes:** occurrence of COPD exacerbation, over 12 weeks **Secondary outcomes:** functional performance
Starting date	2016
Contact information	Iran University of Medical Sciences
Notes	Ongoing; authors did not respond to efforts to obtain data. Funded by the Iran University of Medical Sciences. No declarations of interest reported.

NCT03781895

Study name	NCT03781895
Methods	Double-blind randomised controlled trial **Location:** Dhaka, Bangladesh
Participants	46 vitamin D deficient participants with moderate COPD
Interventions	**Intervention:** 40,000 IU oral vitamin D3 weekly for 90 days **Control:** placebo weekly for 90 days
Outcomes	**Primary outcomes:** spirometry measures including FEV1, FVC, peak expiratory flow rate over 90 days **Secondary outcomes:** exercise tolerance including SpO2, 6-minute walk test
Starting date	2018
Contact information	Samia Hassan, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
Notes	Completed, not yet published. No funding reported. No declarations of interest reported.

25(OH)D: 25-hydroxy vitamin D; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; HHS: Department of Health and Human Services; IU: international units; n: number; NCI: National Cancer Institute; NHLBI: National Heart, Lung and Blood Institute; NIH: National Institutes of Health; ng: nanogram; nmol: nanomol; PImax: respiratory maximal inspiratory pressure; SpO2: oxygen saturations

DATA AND ANALYSES

Comparison 1. Vitamin D versus placebo

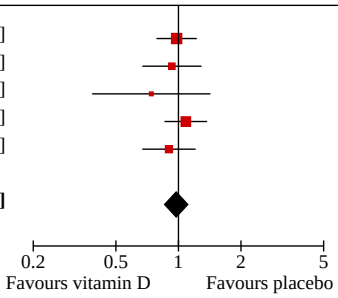
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Rate of moderate or severe exacerbations	5	980	Rate Ratio (IV, Random, 95% CI)	0.98 [0.86, 1.11]
1.2 Rate of moderate or severe exacerbations (stratified by baseline 25(OH)D)	5	975	Rate Ratio (IV, Random, 95% CI)	1.00 [0.88, 1.13]
1.2.1 Baseline 25(OH)D < 25 nmol/L	5	123	Rate Ratio (IV, Random, 95% CI)	0.68 [0.47, 0.99]
1.2.2 Baseline 25(OH)D 25 to 49.9 nmol/L	5	380	Rate Ratio (IV, Random, 95% CI)	0.98 [0.81, 1.18]
1.2.3 Baseline 25(OH)D 50 to 74.9 nmol/L	5	276	Rate Ratio (IV, Random, 95% CI)	0.96 [0.73, 1.26]
1.2.4 Baseline 25(OH)D ≥ 75 nmol/L	5	196	Rate Ratio (IV, Random, 95% CI)	1.37 [1.03, 1.84]
1.3 Rate of moderate or severe exacerbations (stratified by baseline FEV1, % predicted)	5	978	Rate Ratio (IV, Random, 95% CI)	0.99 [0.87, 1.13]
1.3.1 Baseline FEV1 < 50% predicted	5	319	Rate Ratio (IV, Random, 95% CI)	1.00 [0.84, 1.20]
1.3.2 Baseline FEV1 ≥ 50% predicted	5	659	Rate Ratio (IV, Random, 95% CI)	0.97 [0.80, 1.19]
1.4 Rate of moderate or severe exacerbations (stratified by baseline corticosteroid use)	5	980	Rate Ratio (IV, Random, 95% CI)	0.93 [0.82, 1.05]
1.4.1 Any baseline corticosteroid use	5	520	Rate Ratio (IV, Random, 95% CI)	0.92 [0.80, 1.06]
1.4.2 No baseline corticosteroid use	5	460	Rate Ratio (IV, Random, 95% CI)	0.97 [0.72, 1.29]
1.5 Proportion of participants experiencing one or more exacerbations (moderate or severe)	5	980	Odds Ratio (IV, Random, 95% CI)	0.94 [0.72, 1.24]
1.6 Time to first exacerbation	4	624	Hazard Ratio (IV, Random, 95% CI)	0.99 [0.81, 1.21]
1.7 Rate of severe exacerbation, requiring ED attendance or hospitalisation	4	622	Rate Ratio (IV, Random, 95% CI)	1.16 [0.78, 1.71]
1.8 Rate of moderate exacerbation	3	467	Rate Ratio (IV, Random, 95% CI)	0.85 [0.71, 1.03]
1.9 Incidence of study defined exacerbation	5	979	Rate Ratio (IV, Random, 95% CI)	0.96 [0.85, 1.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.10 Inter-arm difference in mean change in FEV1 (% predicted)	7	1063	Mean Difference (IV, Random, 95% CI)	2.82 [-2.42, 8.06]
1.11 Inter-arm difference in mean change in FVC (% predicted)	5	912	Mean Difference (IV, Random, 95% CI)	-1.31 [-4.44, 1.82]
1.12 Proportion of participants with one or more serious adverse event of any cause	5	663	Odds Ratio (M-H, Random, 95% CI)	1.19 [0.82, 1.71]
1.13 Mortality (all-cause)	6	1019	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.57, 2.21]
1.14 Mortality (all-cause), risk difference	6	1019	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.02, 0.03]
1.15 Mortality (respiratory)	5	864	Odds Ratio (M-H, Random, 95% CI)	1.26 [0.33, 4.87]
1.16 Mortality (respiratory), risk difference	5	864	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.01]

Analysis 1.1. Comparison 1: Vitamin D versus placebo, Outcome 1: Rate of moderate or severe exacerbations

Study or Subgroup	log[Rate Ratio]	SE	Vitamin D Total	Placebo Total	Weight	Rate Ratio IV, Random, 95% CI
Lehouck 2012[a]	-0.020203	0.114112	91	91	32.8%	0.98 [0.78 , 1.23]
Martineau 2015[a]	-0.072571	0.167125	122	118	15.3%	0.93 [0.67 , 1.29]
Rafiq 2017[a]	-0.301105	0.334489	22	25	3.8%	0.74 [0.38 , 1.43]
Camargo 2021[b]	0.081949	0.120788	200	156	29.3%	1.09 [0.86 , 1.38]
Rafiq 2022[c]	-0.105361	0.150793	74	81	18.8%	0.90 [0.67 , 1.21]
Total (95% CI)			**509**	**471**	**100.0%**	**0.98 [0.86 , 1.11]**

Heterogeneity: Tau² = 0.00; Chi² = 1.83, df = 4 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.38 (P = 0.70)
Test for subgroup differences: Not applicable

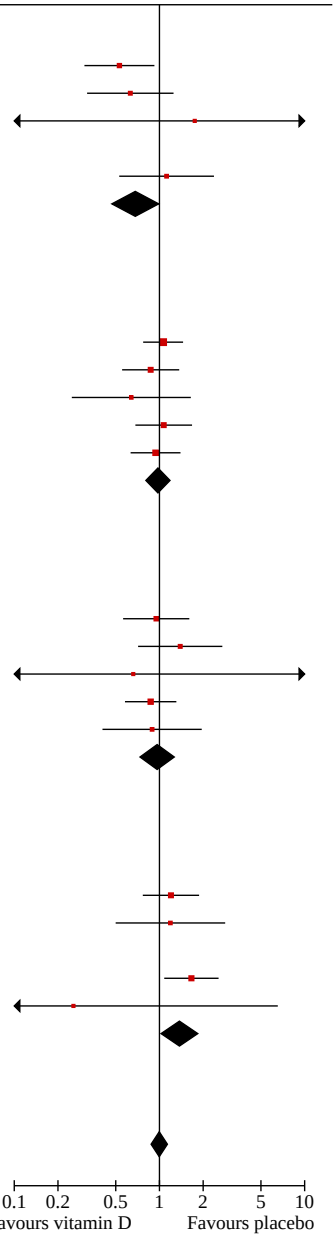


Footnotes

[a]Adjusted for age, sex, baseline COPD severity
[b]Adjusted for age, sex, ethnicity
[c]Adjusted for age, sex, study centre, smoking status

Analysis 1.2. Comparison 1: Vitamin D versus placebo, Outcome 2: Rate of moderate or severe exacerbations (stratified by baseline 25(OH)D)

Study or Subgroup	log[Rate Ratio]	SE	Vitamin D Total	Placebo Total	Weight	Rate Ratio IV, Random, 95% CI
1.2.1 Baseline 25(OH)D < 25 nmol/L						
Lehouck 2012[a]	-0.634878	0.283082	15	16	5.4%	0.53 [0.30 , 0.92]
Martineau 2015[a]	-0.462035	0.349636	29	21	3.5%	0.63 [0.32 , 1.25]
Rafiq 2017[a]	0.559616	1.537854	4	2	0.2%	1.75 [0.09 , 35.65]
Camargo 2021[b]	0	0	3	2		Not estimable
Rafiq 2022[c]	0.113329	0.383165	15	16	3.0%	1.12 [0.53 , 2.37]
Subtotal (95% CI)			**66**	**57**	**12.1%**	**0.68 [0.47 , 0.99]**
Heterogeneity: Tau² = 0.00; Chi² = 2.90, df = 3 (P = 0.41); I² = 0%						
Test for overall effect: Z = 2.02 (P = 0.04)						
1.2.2 Baseline 25(OH)D 25 to 49.9 nmol/L						
Lehouck 2012[a]	0.058269	0.161464	44	41	16.6%	1.06 [0.77 , 1.45]
Martineau 2015[a]	-0.139262	0.230954	49	49	8.1%	0.87 [0.55 , 1.37]
Rafiq 2017[a]	-0.446287	0.481404	12	19	1.9%	0.64 [0.25 , 1.64]
Camargo 2021[b]	0.067659	0.22921	33	42	8.3%	1.07 [0.68 , 1.68]
Rafiq 2022[c]	-0.061875	0.201876	43	48	10.6%	0.94 [0.63 , 1.40]
Subtotal (95% CI)			**181**	**199**	**45.6%**	**0.98 [0.81 , 1.18]**
Heterogeneity: Tau² = 0.00; Chi² = 1.47, df = 4 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.25 (P = 0.80)						
1.2.3 Baseline 25(OH)D 50 to 74.9 nmol/L						
Lehouck 2012[a]	-0.051293	0.267817	18	18	6.1%	0.95 [0.56 , 1.61]
Martineau 2015[a]	0.329304	0.340757	26	35	3.7%	1.39 [0.71 , 2.71]
Rafiq 2017[a]	-0.415515	2.19337	5	3	0.1%	0.66 [0.01 , 48.59]
Camargo 2021[b]	-0.139262	0.207849	91	57	10.0%	0.87 [0.58 , 1.31]
Rafiq 2022[c]	-0.116534	0.40149	11	12	2.7%	0.89 [0.41 , 1.95]
Subtotal (95% CI)			**151**	**125**	**22.6%**	**0.96 [0.73 , 1.26]**
Heterogeneity: Tau² = 0.00; Chi² = 1.47, df = 4 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.26 (P = 0.79)						
1.2.4 Baseline 25(OH)D ≥ 75 nmol/L						
Lehouck 2012[a]	0.182322	0.227718	14	16	8.4%	1.20 [0.77 , 1.88]
Martineau 2015[a]	0.173953	0.443108	18	13	2.2%	1.19 [0.50 , 2.84]
Rafiq 2017[a]	0	0	1	1		Not estimable
Camargo 2021[b]	0.506818	0.219803	72	55	9.0%	1.66 [1.08 , 2.55]
Rafiq 2022[c]	-1.364142	1.65359	3	3	0.2%	0.26 [0.01 , 6.53]
Subtotal (95% CI)			**108**	**88**	**19.7%**	**1.37 [1.03 , 1.84]**
Heterogeneity: Tau² = 0.00; Chi² = 2.23, df = 3 (P = 0.53); I² = 0%						
Test for overall effect: Z = 2.14 (P = 0.03)						
Total (95% CI)			**506**	**469**	**100.0%**	**1.00 [0.88 , 1.13]**
Heterogeneity: Tau² = 0.00; Chi² = 16.86, df = 17 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.05 (P = 0.96)						
Test for subgroup differences: Chi² = 8.79, df = 3 (P = 0.03), I² = 65.9%						



Footnotes

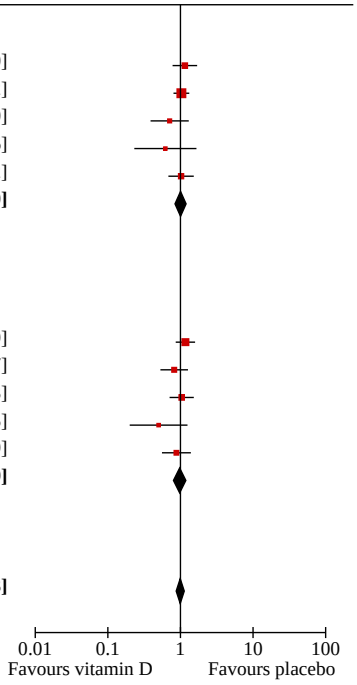
[a]Adjusted for age, sex, baseline COPD severity

[b]Adjusted for age, sex, ethnicity

[c]Adjusted for age, sex, study centre, smoking status

Analysis 1.3. Comparison 1: Vitamin D versus placebo, Outcome 3: Rate of moderate or severe exacerbations (stratified by baseline FEV1, % predicted)

Study or Subgroup	log[Rate Ratio]	SE	Vitamin D Total	Placebo Total	Weight	Rate Ratio IV, Random, 95% CI
1.3.1 Baseline FEV1 < 50% predicted						
Camargo 2021[a]	0.139762	0.198751	15	16	10.8%	1.15 [0.78 , 1.70]
Lehouck 2012[b]	0.029559	0.127751	63	62	26.1%	1.03 [0.80 , 1.32]
Martineau 2015[b]	-0.34249	0.309096	33	33	4.5%	0.71 [0.39 , 1.30]
Rafiq 2017[b]	-0.478036	0.502675	10	8	1.7%	0.62 [0.23 , 1.66]
Rafiq 2022[c]	0.019803	0.205201	38	41	10.1%	1.02 [0.68 , 1.52]
Subtotal (95% CI)			**159**	**160**	**53.2%**	**1.00 [0.84 , 1.20]**
Heterogeneity: Tau² = 0.00; Chi² = 2.69, df = 4 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.03 (P = 0.98)						
1.3.2 Baseline FEV1 ≥ 50% predicted						
Camargo 2021[a]	0.157004	0.156778	185	140	17.3%	1.17 [0.86 , 1.59]
Lehouck 2012[b]	-0.198451	0.222937	28	28	8.6%	0.82 [0.53 , 1.27]
Martineau 2015[b]	0.039221	0.19586	89	85	11.1%	1.04 [0.71 , 1.53]
Rafiq 2017[b]	-0.693147	0.467504	12	17	2.0%	0.50 [0.20 , 1.25]
Rafiq 2022[c]	-0.127833	0.233752	36	39	7.8%	0.88 [0.56 , 1.39]
Subtotal (95% CI)			**350**	**309**	**46.8%**	**0.97 [0.80 , 1.19]**
Heterogeneity: Tau² = 0.00; Chi² = 4.29, df = 4 (P = 0.37); I² = 7%						
Test for overall effect: Z = 0.25 (P = 0.80)						
Total (95% CI)			**509**	**469**	**100.0%**	**0.99 [0.87 , 1.13]**
Heterogeneity: Tau² = 0.00; Chi² = 7.01, df = 9 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.11 (P = 0.91)						
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.83), I² = 0%						



Footnotes

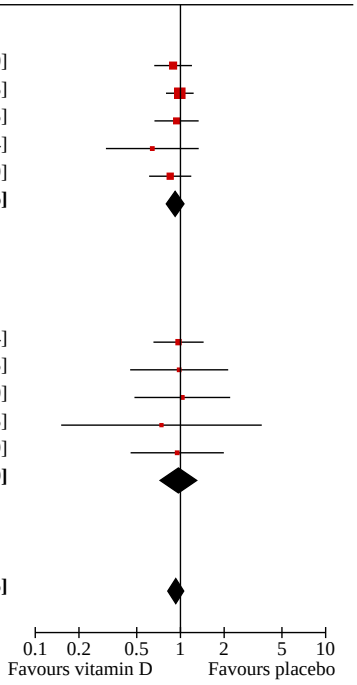
[a]Adjusted for age, sex, ethnicity

[b]Adjusted for age, sex, baseline COPD severity

[c]Adjusted for age, sex, study centre, smoking status

Analysis 1.4. Comparison 1: Vitamin D versus placebo, Outcome 4: Rate of moderate or severe exacerbations (stratified by baseline corticosteroid use)

Study or Subgroup	log[Rate Ratio]	SE	Vitamin D Total	Placebo Total	Weight	Rate Ratio IV, Random, 95% CI
1.4.1 Any baseline corticosteroid use						
Camargo 2021[a]	-0.116534	0.152512	44	26	17.8%	0.89 [0.66 , 1.20]
Lehouck 2012[b]	-0.01005	0.111802	75	75	33.1%	0.99 [0.80 , 1.23]
Martineau 2015[b]	-0.061875	0.178752	78	82	13.0%	0.94 [0.66 , 1.33]
Rafiq 2017[b]	-0.446287	0.375335	17	16	2.9%	0.64 [0.31 , 1.34]
Rafiq 2022[c]	-0.162519	0.170475	57	50	14.2%	0.85 [0.61 , 1.19]
Subtotal (95% CI)			**271**	**249**	**81.0%**	**0.92 [0.80 , 1.06]**
Heterogeneity: Tau² = 0.00; Chi² = 1.64, df = 4 (P = 0.80); I² = 0%						
Test for overall effect: Z = 1.18 (P = 0.24)						
1.4.2 No baseline corticosteroid use						
Camargo 2021[a]	-0.030459	0.202919	156	130	10.0%	0.97 [0.65 , 1.44]
Lehouck 2012[b]	-0.020203	0.396596	16	16	2.6%	0.98 [0.45 , 2.13]
Martineau 2015[b]	0.029559	0.387219	44	36	2.8%	1.03 [0.48 , 2.20]
Rafiq 2017[b]	-0.301105	0.811451	5	9	0.6%	0.74 [0.15 , 3.63]
Rafiq 2022[c]	-0.051293	0.377175	17	31	2.9%	0.95 [0.45 , 1.99]
Subtotal (95% CI)			**238**	**222**	**19.0%**	**0.97 [0.72 , 1.29]**
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 4 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.22 (P = 0.83)						
Total (95% CI)			**509**	**471**	**100.0%**	**0.93 [0.82 , 1.05]**
Heterogeneity: Tau² = 0.00; Chi² = 1.88, df = 9 (P = 0.99); I² = 0%						
Test for overall effect: Z = 1.16 (P = 0.25)						
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%						

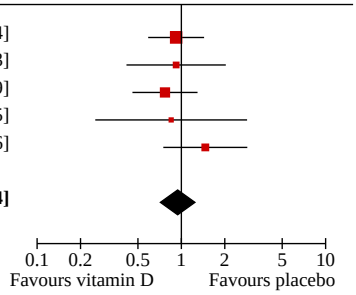


Footnotes

[a]Adjusted for age, sex, ethnicity
[b]Adjusted for age, sex, baseline COPD severity
[c]Adjusted for age, sex, study centre, smoking status

Analysis 1.5. Comparison 1: Vitamin D versus placebo, Outcome 5: Proportion of participants experiencing one or more exacerbations (moderate or severe)

Study or Subgroup	log[Odds Ratio]	SE	Vitamin D Total	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
Camargo 2021[a]	-0.083382	0.227626	200	156	38.0%	0.92 [0.59 , 1.44]
Lehouck 2012[b]	-0.083382	0.404431	91	91	12.0%	0.92 [0.42 , 2.03]
Martineau 2015[b]	-0.261365	0.265029	122	118	28.0%	0.77 [0.46 , 1.29]
Rafiq 2017[b]	-0.162519	0.618132	22	25	5.2%	0.85 [0.25 , 2.85]
Rafiq 2022[c]	0.382165	0.34197	74	81	16.8%	1.47 [0.75 , 2.86]
Total (95% CI)			**509**	**471**	**100.0%**	**0.94 [0.72 , 1.24]**
Heterogeneity: Tau² = 0.00; Chi² = 2.29, df = 4 (P = 0.68); I² = 0%						
Test for overall effect: Z = 0.42 (P = 0.67)						
Test for subgroup differences: Not applicable						



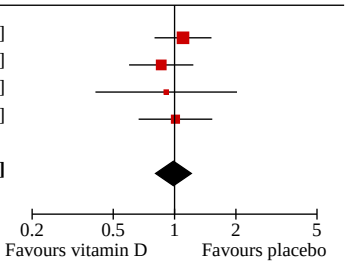
Footnotes

[a]Adjusted for age, sex, ethnicity
[b]Adjusted for age, sex, baseline COPD severity
[c]Adjusted for age, sex, study centre, smoking status

Analysis 1.6. Comparison 1: Vitamin D versus placebo, Outcome 6: Time to first exacerbation

Study or Subgroup	log[Hazard Ratio]	SE	Vitamin D Total	Placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
Lehouck 2012[a]	0.09531	0.164069	91	91	39.3%	1.10 [0.80 , 1.52]
Martineau 2015[a]	-0.150823	0.185191	122	118	30.9%	0.86 [0.60 , 1.24]
Rafiq 2017[a]	-0.094311	0.408077	22	25	6.4%	0.91 [0.41 , 2.02]
Rafiq 2022[b]	0.00995	0.212315	74	81	23.5%	1.01 [0.67 , 1.53]
Total (95% CI)			**309**	**315**	**100.0%**	**0.99 [0.81 , 1.21]**

Heterogeneity: Tau² = 0.00; Chi² = 1.04, df = 3 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.12 (P = 0.90)
Test for subgroup differences: Not applicable

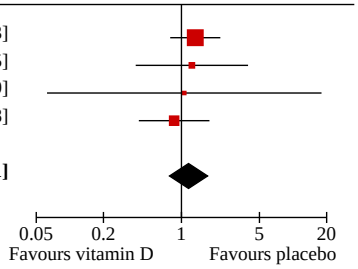


Footnotes
[a]Adjusted for age, sex, baseline COPD severity
[b]Adjusted for age, sex, study centre, smoking status

Analysis 1.7. Comparison 1: Vitamin D versus placebo, Outcome 7: Rate of severe exacerbation, requiring ED attendance or hospitalisation

Study or Subgroup	log[Rate Ratio]	SE	Vitamin D Total	Placebo Total	Weight	Rate Ratio IV, Random, 95% CI
Lehouck 2012[a]	0.285179	0.263799	91	89	57.6%	1.33 [0.79 , 2.23]
Martineau 2015[a]	0.215111	0.5913	122	118	11.5%	1.24 [0.39 , 3.95]
Rafiq 2017[a]	0.058269	1.444659	22	25	1.9%	1.06 [0.06 , 17.99]
Rafiq 2022[b]	-0.150823	0.371668	74	81	29.0%	0.86 [0.42 , 1.78]
Total (95% CI)			**309**	**313**	**100.0%**	**1.16 [0.78 , 1.71]**

Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 3 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.73 (P = 0.47)
Test for subgroup differences: Not applicable

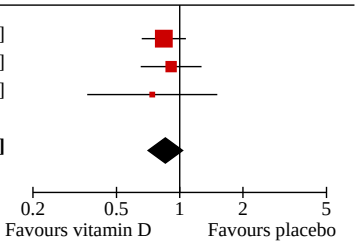


Footnotes
[a]Adjusted for age, sex, baseline COPD severity
[b]Adjusted for age, sex, study centre, smoking status

Analysis 1.8. Comparison 1: Vitamin D versus placebo, Outcome 8: Rate of moderate exacerbation

Study or Subgroup	log[Rate Ratio]	SE	Vitamin D Total	Placebo Total	Weight	Rate Ratio IV, Random, 95% CI
Lehouck 2012[a]	-0.1744	0.1235	91	89	60.9%	0.84 [0.66 , 1.07]
Martineau 2015[a]	-0.0943	0.1701	122	118	32.1%	0.91 [0.65 , 1.27]
Rafiq 2017[a]	-0.3011	0.3639	22	25	7.0%	0.74 [0.36 , 1.51]
Total (95% CI)			**235**	**232**	**100.0%**	**0.85 [0.71 , 1.03]**

Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 2 (P = 0.86); I² = 0%
Test for overall effect: Z = 1.64 (P = 0.10)
Test for subgroup differences: Not applicable

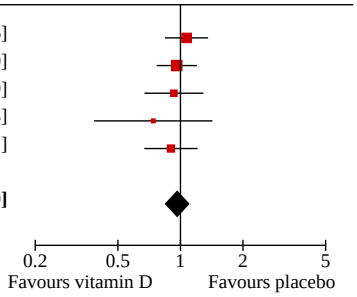


Footnotes
[a]Adjusted for age, sex, baseline COPD severity

Analysis 1.9. Comparison 1: Vitamin D versus placebo, Outcome 9: Incidence of study defined exacerbation

Study or Subgroup	log[Rate Ratio]	SE	Vitamin D Total	Placebo Total	Weight	Rate Ratio IV, Random, 95% CI
Camargo 2021[a]	0.067659	0.12177	200	156	28.9%	1.07 [0.84 , 1.36]
Lehouck 2012[b]	-0.0408	0.1139	91	90	33.0%	0.96 [0.77 , 1.20]
Martineau 2015[b]	-0.0726	0.1669	122	118	15.4%	0.93 [0.67 , 1.29]
Rafiq 2017[b]	-0.301105	0.334489	22	25	3.8%	0.74 [0.38 , 1.43]
Rafiq 2022[c]	-0.105361	0.150793	74	81	18.8%	0.90 [0.67 , 1.21]
Total (95% CI)			**509**	**470**	**100.0%**	**0.96 [0.85 , 1.10]**

Heterogeneity: Tau² = 0.00; Chi² = 1.61, df = 4 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.56 (P = 0.58)
Test for subgroup differences: Not applicable

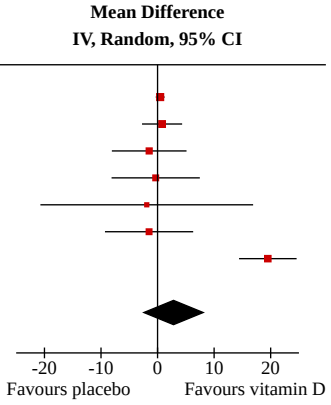


Footnotes
[a]Adjusted for age, sex, ethnicity
[b]Adjusted for age, sex, baseline COPD severity
[c]Adjusted for age, sex, study centre, smoking status

Analysis 1.10. Comparison 1: Vitamin D versus placebo, Outcome 10: Inter-arm difference in mean change in FEV1 (% predicted)

Study or Subgroup	Mean Difference	SE	Vitamin D Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Alavi Foumani 2019	0.46	0.398074	31	32	19.1%	0.46 [-0.32 , 1.24]
Camargo 2021	0.8	1.808648	200	156	17.6%	0.80 [-2.74 , 4.34]
Lehouck 2012	-1.48	3.367614	82	87	14.7%	-1.48 [-8.08 , 5.12]
Martineau 2015	-0.33	3.981391	89	100	13.4%	-0.33 [-8.13 , 7.47]
Rafiq 2017	-1.91	9.595611	19	24	5.5%	-1.91 [-20.72 , 16.90]
Rafiq 2022	-1.5	3.978839	74	81	13.4%	-1.50 [-9.30 , 6.30]
Zendedel 2015	19.5	2.595587	44	44	16.2%	19.50 [14.41 , 24.59]
Total (95% CI)			**539**	**524**	**100.0%**	**2.82 [-2.42 , 8.06]**

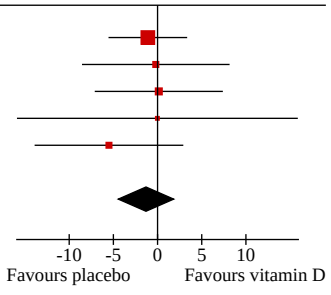
Heterogeneity: Tau² = 37.35; Chi² = 53.58, df = 6 (P < 0.00001); I² = 89%
Test for overall effect: Z = 1.06 (P = 0.29)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Vitamin D versus placebo, Outcome 11: Inter-arm difference in mean change in FVC (% predicted)

Study or Subgroup	Mean Difference	SE	Vitamin D Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Camargo 2021	-1.1	2.270356	200	156	49.5%	-1.10 [-5.55 , 3.35]
Lehouck 2012	-0.2	4.260323	82	87	14.1%	-0.20 [-8.55 , 8.15]
Martineau 2015	0.14	3.697936	89	100	18.7%	0.14 [-7.11 , 7.39]
Rafiq 2017	-0.02	8.10787	19	24	3.9%	-0.02 [-15.91 , 15.87]
Rafiq 2022	-5.5	4.292763	74	81	13.9%	-5.50 [-13.91 , 2.91]
Total (95% CI)			**464**	**448**	**100.0%**	**-1.31 [-4.44 , 1.82]**

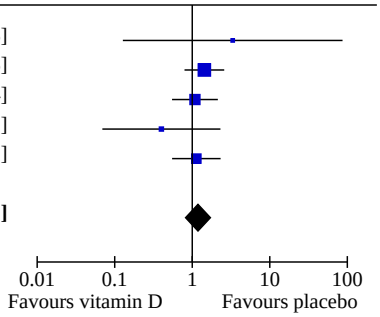
Heterogeneity: Tau² = 0.00; Chi² = 1.21, df = 4 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1: Vitamin D versus placebo, Outcome 12: Proportion of participants with one or more serious adverse event of any cause

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Bjerk 2013	1	19	0	20	1.3%	3.32 [0.13 , 86.75]
Lehouck 2012	56	91	48	91	38.9%	1.43 [0.79 , 2.58]
Martineau 2015	21	122	19	118	29.3%	1.08 [0.55 , 2.14]
Rafiq 2017	2	22	5	25	4.4%	0.40 [0.07 , 2.31]
Rafiq 2022	20	74	20	81	26.1%	1.13 [0.55 , 2.32]
Total (95% CI)		**328**		**335**	**100.0%**	**1.19 [0.82 , 1.71]**
Total events:	100		92			

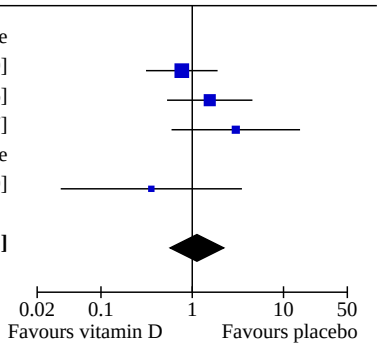
Heterogeneity: Tau² = 0.00; Chi² = 2.34, df = 4 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.91 (P = 0.36)
Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1: Vitamin D versus placebo, Outcome 13: Mortality (all-cause)

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Bjerk 2013	0	19	0	20		Not estimable
Camargo 2021	10	200	10	156	43.2%	0.77 [0.31 , 1.90]
Lehouck 2012	9	91	6	91	32.6%	1.55 [0.53 , 4.56]
Martineau 2015	6	122	2	118	15.9%	3.00 [0.59 , 15.17]
Rafiq 2017	0	22	0	25		Not estimable
Rafiq 2022	1	74	3	81	8.3%	0.36 [0.04 , 3.50]
Total (95% CI)		**528**		**491**	**100.0%**	**1.13 [0.57 , 2.21]**
Total events:	26		21			

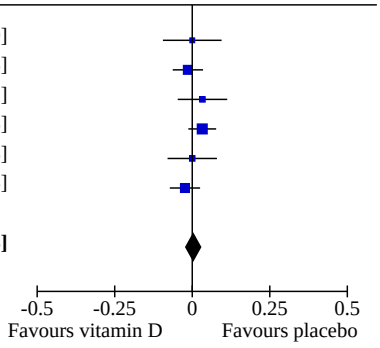
Heterogeneity: Tau² = 0.06; Chi² = 3.41, df = 3 (P = 0.33); I² = 12%
Test for overall effect: Z = 0.34 (P = 0.73)
Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1: Vitamin D versus placebo, Outcome 14: Mortality (all-cause), risk difference

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
Bjerk 2013	0	19	0	20	6.4%	0.00 [-0.09 , 0.09]
Camargo 2021	10	200	10	156	23.8%	-0.01 [-0.06 , 0.03]
Lehouck 2012	9	91	6	91	8.9%	0.03 [-0.05 , 0.11]
Martineau 2015	6	122	2	118	28.2%	0.03 [-0.01 , 0.08]
Rafiq 2017	0	22	0	25	9.0%	0.00 [-0.08 , 0.08]
Rafiq 2022	1	74	3	81	23.8%	-0.02 [-0.07 , 0.03]
Total (95% CI)		**528**		**491**	**100.0%**	**0.00 [-0.02 , 0.03]**
Total events:	26		21			

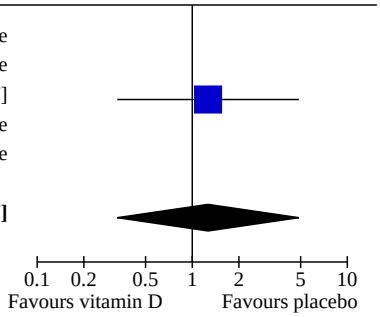
Heterogeneity: Tau² = 0.00; Chi² = 3.81, df = 5 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.25 (P = 0.80)
Test for subgroup differences: Not applicable



Analysis 1.15. Comparison 1: Vitamin D versus placebo, Outcome 15: Mortality (respiratory)

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Bjerk 2013	0	19	0	20		Not estimable
Camargo 2021	0	200	0	156		Not estimable
Lehouck 2012	5	91	4	91	100.0%	1.26 [0.33 , 4.87]
Martineau 2015	0	122	0	118		Not estimable
Rafiq 2017	0	22	0	25		Not estimable
Total (95% CI)		**454**		**410**	**100.0%**	**1.26 [0.33 , 4.87]**
Total events:	5		4			

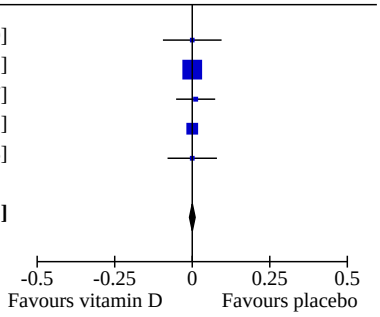
Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.73)
Test for subgroup differences: Not applicable



Analysis 1.16. Comparison 1: Vitamin D versus placebo, Outcome 16: Mortality (respiratory), risk difference

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
Bjerk 2013	0	19	0	20	0.9%	0.00 [-0.09 , 0.09]
Camargo 2021	0	200	0	156	64.8%	0.00 [-0.01 , 0.01]
Lehouck 2012	5	91	4	91	2.0%	0.01 [-0.05 , 0.07]
Martineau 2015	0	122	0	118	31.0%	0.00 [-0.02 , 0.02]
Rafiq 2017	0	22	0	25	1.3%	0.00 [-0.08 , 0.08]
Total (95% CI)		**454**		**410**	**100.0%**	**0.00 [-0.01 , 0.01]**
Total events:	5		4			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.32$, df = 4 (P = 0.99); $I^2 = 0\%$
Test for overall effect: Z = 0.05 (P = 0.96)
Test for subgroup differences: Not applicable



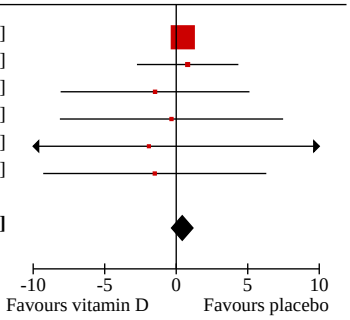
Comparison 2. Sensitivity analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Inter-arm difference in mean change in FEV1 (% predicted), excluding studies at high risk of bias	6	975	Mean Difference (IV, Random, 95% CI)	0.42 [-0.33, 1.17]

Analysis 2.1. Comparison 2: Sensitivity analyses, Outcome 1: Inter-arm difference in mean change in FEV1 (% predicted), excluding studies at high risk of bias

Study or Subgroup	Mean Difference	SE	Vitamin D Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Alavi Foumani 2019	0.46	0.398074	31	32	92.2%	0.46 [-0.32 , 1.24]
Camargo 2021	0.8	1.808648	200	156	4.5%	0.80 [-2.74 , 4.34]
Lehouck 2012	-1.48	3.367614	82	87	1.3%	-1.48 [-8.08 , 5.12]
Martineau 2015	-0.33	3.981391	89	100	0.9%	-0.33 [-8.13 , 7.47]
Rafiq 2017	-1.91	9.595611	19	24	0.2%	-1.91 [-20.72 , 16.90]
Rafiq 2022	-1.5	3.978839	74	81	0.9%	-1.50 [-9.30 , 6.30]
Total (95% CI)			**495**	**480**	**100.0%**	**0.42 [-0.33 , 1.17]**

Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 5 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.10 (P = 0.27)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Definitions of asthma exacerbation used in primary trials

Study	Definition of exacerbation
Alavi Foumani 2019	Exacerbation not defined in published text
Camargo 2021	Any prescription of oral corticosteroids more than 20 days apart for a short period (e.g. several days)
Lehouck 2012	Sustained worsening of respiratory symptoms during 48 hours and requiring oral corticosteroid, antibiotic or combination treatment
Martineau 2015	The occurrence of at least 2 major COPD symptoms (dyspnoea, sputum volume or sputum purulence), or 1 major COPD symptom and at least 1 minor COPD symptom (increase in nasal congestion or discharge, wheeze, sore throat or cough), during at least 2 days consecutively
Rafiq 2017	The presence, for at least 2 consecutive days, of an increase in any 2 major symptoms (dyspnoea, sputum purulence, sputum amount) or an increase in 1 major and 1 minor symptom (wheeze, sore throat, cough, symptoms of a common cold)
Rafiq 2022	Sustained worsening of respiratory symptoms (Antonisen criteria) during 48 hours requiring oral corticosteroid and/or antibiotic treatment that was initiated by a physician
Zendedel 2015	The presence of 2 or more of these major symptoms (increase in sputum purulence, sputum volume or dyspnoea) or any of the major symptoms accompanied by any of the minor symptoms (increase in nasal discharge, wheeze, sore throat, cough or fever) for at least 2 consecutive days

COPD: chronic obstructive pulmonary disease.

Table 2. Sensitivity analysis: random-effects versus fixed-effect models

Analysis	Random-effects model	Fixed-effect model
Rate ratio of moderate or severe AECOPD	RR 0.98, 95% CI 0.86 to 1.11	RR 0.98, 95% CI 0.86 to 1.11

Table 2. Sensitivity analysis: random-effects versus fixed-effect models *(Continued)*

Proportion of participants experiencing one or more exacerbations (moderate or severe)	OR 0.94, 95% CI 0.71 to 1.24	OR 0.94, 95% CI 0.71 to 1.24
Inter-arm difference in mean change in FEV1 (% predicted)	MD 2.82 higher in intervention arm, 95% CI -2.42 to 8.06	MD 0.83 higher in intervention arm, 95% CI 0.08 to 1.57
Inter-arm difference in mean change in FEV1 (% predicted)(excluding trial at high risk of bias)	MD 0.42 higher in intervention arm, 95% CI -0.33 to 1.17	MD 0.42 higher in intervention arm, 95% CI -0.33 to 1.17
Proportion of participants with one or more serious adverse event of any cause	OR 1.19, 95% CI 0.82 to 1.71	OR 1.18, 95% CI 0.82 to 1.70
Deaths (all-cause)	OR 1.13, 95% CI 0.57 to 2.21	OR 1.12, 95% CI 0.62 to 2.03
Deaths (respiratory)	OR 1.26, 95% CI 0.33 to 4.87	OR 1.26, 95% CI 0.33 to 4.87

AECOPD: acute exacerbations of chronic obstructive pulmonary disease; CI: confidence interval; FEV1: forced expiratory volume (the amount of air that a person can force out of their lungs in 1 second); MD: mean difference; OR: odds ratio; RR: risk ratio.

APPENDICES

Appendix 1. Search strategy to identify relevant studies from the Cochrane Airways Trials Register

#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All
#2 MeSH DESCRIPTOR Bronchitis, Chronic
#3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
#4 COPD:MISC1
#5 (COPD OR COAD OR COBD OR AECOPD):TI,AB,KW
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 MeSH DESCRIPTOR Vitamin D Explode All
#8 MeSH DESCRIPTOR Vitamin D Deficiency Explode All
#9 vitamin* NEXT d*
#10 cholecalciferol
#11 ergocalciferol
#12 Calcitriol
#13 alfacalcidol
#14 Calcifediol
#15 calcidiol
#16 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#17 #6 and #16

Appendix 2. Sources and search methods for core databases

Electronic searches: core databases

Database	Dates searched
Airways Register (via the Cochrane Register of Studies (CRS))	From inception to 24 August 2022
CENTRAL (via the CRS)	From inception to 24 August 2022
MEDLINE (Ovid)	1946 to 24 August 2022
Embase (Ovid)	1974 to 24 August 2022

(Continued)

Clinicaltrial.gov	From inception to 24 August 2022
WHO trials portal	From inception to 24 August 2022
ISRCTN registry	From inception to 23 December 2023
Australian New Zealand Clinical Trials Registry	From inception to 23 December 2023
UMIN Clinical Trials Registry	From inception to 23 December 2023

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 to Jan 2023
American Thoracic Society (ATS)	2001 to Jan 2023
Asia Pacific Society of Respirology (APSR)	2004 to Jan 2023
British Thoracic Society Winter Meeting (BTS)	2000 to Jan 2023
Chest Meeting	2003 to Jan 2023
European Respiratory Society (ERS)	1992, 1994, 2000 to Jan 2023
International Primary Care Respiratory Group Congress (IPCRG)	2002 to Jan 2023
Thoracic Society of Australia and New Zealand (TSANZ)	1999 to Jan 2023

CENTRAL search strategy

#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All
#2 MeSH DESCRIPTOR Bronchitis, Chronic
#3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
#4 COPD:MISC1
#5 (COPD OR COAD OR COBD OR AECOPD):TI,AB,KW
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 MeSH DESCRIPTOR Vitamin D Explode All
#8 MeSH DESCRIPTOR Vitamin D Deficiency Explode All
#9 vitamin* NEXT d*
#10 cholecalciferol
#11 ergocalciferol
#12 Calcitriol
#13 alfacalcidol
#14 Calcifediol
#15 calcidiol
#16 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#17 #6 and #16

MEDLINE (Ovid) search strategy

COPD search (MEDLINE)

1 Lung Diseases, Obstructive/
2 exp Pulmonary Disease, Chronic Obstructive/
3 (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).tw.
4 (COPD or AECOPD or AECB).ti,ab.
5 or/1-4
6 exp Vitamin D/
7 exp Vitamin D Deficiency/
8 vitamin d$.tw.
9 cholecalciferol.tw.
10 ergocalciferol.tw.
11 Calcitriol.tw.
12 alfacalcidol.tw.
13 Calcifediol.tw.
14 calcidiol.tw.
15 or/6-14
16 5 and 15
17 (controlled clinical trial or randomized controlled trial).pt.
18 (randomized or randomised).ab,ti.
19 placebo.ab,ti.
20 dt.fs.
21 randomly.ab,ti.
22 trial.ab,ti.
23 groups.ab,ti.
24 or/17-23
25 Animals/
26 Humans/
27 25 not (25 and 26)
28 24 not 27
29 16 and 28
30 from 29 keep 1-145

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

Embase search strategy

1	exp chronic obstructive lung disease/
2	obstructive airway disease/
3	(obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).tw.
4	(COPD or AECOPD or AECB).tw.
5	or/1-4
6	exp vitamin d/
7	exp vitamin D deficiency/
8	cholecalciferol.tw.
9	ergocalciferol.tw.
10	Calcitriol.tw.
11	alfacalcidol.tw.
12	Calcifediol.tw.

(Continued)

13	calcidiol.tw.
14	or/6-13
15	4 and 14
16	Randomized Controlled Trial/
17	randomization/
18	controlled clinical trial/
19	Double Blind Procedure/
20	Single Blind Procedure/
21	Crossover Procedure/
22	(clinica$ adj3 trial$).tw.
23	((singl$ or doubl$ or trebl$ or tripl$) adj3 (mask$ or blind$ or method$)).tw.
24	exp Placebo/
25	placebo$.ti,ab.
26	random$.ti,ab.
27	((control$ or prospectiv$) adj3 (trial$ or method$ or stud$)).tw.
28	(crossover$ or cross-over$).ti,ab.
29	or/16-28
30	exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
31	human/ or normal human/ or human cell/
32	30 and 31
33	30 not 32
34	29 not 33
35	15 and 34

CT.gov search strategy

Field	Search terms
condition	COPD

(Continued)

Intervention	Vitamin D OR cholecalciferol OR ergocalciferol OR Calcitriol OR alfacalcidol OR Calcifediol OR calcidiol
Study type	interventional

WHO portal search strategy

Field	Search terms
Condition	COPD
Intervention	Vitamin D OR cholecalciferol OR ergocalciferol OR Calcitriol OR alfacalcidol OR Calcifediol OR calcidiol

HISTORY

Protocol first published: Issue 3, 2019

CONTRIBUTIONS OF AUTHORS

Adrian R Martineau (ARM), David Jolliffe (DJ), Aziz Sheikh (AS), Wim Janssens (WJ) and Christopher J Griffiths (CJG) were involved in the conception and design of the review.

Anne Williamson (AW), ARM and DJ were involved in co-ordination of the review and searches.

AW, AS, CJG, DJ and ARM assessed the eligibility of trials for inclusion, and AW, AS, CJG and ARM performed assessments of risk of bias.

John Sluyter (JS), AW, ARM, CJG and DJ extracted data from published and unpublished text.

AW entered data into Review Manager 5.4 for statistical analysis, which ARM, DJ and JS cross-checked.

AW, AS, CJG, JS and ARM performed assessments of the certainty of evidence.

Renate de Jongh (RdJ), Rachida Rafiq (RR), DJ, JS and WJ provided individual participant data and/or study meta-data, and contributed to statistical analysis.

AW drafted the manuscript, and ARM, CJG, AS, JS, RdJ and RR commented on it.

All review authors contributed to interpretation of data, critically evaluated the manuscript for important intellectual content and gave final approval of the version to be published.

AW is the guarantor of the review.

DECLARATIONS OF INTEREST

AW: works as a junior doctor at Guy's and St Thomas' Foundation Trust.

ARM declares speaker fees from Linus Pauling Institute (personal payment); consulting fees from DSM Nutritional Products (personal payment); grants from Cytoplan, DSM Nutritional Products Ltd, Hyphens Pharma Ltd, Pharma Nord Ltd, Synergy Biologics and Thornton & Ross Ltd (all paid to institution); and travel expenses from Abiogen Pharma Ltd and Pharma Nord Ltd (both paid to institution). 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), London School of Hygiene and Tropical Medicine, and the Trial of Vitamin D and Zinc Supplementation for Improving Treatment Outcomes Among COVID-19 Patients in India (NCT04641195), Harvard School of Public Health (both paid to institution). ARM also declares unpaid work as a Programme Committee member for the Vitamin D Workshop. ARM declares that he has given opinions on the topic in multiple interviews in printed and broadcast media. Lastly, ARM declares being involved in two studies eligible for inclusion in the review. The first, Martineau 2015, was funded by NIHR and sponsored by Queen Mary University of London*. This study was assessed by AW and JS for eligibility, data extraction and risk of bias, and by AW and AS

for certainty of evidence**. The second, Camargo 2021, was funded by the Health Research Council of New Zealand* and assessed by AW and CJG for inclusion, data extraction and risk of bias, and by AW and AS for certainty of evidence**.

DJ: investigator on a study included in the review (Martineau 2015); the study was funded by the NIHR and sponsored by Queen Mary University of London*. This study was assessed by AW and JS for eligibility, data extraction and risk of bias, and by AW and AS for certainty of evidence**.

AS: works as a Consultant in Paediatric Allergy.

WJ works as a health professional at KU Leuven. WJ declares having received grants, consultancy fees and payments for advisory board activities from Astra Zeneca, Chiesi and Boehringer Ingelheim (none of whom manufacture or distribute vitamin D), all paid to his institution (KU Leuven). WJ declares that he was involved in a study eligible for inclusion in the review (Lehouck 2012); the study was funded by FWO Vlaanderen*, paid to KU Leuven. This study was assessed by AW and ARM for inclusion, data extraction, risk of bias and certainty of evidence**.

JS: declares that he was involved in the analysis and publication of the ViDA study (Camargo 2021), which is included in the review; the study was funded by the Health Research Council of New Zealand*. This study was assessed by AW and CJS for inclusion, data extraction, risk of bias and certainty of evidence**.

RR: declares that she was involved in the Rafiq 2017 study included in the review, which had no specific funding sources. She was also involved in the Rafiq 2022 study included in the review; this study was funded by a grant from the Lung Foundation, Netherlands (project number 5.1.13.033) and an unrestricted grant from Almirall (who do not manufacture vitamin D)*. These two studies were assessed by AW and ARM for inclusion, data extraction, risk of bias and certainty of evidence**.

RdJ: declares speaker fees from Amgen (personal payment) and a grant from Takeda Pharmaceutical Company (paid to institution; however, she has control over the funds) for a pharmacy-initiated study (SHP634-401) on which she is principal investigator; neither of these companies manufacture or distribute vitamin D. RdJ also declares writing assistance from Faes Farma SA, who produce calcifediol (paid to institution). Further, RdJ declares that she was the principal investigator on two RCTs included in this Cochrane review. The first, Rafiq 2017, had no specific funding sources. The second, Rafiq 2022, was funded by a grant from the Lung Foundation, Netherlands (project number 5113033) and an unrestricted grant from Almirall (who do not manufacture vitamin D)*. These two studies were assessed by AW and ARM for inclusion, data extraction, risk of bias and certainty of evidence**.

CJG: is supported by the National Institute for Health Research ARC North Thames; the views expressed in this publication are those of the author(s) and not necessarily those of the National Institute for Health Research or the Department of Health and Social Care. CJG is a collaborator on the Genes & Health study, which is funded by Alnylam Pharmaceuticals, Genomics PLC; and a Life Sciences Industry Consortium of AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Maze Therapeutics, Merck Sharp and Dohme, Novo Nordisk, Pfizer and Takeda Development Center Americas Inc (none of whom produce or distribute vitamin D or cholecalciferol), all paid to institution. CJG received funds to enable his institution to host an academic conference on the clinical aspects of vitamin D. CJG declares that he was a trialist on a study eligible for inclusion in the review (Martineau 2015); the study was funded by NIHR*. This study was assessed by AW and JS for eligibility, data extraction and risk of bias, and by AW and AS for certainty of evidence**.

*For each study with declared funders, the funders played no role in the design, conduct or publication of the research.

**To minimise the risk of bias, authors who were investigators on any study to be included in the review were not involved in the decision about eligibility, nor did they extract data, or assess the risk of bias for that study or GRADE the overall certainty of outcomes to which the study contributed. These tasks were performed by two independent review authors.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Search

The protocol listed three additional databases, PsycINFO, CINAHL and AMED, which could not be searched for this review. These databases were previously included in the Cochrane Airways Register Group searches. However, due to the closure of this group, we were unable to confirm whether these databases were included or to repeat the search. This raises a potential gap in the search. However, we carried out our search strategy across all other pre-specified databases, which also include psychology, allied health and nursing sources, and checked the references of existing studies and other systematic reviews.

Objectives

We have edited this section to summarise the overall objectives of the review: to assess the effects of vitamin D for the management of acute exacerbations and symptoms for people with COPD. The protocol stated each of the outcomes as Objectives, which are instead summarised under Methods.

Methods

- We added the clarification that trials in which vitamin D_3 or vitamin D_2 were administered only in combination with other micronutrients were excluded, as the specific effect of vitamin D could not be distinguished.
- We added clarification for studies reporting data over multiple time points. We used the time point furthest from the start in order to draw on all available data.
- Further details are provided under ‘Measures of treatment effect’: where individual participant data were provided, we calculated adjusted ratios adjusting for age, sex and baseline COPD severity. Where event rates but not rate ratios were not published, we calculated ratios manually from the stated event rates and participant years of follow-up, following Higgins 2022.
- Standardised mean differences were not used in contributing trials for relevant outcomes, so this methodology listed in the protocol was not applied.
- Risk of bias: we asked all authors to provide key data where not reported in the published results. We added the following, in line with GRADE methodology: "Where this is not possible, and the missing data are thought to introduce serious bias, we will take this into consideration in the GRADE rating for affected outcomes."
- We planned to resolve disagreements regarding the eligibility of studies for inclusion, or risk of bias assessment of eligible studies, by discussion as a first method of resolution. If this did not successfully reconcile any disagreement, we would have consulted a third author who would have come to an independent decision. However, there were no such disagreements.
- In the protocol, we pre-specified that if we were able to pool more than 10 studies, we would create and examine a funnel plot. As we did not pool more than 10 studies for any outcome, we instead added the following: “we followed the recommended approach and assessed for selective non-reporting amongst eligible studies and trial protocols.”

Outcomes

We analysed one pre-specified outcome, 'Mean difference in lung function (FEV_1 % predicted)', using the metric 'inter-arm difference in mean change in FEV1 (% predicted)'. This is because the protocol was not specific about which metric to use to compare this outcome, and this was the metric reported on most consistently across the included studies. Studies reporting on this outcome in another way were included narratively.

The published protocol stated that we would perform sensitivity analyses using fixed-effect models for outcomes where random-effects and fixed-effect models yielded different results. However, this would require anticipating where results would differ, so we pre-emptively conducted this sensitivity analysis for the primary outcome and all outcomes presented in the summary of findings table.

We also changed the outcomes included in the summary of findings table from the published protocol, from ‘Proportion of participants with one or more moderate AECOPD’ and ‘Proportion of participants with one or more severe AECOPD’ to the pooled outcome of ‘Proportion of participants with one or more moderate or severe AECOPD’ to focus on the outcome deemed most clinically relevant (as both moderate and severe AECOPD require medical treatment). However, we reported the full set of prespecified outcomes in the text.

Unused methods

Had there been disagreements regarding eligibility of studies for inclusion, data extraction, risk of bias assessment of eligible studies and grading of the certainty of the evidence, we would have reconciled this disagreement through a third author coming to an independent decision. No such disagreements occurred.

If data had been expressed in unconventional units of analysis, we would have converted them to conventional units, liaising with the authors where required. If graphs had been presented without numerical values, we would have sought to obtain data from study authors, or extracted data values from these graphs if they had not responded.

If we had been able to pool more than 10 studies, we would have created and examined a funnel plot to explore possible small study and publication biases.

Had meta-analysis of dichotomous outcomes revealed a beneficial effect of allocation to vitamin D, we would have calculated the number needed to treat for an additional beneficial outcome (NNTB) using the Visual Rx NNT calculator (www.nntonline.net/visualrx). We similarly would have calculated the number needed to treat for an additional harmful outcome (NNTH), had meta-analysis of dichotomous outcomes revealed harmful effects of vitamin D.

We prespecified that we would also carry out the following subgroup analyses for the same outcome:

1. the dose of vitamin D administered (< 400 IU versus ≥ 400 IU daily equivalent);
2. the type of vitamin D or vitamin D metabolite administered (cholecalciferol versus ergocalciferol versus 25(OH)D versus 1,25(OH)2D); and
3. the frequency of administration (e.g. daily versus weekly/two-weekly versus less frequently administered intermittent bolus doses).

However, limitations of the available data (for example, where numbers of participants or events or both within a subgroup were small or where all studies administered the same type of vitamin D) precluded the conduct of such subgroup analyses.

We would also have conducted a sensitivity analysis excluding studies in which another intervention was given concurrently, had such studies been included in meta-analysis.

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; *Disease Progression; *Pulmonary Disease, Chronic Obstructive [drug therapy]; Quality of Life; *Randomized Controlled Trials as Topic; *Vitamin D [therapeutic use]; *Vitamin D Deficiency [complications] [drug therapy]; *Vitamins [therapeutic use]

MeSH check words

Humans