**Vitamin D to prevent exacerbations of COPD: systematic review and meta-analysis of individual participant data from randomised controlled trials**

**APPENDIX**

## Search Strategies

A. PubMed

*Cochrane Highly Sensitive Search Strategy for identifying randomized controlled trials*

#1. randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]

#2. animals [mh] NOT humans [mh]

#3. #1 NOT #2

*Terms specific to vitamin D*

#4. Vitamin D OR vitamin D2 OR vitamin D3 OR cholecalciferol OR ergocalciferol OR alphacalcidol OR alfacalcidol OR calcitriol OR paricalcitol OR doxerocalciferol

*Terms specific to chronic obstructive pulmonary disease*

#5 COPD OR chronic obstructive pulmonary disease OR emphysema

*Combination of terms to identify randomized controlled trials of vitamin D conducted in patients with asthma*

#3 AND #4 AND #5

B. EMBASE

*Terms for identifying randomized controlled trials*

#1 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
#2 random*:ab,ti OR placebo*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEXT/1 blind*):ab,ti OR trial:ti
#3. #1 OR #2

*Terms specific to vitamin D*

#4. vitamin AND d OR vitamin AND d2 OR vitamin AND d3 OR cholecalciferol OR ergocalciferol OR alphacalcidol OR alfacalcidol OR calcitriol OR paricalcitol OR doxerocalciferol

*Terms specific to chronic obstructive pulmonary disease*

#5. Chronic Obstructive Pulmonary Disease OR COPD OR COAD OR emphysema OR chronic bronchitis OR AECB OR AECOPD

*Combination of terms to identify randomized controlled trials of vitamin D conducted in patients with chronic obstructive pulmonary disease*

#3 AND #4 AND #5

C. Cochrane Central

*Terms specific to vitamin D*

#1. Vitamin D OR vitamin D2 OR vitamin D3 OR cholecalciferol OR ergocalciferol OR alphacalcidol OR alfacalcidol OR calcitriol OR paricalcitol OR doxerocalciferol

*Terms specific to chronic obstructive pulmonary disease*

#2. Chronic Obstructive Pulmonary Disease OR COPD OR COAD OR emphysema OR chronic bronchitis OR AECB OR AECOPD

*Combination of terms to identify randomised controlled trials of vitamin D conducted in patients with chronic obstructive pulmonary disease*

#1 AND #2

D. Web of Science

TS =(Vitamin D OR vitamin D2 OR vitamin D3 OR cholecalciferol OR ergocalciferol OR alphacalcidol OR alfacalcidol OR calcitriol OR paricalcitol OR doxerocalciferol) AND TS =( Chronic Obstructive Pulmonary Disease OR COPD OR COAD OR emphysema OR chronic bronchitis OR AECB OR AECOPD) AND TS =(placebo* or random* or clinical trial* or double blind* or single blind* or rct)

**Data Extraction and Quality Assurance**

We requested IPD from the principal investigator for each eligible trial, and the terms of collaboration were specified in a data transfer agreement, signed by representatives of the data provider and the recipient (Queen Mary University of London). Data were de-identified at source prior to transfer *via* email. On receipt, three investigators (DAJ, RLH and LG) assessed data integrity by performing internal consistency checks and by attempting to replicate results of the analysis for incidence of COPD exacerbations that was published in the trial report. We contacted study authors to obtain missing data and to resolve queries arising from these integrity checks. Once queries had been resolved, clean data were uploaded to the main study database, which was held in STATA IC version 12 (College Station, TX, USA).

We extracted data relating to study characteristics for the following variables: setting, eligibility criteria, details of intervention and control regimens and study duration. We extracted IPD for the following variables relating to baseline characteristics: age, sex, racial/ethnic origin, weight, height, serum 25(OH)D concentration, inhaled corticosteroid use, percent predicted forced expiratory volume in one second ($FEV_1$), percent predicted forced vital capacity (FVC), study allocation (vitamin D *vs* placebo) and genotype for single nucleotide polymorphisms (SNPs) in the genes encoding the vitamin D receptor (*VDR*, rs731236 and rs11568820) and the vitamin D binding protein (*DBP*, rs7041 and rs4588). Follow-up data were requested for the total number of COPD exacerbations requiring treatment with systemic corticosteroids or antibiotics, or both, and the time from the first dose of study medication to the first such COPD

exacerbation; the total number of COPD exacerbations resulting in emergency department attendance or hospitalisation, or both; occurrence of serious adverse events and potential adverse reactions to vitamin D supplementation (hypercalcemia or renal stones); serum 25(OH)D concentration at final follow-up; duration of participant follow-up; body-mass index (BMI) at final follow-up; and percent predicted $FEV_1$ and FVC at final follow-up.

**Risk of Bias Assessment for Individual Studies**

We used the Cochrane Collaboration Risk of Bias tool[1] to assess the following variables: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, completeness of outcome data, evidence of selective outcome reporting and other potential threats to validity. We assessed selectivity of reporting either by comparing study protocols against study reports[2] or by specifically asking study authors whether all pre-specified outcomes were reported.[3,4] ARM and DAJ assessed the quality of the trials by Lehouck and colleagues,[3] Rafiq and colleagues[4] and Zendedel and colleagues,[5] and WJ and CM assessed the quality of the trial by Martineau and colleagues.[2] Discrepancies in quality assessments were resolved by consensus.

## RESULTS

**Appendix Table 1:** Baseline characteristics of participants in included trials by allocation

| | **Control group (n=235)** | **Intervention group (n=237)** |
|---|---|---|
| **Sex** | | |
| Male, n (%) | 155 (66.0) | 160 (67.5) |
| Female, n (%) | 80 (34.0) | 77 (32.5) |
| **Mean age, years (sd)** | 65.6 (8.5) | 65.8 (8.3) |
| **Ethnicity** | | |
| White European, n (%) | 229 (97.4) | 229 (96.6) |
| Other, n (%) | 6 (2.6) | 8 (3.4) |
| **Setting** | | |
| UK, n (%) | 118 (50.2) | 122 (51.5) |
| Belgium, n (%) | 91 (38.7) | 91 (38.4) |
| Netherlands, n (%) | 26 (11.1) | 24 (10.1) |
| **Serum 25(OH)D concentration** | | |
| <25 nmol/L, n (%) | 39 (16.6) | 48 (20.3) |
| ≥25 nmol/L, n (%) | 196 (83.4) | 189 (79.7) |
| **Mean serum 25(OH)D concentration, nmol/L (sd)** | 47.1 (24.6) | 46.9 (28.1) |
| **Body mass index** | | |
| <25 kg/$m^2$, n (%) | 121 (51.5) | 94 (39.7) |
| ≥25 kg/$m^2$, n (%) | 114 (48.5) | 143 (60.3) |
| **Mean % predicted $FEV_1$ (sd)** | 55.3 (21.4) | 55.7 (21.0) |
| **Mean % predicted FVC (sd)** | 91.4 (22.1) | 90.1 (20.5) |
| **GOLD spirometric grade** | | |
| 1, n (%) | 33 (14.0) | 40 (16.9) |
| 2, n (%) | 94 (40.0) | 88 (37.1) |
| 3, n (%) | 80 (34.1) | 76 (32.1) |
| 4, n (%) | 28 (11.9) | 33 (13.9) |

**Appendix Table 2:** Risk of Bias Assessment

| | Sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other bias |
|---|---|---|---|---|---|---|---|
| Lehouck 2012 [3] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓[1] |
| Martineau 2015 [2] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓[2] |
| Zendedel 2015 [5] | ? | ? | ? | ? | ? | ? | x[3] |
| Rafiq 2017 [4] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓[4] |

✓ = low risk of bias, ? = unclear risk of bias, x = high risk of bias

1, funder not deemed to be a potential source of bias: Applied Biomedical Research Program, Agency for Innovation by Science and Technology (IWT-TBM), Belgium

2, funder not deemed to be a potential source of bias: National Institute for Health Research (NIHR), UK

3, source of other bias: very high event rates (average of 9-18 exacerbations over 6 months) reported on the basis of 2-monthly ascertainment via telephone calls validity of ascertainment of primary outcome into question; funder not stated in study report.

4, funder not deemed to be a potential source of bias: not externally funded.

## **Appendix Table 3:** Summary of Findings Table

### Vitamin D compared to placebo for prevention of COPD exacerbation

**Patient or population**: adults with COPD
**Setting**: primary and secondary care
**Intervention**: oral vitamin D supplementation
**Comparison**: oral placebo

| Outcomes | **Anticipated absolute effects*** (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | **Risk with placebo** | **Risk with vitamin D** | | | | |
| Rate ratio, moderate or severe exacerbations, overall. | 1.97 events per participant year | 1.85 events per participant year (1.62 to 2.13) | **aIRR 0.94** (0.78 to 1.13) | 469 (3 RCTs) | ⊕⊕⊕⊕ HIGH | |
| Rate ratio, moderate or severe exacerbations, baseline 25(OH)D <25 nmol/L | 2.10 events per participant year | 1.22 events per participant year (0.86 to 1.75) | **aIRR 0.55** (0.36 to 0.84) | 87 (3 RCTs) | ⊕⊕⊕◯ MODERATE | Quality downgraded one level for imprecision |
| Rate ratio, moderate or severe exacerbations, baseline 25(OH)D ≥25 nmol/L | 1.94 events per participant year | 1.98 events per participant year (1.69 to 2.68) | **aIRR 1.04** (0.85 to 1.27) | 382 (3 RCTs) | ⊕⊕⊕⊕ HIGH | |
| Proportion with ≥1 severe exacerbation | 150 per 1,000 | 232 per 1,000 (133 to 401) | **aOR 1.45** (0.85 to 2.46) | 469 (3 RCTs) | ⊕⊕⊕⊕ HIGH | |
| Proportion with ≥1 serious adverse event | 308 per 1,000 | 363 per 1,000 (234 to 560) | **aOR 1.16** (0.76 to 1.75) | 469 (3 RCTs) | ⊕⊕⊕⊕ HIGH | |

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

**Severe exacerbation:** acute worsening of symptoms precipitating emergency department attendance or hospitalisation.
**Moderate exacerbation:** acute worsening of symptoms requiring treatment with antibiotics or systemic corticosteroids, or both, but not precipitating emergency department attendance or hospitalisation. **CI:** Confidence interval, **aIRR:** adjusted incidence rate ratio, **aOR:** adjusted odds ratio

**GRADE Working Group grades of evidence**
**High quality:** We are very confident that the true effect lies close to that of the estimate of the effect
**Moderate quality:** 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 quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
**Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

**Appendix Table 4:** Responder analysis, one-step individual participant data meta-analysis

| | **No. participants (no. trials)** | **Rate of moderate or severe COPD exacerbations per participant-year** | **Adjusted incidence rate ratio (95% CI)[1]** | **P value** |
|---|---|---|---|---|
| Intervention, end-study 25(OH)D < 75 nmol/L | 66 (3) | 84/62.97 (1.33) | 1 | 0.44 |
| Intervention, end-study 25(OH)D ≥75 nmol/L | 138 (3) | 274/124.76 (2.20) | 1.15 (0.81 to 1.62) | |
| | **No. participants (no. trials)** | **Proportion with ≥1 moderate or severe COPD exacerbation (%)** | **Adjusted odds ratio (95% CI)[2]** | **P value** |
| Intervention, end-study 25(OH)D < 75 nmol/L | 66 (3) | 34/66 (51.5) | 1 | 0.14 |
| Intervention, end-study 25(OH)D ≥ 75 nmol/L | 138 (3) | 97/138 (70.3) | 1.69 (0.85 to 3.36) | |
| | **No. participants (no. trials)** | **Median time to first moderate or severe COPD exacerbation, days (IQR)** | **Adjusted hazard ratio (95% CI)[1]** | **P value** |
| Intervention, end-study 25(OH)D < 75 nmol/L | 66 (3) | 351 (68 to --)[3] | 1 | 0.52 |
| Intervention, end-study 25(OH)D ≥ 75 nmol/L | 138 (3) | 95 (33 to --)[3] | 1.17 (0.72 to 1.90) | |

1, adjusted for age, sex, trial, and COPD severity. 2, adjusted for age, sex, trial, COPD severity, and duration of participant follow-up. 3, 75$^{th}$ centiles for time to first event in these groups cannot be defined. CI, confidence interval; IQR, inter-quartile range

## REFERENCES


1. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928.
2. Martineau AR, James WY, Hooper RL, et al. Vitamin D3 supplementation in patients with chronic obstructive pulmonary disease (ViDiCO): a multicentre, double-blind, randomised controlled trial. *The Lancet Respiratory Medicine* 2015; **3**(2): 120-30.
3. Lehouck A, Mathieu C, Carremans C, et al. High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2012; **156**(2): 105-14.
4. Rafiq R, Prins HJ, Boersma WG, et al. Effects of daily vitamin D supplementation on respiratory muscle strength and physical performance in vitamin D-deficient COPD patients: a pilot trial. *International Journal of Chronic Obstructive Pulmonary Disease* 2017; **12**: 2583-92.
5. Zendedel A, Gholami M, Anbari K, Ghanadi K, Bachari EC, Azargon A. Effects of Vitamin D Intake on FEV1 and COPD Exacerbation: A Randomized Clinical Trial Study. *Global Journal of Health Science* 2015; **7**(4): 243-8.