Vitamin D_3 supplementation in patients with chronic obstructive pulmonary disease (ViDiCO): a multicentre, double-blind, randomised controlled trial

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Summary

Background **Patients with chronic obstructive pulmonary disease (COPD) often have vitamin D deficiency, which is associated with increased susceptibility to upper respiratory infection—a major precipitant of exacerbation. Multicentre trials of vitamin D supplementation for prevention of exacerbation and upper respiratory infection in patients with COPD are lacking. We therefore investigated whether vitamin D_3 (colecalciferol) supplementation would reduce the incidence of moderate or severe COPD exacerbations and upper respiratory infections.**

Methods **We did a randomised, double-blind, placebo-controlled trial of vitamin D_3 supplementation in adults with COPD in 60 general practices and four Acute National Health Service Trust clinics in London, UK. Patients were allocated to receive six 2-monthly oral doses of 3 mg vitamin D_3 or placebo over 1 year in a 1:1 ratio using computer-generated permuted block randomisation. Participants and study staff were masked to treatment assignment. Coprimary outcomes were time to first moderate or severe exacerbation and first upper respiratory infection. Analysis was by intention to treat. A prespecified subgroup analysis was done to assess whether effects of the intervention on the coprimary outcomes were modified by baseline vitamin D status. This trial is registered with ClinicalTrials.gov, number NCT00977873.**

Findings **240 patients were randomly allocated to the vitamin D_3 group (n=122) and placebo group (n=118). Vitamin D_3 compared with placebo did not affect time to first moderate or severe exacerbation (adjusted hazard ratio 0·86, 95% CI 0·60–1·24, p=0·42) or time to first upper respiratory infection (0·95, 0·69–1·31, p=0·75). Prespecified subgroup analysis showed that vitamin D_3 was protective against moderate or severe exacerbation in participants with baseline serum 25-hydroxyvitamin D concentrations of less than 50 nmol/L (0·57, 0·35–0·92, p=0·021), but not in those with baseline 25-hydroxyvitamin D levels of at least 50 nmol/L (1·45, 0·81–2·62, p=0·21; p=0·021 for interaction between allocation and baseline serum 25-hydroxyvitamin D status). Baseline vitamin D status did not modify the effect of the intervention on risk of upper respiratory infection ($p_{interaction}$=0·41).**

Interpretation **Vitamin D_3 supplementation protected against moderate or severe exacerbation, but not upper respiratory infection, in patients with COPD with baseline 25-hydroxyvitamin D levels of less than 50 nmol/L. Our findings suggest that correction of vitamin D deficiency in patients with COPD reduces the risk of moderate or severe exacerbation.**

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Introduction

Acute exacerbations are the major cause of morbidity and mortality in patients with chronic obstructive pulmonary disease (COPD). Upper respiratory infections are common precipitants of COPD exacerbations, but there are no interventions to prevent these.[1] Inadequate vitamin D status (serum 25-hydroxyvitamin D concentration <75 nmol/L) is associated with susceptibility to upper respiratory infections in patients with COPD.[2] Vitamin D metabolites exert pleiotropic antimicrobial and anti-inflammatory responses in vitro, suggesting that vitamin D supplementation might have a role in the prevention of exacerbations and upper respiratory infections in patients with COPD.[3] Despite the absence of association between vitamin D deficiency and risk of exacerbation in observational studies,[4,5] the results from a single-centre trial of patients recruited from a hospital setting showed that vitamin D supplementation reduced the risk of exacerbation in a subset of individuals with severe deficiency.[6] Multicentre trials of vitamin D supplementation for prevention of exacerbation in patients with COPD recruited from both hospital and community settings might provide generalisable findings, but they have not been done yet.

We therefore did a multicentre, double-blind, randomised placebo-controlled trial of vitamin D_3 (colecalciferol) supplementation in a cohort of patients with COPD recruited from both community and hospital settings to test the hypothesis that this intervention reduces the incidence of moderate or severe exacerbations and upper

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respiratory infections. In the absence of a consensus on the threshold concentration of 25-hydroxyvitamin D needed to afford protection against exacerbation and upper respiratory infection we enrolled patients with a broad range of baseline 25-hydroxyvitamin D concentrations so that we could do prespecified interaction analyses to ascertain whether the effects of supplementation on coprimary outcomes varied according to baseline vitamin D status.

Methods

Patients and procedures

Individuals with a medical record diagnosis of COPD, emphysema, or chronic bronchitis were identified in 60 general practices and at COPD clinics in four Acute National Health Service Trusts in London, UK. They were invited to attend a screening visit. Full eligibility criteria are listed in the appendix; the main exclusion criteria were age younger than 40 years, ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) or slow vital capacity of more than 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.

See Online for appendix

The East London and the City Research Ethics Committee 1 (reference 09/H0703/76) provided the ethics approval for the study. All participants provided written informed consent before enrolment.

Patients attending the screening visit had a baseline assessment as detailed in the appendix. Individuals who met the eligibility criteria entered a run-in period of at least 2 weeks 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 (appendix).

Exacerbation of COPD was defined as the occurrence of at least two major COPD symptoms, or one major COPD symptom and at least one minor COPD symptom, during at least 2 days consecutively.[7] Major symptoms were defined as an increase in dyspnoea occurrence, sputum volume, or sputum purulence compared with the patient's usual symptoms; minor symptoms were defined as increase in nasal congestion or discharge, wheeze, sore throat, or cough.[7] Exacerbations that were not treated with systemic steroids or antibiotics were classified as unreported; those that were treated with systemic steroids or antibiotics, but did not result in emergency hospital attendance were classified as moderate; and those resulting in emergency hospital attendance were classified as severe.[8] Exacerbation symptom severity was calculated by coding each of the seven exacerbation symptoms (increase in dyspnoea, sputum volume, sputum purulence, nasal congestion or discharge, wheeze, sore throat, or cough) as 0 (symptom absent) or 1 (symptom present), and summing them to give an exacerbation symptom score of 0 to 7.[9]

Upper respiratory infection was defined as an influenza-like illness (indicated by the presence of cough, feeling of fever or chills, and muscle pain)[10] or a cold, defined with the Jackson criteria[11] (appendix). We have previously validated this definition with PCR detection of 11 respiratory viruses in nasopharyngeal swabs.[12]

Randomisation and masking

Eligible participants were randomly assigned in a 1:1 ratio to receive six 2-monthly oral doses of 6 mL Vigantol oil (Merck Serono, Darmstadt, Germany) containing 3 mg (120 000 IU) vitamin D_3 or 6 mL organoleptically identical placebo (Miglyol oil, Caesar and Loretz, Hilden, Germany). We used a bolus dosing regimen to allow supervised administration of trial medication to achieve maximum compliance with the intervention. Before the start of recruitment, Nova Laboratories (Wigston, UK) prepared 300 packs of study preparation: 150 packs contained vitamin D_3 and 150 packs contained placebo. They then generated a randomisation sequence using a computer program that assigned the term active or placebo to the numbers 1 to 300 with permuted blocks of ten. Each pack was then assigned a number according to this computer-generated randomisation sequence. On recruitment, study staff enrolling patients classified them into one of four strata based on baseline FEV_1 (<50% predicted *vs* ≥50% predicted) and participation versus non-participation in the sputum induction substudy. Initially each stratum was assigned a batch of ten consecutive randomisation numbers, and each new patient within a given stratum was assigned the next consecutive randomisation number available for that stratum. When all ten randomisation numbers in a stratum had been issued, a new batch of ten consecutive randomisation numbers was assigned to that stratum. Enrolment to the sputum induction substudy continued until a total of 50 patients had been randomly assigned, and enrolment to the trial as a whole continued until a total of 240 patients had been randomly assigned. Treatment allocation was concealed from participants and study staff. Randomly assigned participants were invited to attend a second study visit, at which the first dose of study medication was administered under direct supervision. Five further doses of study medication were administered at 2-monthly intervals after the first dose: the administration of doses at 2 months and 6 months was directly observed, and doses at 4 months, 8 months, and 10 months were taken during a telephone call scheduled with a member of the study team. Face-to-face follow-up visits were at 2 months, 6 months, and 12 months. Blood samples for the assessment of vitamin D status and parathyroid hormone were taken at 2 months and 12 months; assessments for the other timepoints are detailed in the appendix.

Serum concentrations of 25-hydroxyvitamin D were assessed with isotope-dilution liquid chromatography–tandem mass spectrometry.[13] Methods for other laboratory analyses are detailed in the appendix.

Outcomes

Coprimary endpoints for the trial were time to first moderate or severe COPD exacerbation and time to first upper respiratory infection.

Prespecified secondary endpoints were the proportion of participants who had at least one 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; FEV_1 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 [QALYs] and incremental net benefit over 1 year); serum concentrations of 25-hydroxyvitamin D, parathyroid hormone, and corrected calcium; and incidence of adverse events. Prespecified subgroup analyses were done to ascertain whether the effect of vitamin D_3 supplementation on coprimary outcomes was modified by baseline vitamin D status.

Statistical analysis

Assuming a median time of 60 days to moderate or severe exacerbation and upper respiratory infection,[14,15] we calculated that a total of 192 participants (96 in each group) would need to be randomly assigned to detect a 30-day difference in median time to event between intervention and control groups with 80% power using a two-sided test at the 5% significance level.[16] This effect size represents a hazard ratio of 0·67—smaller than that previously reported in patients with COPD and vitamin deficiency by Lehouck and colleagues (rate ratio 0·57).[6] We increased this number by 25% to compensate for participant dropout, giving a total sample size of 240.

Analysis was by intention to treat, and significance was tested at the 5% level. Time-to-event outcomes were analysed with Cox regression adjusted for stratification factors. Methods for statistical analysis of secondary outcomes are detailed in the appendix. A single prespecified interim efficacy analysis of time-to-coprimary outcomes (requiring $p<0·001$ to stop) was done after enrolment of 120 participants. Seven interim safety analyses were done at 6-monthly intervals throughout the course of the trial; their results were reviewed by the data monitoring committee, which recommended continuation of the trial after each review.

This trial is registered with ClinicalTrials.gov, number NCT00977873.

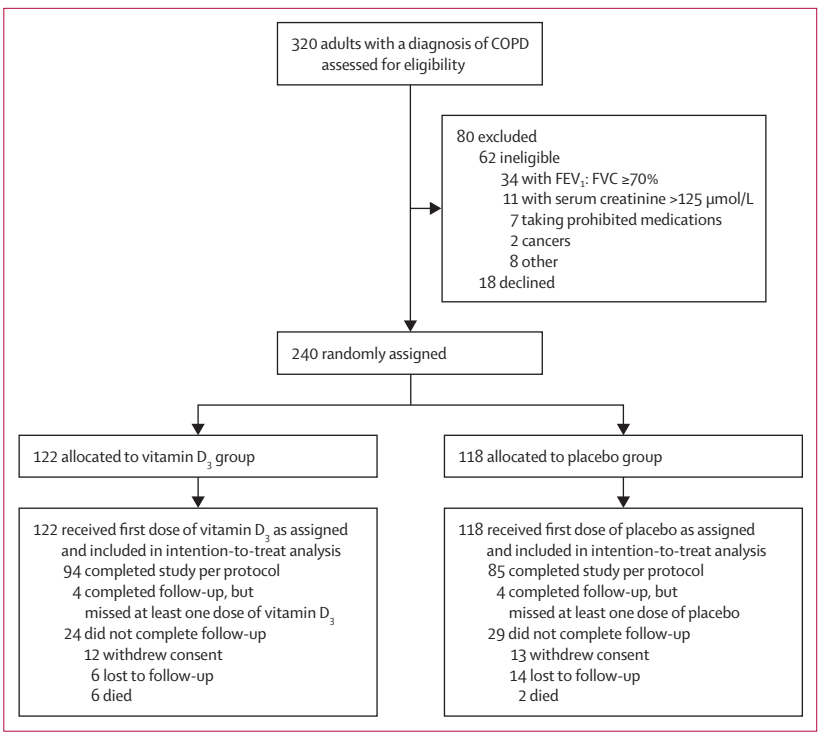

Figure 1: **Trial profile**
COPD=chronic obstructive pulmonary disease. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. Vitamin D_3=colecalciferol.

Role of the funding source

The UK National Institute of Health Research was not involved in the study design; gathering, analysis, or interpretation of data; writing of the report; or decision to submit the report for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

320 adults with a medical record diagnosis of COPD, emphysema, or chronic bronchitis were assessed for eligibility to participate in the trial between Sept 11, 2009, and April 12, 2012. 62 individuals were ineligible to participate and 18 were eligible but declined randomisation. The remaining 240 participants were randomly assigned—122 to the intervention group and 118 to the control group. All patients received at least one dose of study medication, and were included in the intention-to-treat analysis (figure 1). Clinical and

	Vitamin D_3 group (n=122)	Placebo group (n=118)
Age (years)	64·8 (7·9)	64·5 (9·2)
Sex		
Male	75 (61%)	69 (58%)
Female	47 (39%)	49 (42%)
Ethnic origin		
White	114 (93%)	113 (96%)
Other	8* (7%)	5† (4%)
Body-mass index, kg/m²	27·9 (6·1)	27·2 (6·7)
Smoking status		
Current smoker	56 (46%)	42 (36%)
Ex-smoker	66 (54%)	76 (64%)
Pack-years smoked	50·2 (25·4)	46·4 (28·4)
Lung function		
Mean post-bronchodilator FEV_1 (L)	1·73 (0·68)	1·74 (0·66)
Mean post-bronchodilator FEV_1 (% predicted)	63·7 (20·6)	64·5 (20·7)
Mean post-bronchodilator FVC (L)	3·30 (0·98)	3·30 (0·86)
Mean post-bronchodilator FVC (% predicted)	96·6 (16·8)	98·6 (21·1)
Mean FEV_1:FVC ratio	0·52 (0·13)	0·52 (0·13)
Time since last moderate or severe exacerbation (days)‡	135 (54–301)	133 (43–252)
Number of moderate or severe exacerbations in previous year‡	1·6 (1·6)	1·6 (1·6)
GOLD stage		
I (FEV_1 ≥80% predicted)	32 (26%)	29 (25%)
II (50% ≤FEV_1 <80% predicted)	57 (47%)	56 (47%)
III (30% ≤FEV_1 <50% predicted)	25 (20%)	27 (23%)
IV (FEV_1 <30% predicted)	8 (7%)	6 (5%)
COPD medication use		
None	8 (7%)	8 (7%)
Shortacting bronchodilator	101 (83%)	98 (83%)
Longacting β agonist§	69 (57%)	72 (61%)
Any inhaled corticosteroid¶	78 (64%)	82 (69%)
Inhaled corticosteroid and longacting β agonist combination	58 (48%)	62 (53%)
Inhaled corticosteroid only	20 (16%)	20 (17%)
Tiotropium	53 (43%)	56 (47%)
Inhaled corticosteroid dose at entry in betamethasone equivalents, µg‖	400 (0–1000)	400 (0–1000)
COPD managed exclusively in primary care in previous year	93 (76%)	90 (76%)
Vaccine uptake		
Influenza vaccine within 1 year of enrolment	112 (92%)	109 (92%)
Ever received pneumococcal vaccine	79 (65%)	75 (64%)
COPD duration (years)	5·0 (2·0–7·0)	4·0 (2·0–8·0)
SGRQ score	44·4 (19·4)	48·1 (18·4)

(Table 1 continues in next column)

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	Vitamin D_3 group (n=122)	Placebo group (n=118)
Month of enrolment		
January to March	33 (27%)	34 (29%)
April to June	23 (19%)	24 (20%)
July to September	33 (27%)	30 (25%)
October to December	33 (27%)	30 (25%)
Vitamin D status		
Serum 25-hydroxyvitamin D (nmol/L)	45·4 (27·9)	46·7 (23·3)
Serum 25-hydroxyvitamin D <75 nmol/L	104 (85%)	105 (89%)
Serum 25-hydroxyvitamin D <50 nmol/L	78 (64%)	70 (59%)
Serum 25-hydroxyvitamin D <25 nmol/L	29 (24%)	21 (18%)
Parathyroid hormone status		
Serum parathyroid hormone (pmol/L)	5·7 (2·2)	5·6 (2·2)
Parathyroid hormone >6·8 pmol/L	28 (23%)	25 (21%)
Randomised to sputum substudy	28 (23%)	22 (19%)

Data are number (%), mean (SD), or median (IQR). Vitamin D_3=colecalciferol. COPD=chronic obstructive pulmonary disease. GOLD=Global Initiative on Obstructive Lung Disease. SGRQ=St George's Respiratory Questionnaire. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. *Participants were black African (n=1), Indian (n=1), Pakistani (n=1), mixed white and black African (n=1), mixed white and black Caribbean (n=1), Mauritian (n=1), and unclassified (n=2). †Participants were Caribbean (n=1), Pakistani (n=1), mixed white and Asian (n=1), mixed white and black Caribbean (n=1), and Filipino (n=1). ‡Moderate or severe exacerbation defined as one treated with systemic corticosteroids or antibiotics, or both. §Includes combinations of inhaled corticosteroid plus longacting β agonist and longacting β agonist only. ¶Includes combinations of inhaled corticosteroid plus longacting β agonist and inhaled corticosteroid only. ‖1 µg betamethasone assumed to be equivalent to 1 µg budesonide, 0·5 µg fluticasone dipropionate, and 0·75 µg ciclesonide.

Table 1: **Baseline characteristics of participants in the vitamin D_3 and placebo groups**

demographic characteristics of participants were similar in the intervention and control groups (table 1): 209 (87%) of 240 patients had inadequate vitamin D status (serum 25-hydroxyvitamin D <75 nmol/L)[17] at baseline, and 160 (67%) were taking inhaled corticosteroids. The trial ended on the date of the final study visit of the final participant being followed up.

In the whole study population, allocation to vitamin D_3 compared with placebo did not affect the median time to first moderate or severe COPD exacerbation (adjusted hazard ratio [HR] 0·86; p=0·42) or time to first upper respiratory infection (0·95; p=0·75; figure 2, table 2). Prespecified subgroup analysis suggested a differential effect of vitamin D_3 supplementation on time to first moderate or severe exacerbation according to baseline vitamin D status (figure 3). In participants with baseline 25-hydroxyvitamin D concentrations less than 50 nmol/L (n=148), vitamin D_3 supplementation was associated with

reduced risk of moderate or severe exacerbation (adjusted HR 0·57; p=0·021; figure 3); by contrast, in patients with baseline 25-hydroxyvitamin D of at least 50 nmol/L, no effect of treatment was noted (1·45; p=0·21; $p_{interaction}$=0·021). There was no evidence of effect modification by baseline vitamin D status for time to first upper respiratory infection ($p_{interaction}$=0·41).

With respect to secondary outcomes, allocation to vitamin D_3 compared with placebo did not affect the rate of moderate or severe exacerbations or upper respiratory infections, or the proportion of participants who had at least one of these outcomes (table 2). Vitamin D_3 supplementation ameliorated symptoms of moderate or severe exacerbation, as shown by a small reduction in mean peak symptom score for exacerbations arising in participants allocated to intervention versus control (mean difference –0·50; p=0·042; table 2), and reduced symptom score area under the curve for moderate or severe exacerbations arising in participants allocated to intervention versus control (–14·1; p=0·032; table 2; figure 4). No significant effect of the intervention was noted on symptom score outcomes for upper respiratory infection (table 2). Mean trough serum 25-hydroxyvitamin D concentration at 12 months was significantly higher in intervention versus control groups (adjusted mean difference 19·8 nmol/L; p<0·0001; table 2); this was associated with reduced serum concentration of parathyroid hormone (0·58 pmol/L; p=0·022; table 2). Of 97 participants in the intervention group for whom data were available, 71 (73%) had a reduction in their levels of parathyroid hormone at 12 months compared with baseline. Stratification of this analysis by baseline 25-hydroxyvitamin D concentrations showed that most participants had a reduction in their parathyroid hormone levels after vitamin D_3 supplementation, even those with higher 25-hydroxyvitamin D levels at baseline. The parathyroid hormone levels fell in response to vitamin D supplementation in 17 (85%) of 20 participants with baseline 25-hydroxyvitamin D concentration of less than 25 nmol/L; 29 (74%) of 39 participants with baseline 25-hydroxyvitamin D concentration of 25–49 nmol/L; 13 (57%) of 23 participants with baseline 25-hydroxyvitamin D concentration of 50–74 nmol/L; and 12 (75%) of 16 participants with baseline 25-hydroxyvitamin D concentration of at least 75 nmol/L.

The intervention did not affect the differential white cell counts or inflammatory profile in induced sputum (table 3), incidence of unreported exacerbations, FEV_1, FVC, or body-mass index (appendix), or use of inhaled medications or antimicrobials (appendix). Daily use of shortacting bronchodilators did not differ in relation to the timing of administration of intermittent bolus doses of study medication (appendix). Allocation to vitamin D_3 compared with placebo did not affect health service uptake, quality of life (SGRQ and EQ5D scores), work absence due to COPD symptoms or upper respiratory

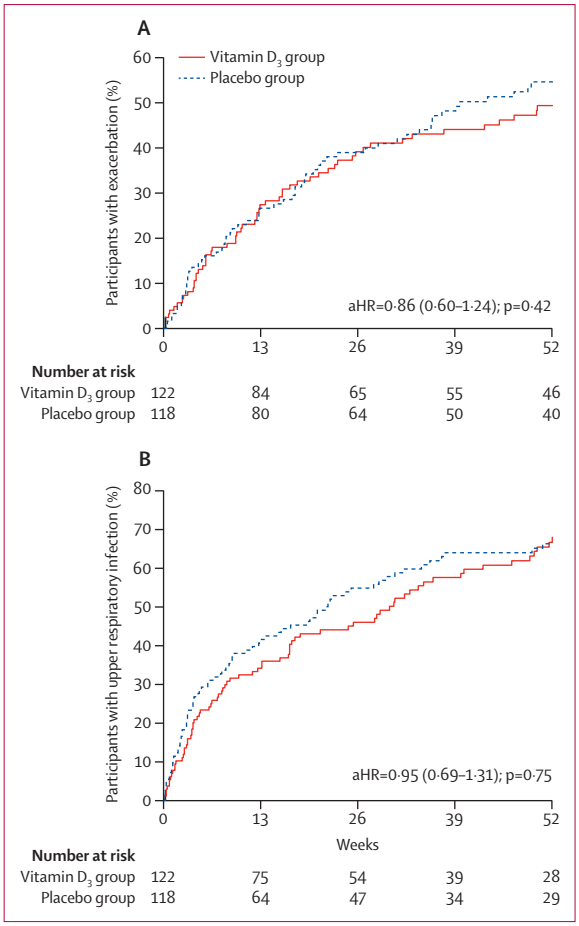

Figure 2: **Time to moderate or severe exacerbation (A) and upper respiratory infection (B) in vitamin D_3 and placebo groups**
Vitamin D_3=colecalciferol. aHR=adjusted hazard ratio.

infections or health economic outcomes (costs associated with exacerbation or upper respiratory infections, QALYs, and incremental net benefit; all data in appendix). The probability that vitamin D_3 is cost effective compared with placebo for the prevention of exacerbations and upper respiratory infections in patients with COPD was about 90% at a realistic willingness to pay (£20 000) for a QALY gain.

54 serious adverse events were reported in 40 (17%) of 240 participants who had received at least one dose of study medication—30 in the intervention group and 24 in the control group. Eight participants died during the study—six in the intervention group and two in the control group (appendix). No serious adverse event was attributed to study medication. 661 non-serious adverse events were reported in 198 (83%) of 240 participants: 94 in the intervention group and 104 in the control group; with the exception of a trend towards fewer self-reported COPD exacerbations in the intervention group versus the control group (103 *vs* 125, respectively), the non-serious adverse events were equally distributed between study groups (appendix).

	Vitamin D_3 group (n=122)	Placebo group (n=118)	Adjusted hazard ratio* (95% CI)	Adjusted odds ratio (95% CI)	Adjusted incidence rate ratio (95% CI)	Mean difference (95% CI)	p value
Moderate or severe COPD exacerbations							
Median time to first moderate or severe exacerbation (days; IQR)	Undefined (87 to undefined)	278 (89 to undefined)	0·86 (0·60 to 1·24)	..	..	..	0·42
Proportion of participants with at least one moderate or severe exacerbation†	56/103 (54%)	62/97 (64%)	..	0·69 (0·39 to 1·23)	..	..	0·21
Rate of moderate or severe exacerbations per participant-year	117·0/112·0 (1·04)	120·0/107·9 (1·11)	..	..	0·94 (0·67 to 1·30)	..	0·70
Proportion of moderate or severe exacerbations associated with upper respiratory infection	42/117 (36%)	54/120 (45%)	..	0·39 (0·13 to 1·18)	..	..	0·10
Mean peak exacerbation symptom score per moderate or severe exacerbation (SD)‡	5·47 (1·53)	5·94 (1·42)	..	..	..	−0·50 (−0·97 to −0·02)	0·042
Mean area under curve per moderate or severe exacerbation (exacerbation symptom score; SD)§	79·9 (31·0)	91·9 (36·4)	..	..	..	−14·1 (−27·0 to −1·2)	0·032
Upper respiratory infections							
Time to first upper respiratory infection (days; IQR)	212 (44 to undefined)	152 (27 to undefined)	0·95 (0·69 to 1·31)	..	..	..	0·75
Proportion of participants with at least one upper respiratory infection†	76/102 (75%)	75/103 (73%)	..	1·15 (0·61 to 2·17)	..	..	0·66
Rate of upper respiratory infections per participant-year	183·0/112·0 (1·63)	213·0/107·9 (1·97)	..	..	0·85 (0·64 to 1·15)	..	0·29
Mean peak Jackson symptom score per upper respiratory infection (SD)¶	10·1 (5·0)	11·2 (5·1)	..	..	..	−1·0 (−2·3 to 0·4)	0·16
Mean area under curve per upper respiratory infection (Jackson symptom score; SD)‖	102·7 (74·3)	119·9 (75·2)	..	..	..	−18·1 (−40·4 to 4·1)	0·11
Vitamin D status							
Mean trough serum 25-hydroxyvitamin D at 2 months (nmol/L; SD)**	57·9 (22·7)	47·1 (25·2)	..	..	..	10·8 (5·6 to 16·1)	<0·0001
Mean trough serum 25-hydroxyvitamin D at 12 months (nmol/L; SD)††	67·4 (27·5)	47·1 (26·9)	..	..	..	19·8 (14·0 to 25·5)	<0·0001
Parathyroid status							
Mean serum parathyroid hormone at 2 months (pmol/L; SD)‡‡	5·98 (2·46)	6·39 (2·79)	..	..	..	−0·49 (−0·95 to −0·03)	0·037
Mean serum parathyroid hormone at 12 months (pmol/L; SD)††	4·16 (2·09)	4·81 (2·21)	..	..	..	−0·58 (−1·07 to −0·08)	0·022

Vitamin D_3=colecalciferol. Undefined=75th centile for time to event could not be defined. COPD=chronic obstructive pulmonary disease. FEV_1=forced expiratory volume in 1 s. *Adjusted for stratification factors—ie, baseline % predicted FEV_1 (<50% *vs* ≥50%) and inclusion in or exclusion from sputum induction substudy. †Participants who withdrew from the trial without exacerbation or upper respiratory infection before the date of withdrawal were excluded from these analyses. ‡Data were analysed for 237 moderate or severe exacerbations (117 in the vitamin D_3 group and 120 in the placebo group). §Area under the curve was calculated for exacerbation symptom score from 7 days before onset of exacerbation to 20 days after onset; data were analysed for 188 moderate or severe exacerbations (99 in the vitamin D_3 group and 89 in the placebo group) with complete symptom scores for this period. ¶Jackson symptoms (sneezing, sore throat, headache, subjective sensation of fever or chills, malaise, nasal discharge, nasal obstruction, or cough) each scored from 0 (no symptoms) to 3 (severe symptoms) and summed for each day of the upper respiratory infection. ‖Area under the curve calculated for total Jackson symptom score from 7 days before onset of upper respiratory infection to 20 days after onset; data were analysed for 307 upper respiratory infections (144 in the vitamin D_3 group and 163 in the placebo group) with complete symptom scores for this period. **Data were analysed for 227 participants (116 in the vitamin D_3 group and 111 in the placebo group). ††Data were analysed for 185 participants (97 in the vitamin D_3 group and 88 in the placebo group). ‡‡Data were analysed for 222 participants (113 in the vitamin D_3 group and 109 in the placebo group).

Table 2: **Clinical and biochemical outcomes of participants in the vitamin D_3 and placebo groups**

Discussion

In the study population as a whole, vitamin D_3 supplementation did not affect the time to exacerbation and upper respiratory infection in patients with COPD, but the results of a prespecified subgroup analysis showed a protective effect of vitamin D_3 supplementation against moderate or severe exacerbation, but not against upper respiratory infections, in participants with baseline

serum 25-hydroxyvitamin D concentrations of less than 50 nmol/L. Analysis of secondary outcomes showed reduced peak symptom severity and symptom score area under the curve for moderate or severe exacerbations in the intervention group compared with the control group. Our study is the largest and first multicentre trial of vitamin D supplementation for the prevention of exacerbation and upper respiratory infection in patients with COPD.

Our findings support and extend those from the trial by Lehouck and colleagues,[6] who investigated the effects of a monthly oral dose of 2·5 mg vitamin D_3 on exacerbation risk in a cohort of patients with moderate to very severe COPD (panel). In Lehouck and colleagues' trial,[6] no effect of the intervention was noted on the primary outcome in the study population as a whole, but a post-hoc subgroup analysis showed a significantly reduced exacerbation rate in patients with baseline 25-hydroxyvitamin D concentration of less than 25 nmol/L. Subsequent exploratory analyses showed an increased exacerbation risk in patients with the highest baseline 25-hydroxyvitamin D levels (>100 nmol/L).[19] We prespecified analogous subgroup analyses (using the 50 nmol/L 25-hydroxyvitamin D threshold) for the ViDiCO trial, in which we enrolled patients with less severe disease, and noted a significant protective effect of vitamin D supplementation against exacerbation in patients with lower baseline concentrations, with an opposite effect in those with higher baseline levels, and a significant interaction term. Taken together, findings from these two trials suggest that vitamin D supplementation should be offered to COPD patients with lower vitamin D status to reduce the risk of moderate or severe exacerbation.

How might protective effects of vitamin D_3 against COPD exacerbation be mediated in deficient patients? Contrary to expectation, we did not find evidence that vitamin D_3 prevented upper respiratory infections, either in the study population as a whole or in the subgroup of participants with lower baseline vitamin D status. However, we did note a non-significant (p=0·10) difference in the percentage of moderate or severe exacerbations that were associated with upper respiratory infection in the intervention group compared with the control group (36% *vs* 45%, respectively; table 2). This finding raises the possibility that vitamin D_3 might therefore attenuate the potential for an upper respiratory infection to precipitate an exacerbation. Our finding that vitamin D_3 ameliorated symptoms of moderate or severe exacerbation might be attributable to vitamin-D-mediated suppression of pro-inflammatory cytokines and chemokines such as interleukin 6 and CCL5, which have been implicated in the pathogenesis of exacerbations.[20,21] Vitamin D_3 has previously been shown to suppress circulating and antigen-stimulated levels of these inflammatory mediators in patients with pulmonary tuberculosis;[22] if it exerts similar anti-inflammatory effects in the airway during COPD exacerbations, this could explain its favourable

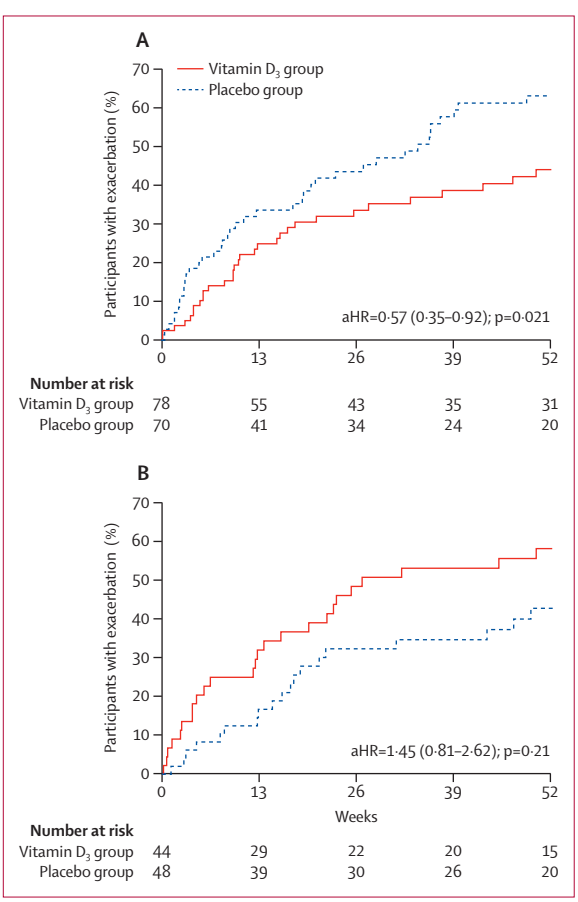

Figure 3: **Time to moderate or severe exacerbation by baseline 25-hydroxyvitamin D concentration of less than 50 nmol/L (A) or at least 50 nmol/L (B) in the vitamin D_3 and placebo groups**
p=0·021 for interaction between allocation and baseline serum 25-hydroxyvitamin D status. Vitamin D_3=colecalciferol.

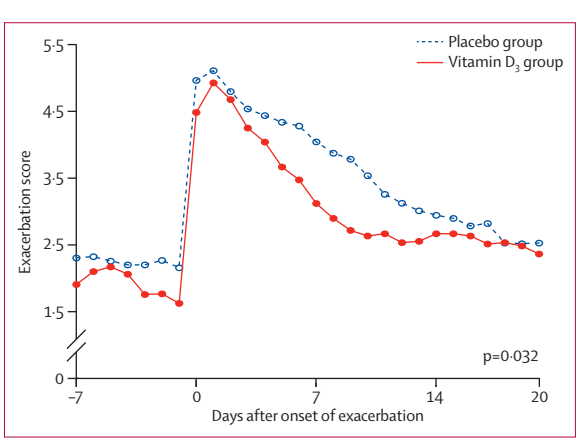

Figure 4: **Area under the curve for mean exacerbation symptom score by vitamin D_3 and placebo groups**
Data are for 188 moderate or severe exacerbations (99 in the vitamin D_3 group and 89 in the placebo group) with complete symptom scores from 7 days before onset to 20 days after onset. Vitamin D_3=colecalciferol .

	Vitamin D_3 group		Placebo group		Mean difference (95% CI)		Odds ratio (95% CI)		Ratio of geometric means (95% CI)		p value*
	2 months (n=21)	12 months (n=18)	2 months (n=16)	12 months (n=12)	2 months	12 months	2 months	12 months	2 months	12 months	
Differential white cell counts											
Eosinophils (%)†	1·17 (0·75 to 2·83)	1·50 (0·50 to 3·67)	1·04 (0·59 to 4·88)	2·04 (1·08 to 5·96)	..	..	..	..	1·09 (0·55 to 2·16)	0·96 (0·45 to 2·06)	0·95
Lymphocytes (%)	0·53 (0·31)	0·47 (0·24)	0·55 (0·29)	0·45 (0·26)	–0·09 (–0·28 to 0·10)	–0·08 (–0·29 to 0·14)	..	..	..	..	0·55
Macrophages (%)	22·5 (12·1)	22·5 (9·8)	22·1 (8·1)	24·1 (12·2)	2·86 (–2·09 to 7·80)	0·97 (–4·48 to 6·43)	..	..	..	..	0·52
Neutrophils (%)	73·2 (13·2)	72·9 (12·1)	72·0 (12·5)	70·7 (14·2)	–2·59 (–8·07 to 2·89)	–1·22 (–7·26 to 4·82)	..	..	..	..	0·65
Sputum culture positive	4/21 (19%)	4/18 (22%)	6/15 (40%)‡	1/11 (9%)‡	..	..	0·26 (0·03 to 2·61)	5·98 (0·20 to 180·19	..	..	0·25
Supernatant concentrations of inflammatory markers§											
Interleukin-1 receptor antagonist (pg/mL)†	381·0 (247·2 to 595·4)	418·2 (179·1 to 595·5)	323·5 (172·4 to 567·4)	462·7 (244·8 to 1366·1)	..	..	..	..	1·45 (0·64 to 3·28)	0·89 (0·36 to 2·20)	0·55
Interleukin-2 receptor (pg/mL)†	21·4 (10·1 to 41·4)	17·2 (0·0 to 33·3)	25·5 (12·5 to 37·2)	21·9 (0·0 to 38·1)	..	..	..	..	0·58 (0·14 to 2·42)	1·80 (0·37 to 8·81)	0·45
Interleukin 4 (pg/mL)†	0·0 (0·0 to 6·0)	1·3 (0·0 to 6·3)	0·0 (0·0 to 2·1)	0·0 (0·0 to 1·8)	..	..	..	..	1·31 (0·54 to 3·17)	2·03 (0·77 to 5·37)	0·36
Interleukin 5 (pg/mL)†	0·6 (0·0 to 1·8)	0·0 (0·0 to 1·6)	0·7 (0·0 to 1·2)	0·8 (0·3 to 1·2)	..	..	..	..	1·27 (0·71 to 2·26)	0·76 (0·40 to 1·44)	0·31
Interleukin 6 (pg/mL)†	37·8 (22·1 to 77·7)	59·8 (18·7 to 95·2)	36·0 (21·7 to 54·1)	42·6 (27·3 to 62·2)	..	..	..	..	1·54 (0·80 to 2·95)	1·26 (0·61 to 2·59)	0·42
Interleukin 7 (pg/mL)†	14·7 (0·0 to 22·6)	0·0 (0·0 to 22·7)	17·3 (6·4 to 19·1)	15·6 (12·1 to 24·3)	..	..	..	..	0·92 (0·23 to 3·64)	0·36 (0·08 to 1·63)	0·38
Interleukin 10 (pg/mL)†	1·3 (0·0 to 4·9)	0·9 (0·0 to 5·0)	1·4 (0·0 to 2·9)	0·0 (0·0 to 1·8)	..	..	..	..	1·14 (0·63 to 2·06)	1·55 (0·81 to 2·97)	0·41
Interleukin 12 (pg/mL)†	6·3 (0·0 to 9·5)	6·8 (0·0 to 11·2)	6·7 (0·0 to 14·4)	13·0 (0·0 to 18·4)	..	..	..	..	1·39 (0·36 to 5·43)	0·71 (0·16 to 3·21)	0·72
Interleukin 13 (pg/mL)†	4·3 (0·0 to 6·7)	4·3 (0·0 to 8·6)	3·3 (0·0 to 5·3)	5·7 (1·1 to 8·9)	..	..	..	..	0·54 (0·18 to 1·68)	0·95 (0·27 to 3·31)	0·55
Interleukin 15 (pg/mL)†	6·8 (0·0 to 50·6)	24·8 (0·0 to 122·5)	7·6 (0·0 to 26·5)	34·0 (5·9 to 47·0)	..	..	..	..	2·11 (0·29 to 15·37)	0·97 (0·11 to 8·86)	0·74
Granulocyte-colony-stimulating factor (pg/mL)†	118·9 (59·2 to 159·5)	85·2 (39·0 to 339·3)	85·0 (44·1 to 156·1)	120·7 (88·8 to 136·0)	..	..	..	..	1·31 (0·54 to 3·18)	0·83 (0·31 to 2·22)	0·69
Granulocyte-macrophage colony-stimulating factor (pg/mL)†	2·0 (1·7 to 2·8)	2·0 (1·7 to 3·2)	2·5 (1·9 to 3·1)	2·5 (1·9 to 3·0)	..	..	..	..	0·88 (0·70 to 1·11)	0·89 (0·69 to 1·14)	0·51
CCL2 (pg/mL)†	25·2 (13·9 to 69·0)	38·9 (8·7 to 116·4)	38·8 (18·4 to 88·7)	70·5 (34·2 to 83·7)	..	..	..	..	0·44 (0·11 to 1·82)	0·59 (0·12 to 2·89)	0·48
CCL3 (pg/mL)†	13·1 (10·1 to 21·8)	11·3 (7·4 to 17·9)	13·1 (9·1 to 19·7)	10·9 (0·0 to 20·2)	..	..	..	..	0·94 (0·26 to 3·43)	4·67 (1·12 to 19·57)	0·07

(Table 3 continues on next page)

	Vitamin D_3 group		Placebo group		Mean difference (95% CI)		Odds ratio (95% CI)		Ratio of geometric means (95% CI)		p value*
	2 months (n=21)	12 months (n=18)	2 months (n=16)	12 months (n=12)	2 months	12 months	2 months	12 months	2 months	12 months	
(Continued from previous page)											
CCL4 (pg/mL)†	18·1 (10·4 to 32·2)	18·9 (11·9 to 47·6)	17·8 (12·4 to 23·7)	15·8 (13·1 to 35·1)	..	..	..	..	2·00 (0·59 to 6·74)	1·88 (0·49 to 7·21)	0·46
CCL11 (pg/mL)†	0·7 (0·0 to 1·5)	0·8 (0·0 to 1·5)	0·4 (0·0 to 1·1)	0·9 (0·0 to 1·3)	..	..	..	..	1·24 (0·80 to 1·93)	1·37 (0·84 to 2·23)	0·40
CXCL-8 (pg/mL)†	1274·7 (347·6 to 4589·0)	2574·8 (331·7 to 3908·4)	2147·3 (804·7 to 3776·3)	3010·7 (1900·8 to 4250·1)	..	..	..	..	1·06 (0·41 to 2·73)	0·94 (0·33 to 2·69)	0·98
CXCL-9 (pg/mL)†	18·4 (6·0 to 63·8)	24·1 (0·0 to 74·5)	17·1 (0·0 to 28·6)	20·4 (7·0 to 38·0)	..	..	..	..	2·77 (0·50 to 15·21)	0·96 (0·15 to 6·35)	0·45
CXCL-10 (pg/mL)†	17·6 (4·4 to 61·6)	14·2 (3·5 to 139·0)	9·2 (2·1 to 34·2)	12·8 (6·3 to 48·6)	..	..	..	..	2·67 (0·59 to 12·11)	1·53 (0·29 to 8·16)	0·44
Epidermal growth factor (pg/mL)†	8·8 (0·0 to 38·0)	10·8 (0·0 to 36·8)	19·9 (9·0 to 23·1)	16·8 (3·4 to 27·2)	..	..	..	..	0·53 (0·11 to 2·59)	1·26 (0·22 to 7·36)	0·66
HGF (pg/mL)†	59·2 (27·5 to 113·1)	60·5 (31·8 to 120·2)	80·9 (59·7 to 98·6)	94·2 (61·4 to 113·8)	..	..	..	..	3·18 (0·82 to 12·32)	1·57 (0·35 to 7·03)	0·25
Vascular endothelial growth factor (pg/mL)†	17·3 (7·5 to 31·3)	14·1 (10·1 to 33·6)	10·8 (8·2 to 16·4)	14·8 (12·2 to 26·0)	..	..	..	..	2·83 (0·86 to 9·35)	1·38 (0·36 to 5·25)	0·23

Data are n/N (%), mean (SD), and median (IQR), unless otherwise indicated. Vitamin D_3=colecalciferol. CCL=C-C motif ligand. CXCL=C-X-C motif ligand. HGF=hepatocyte growth factor.*None of the p values were significant according to a Benjamini and Hochberg procedure[18] controlling the false discovery rate at 20%. †A small constant (0·05) was added to each value before the log transformation for the regression analysis to avoid taking logs of 0. ‡Culture results were not available for one induced sputum sample. §Median concentrations of the inflammatory mediators interleukin 1β, interleukin 2, interleukin 17, interferon αA2, interferon γ, tumour necrosis factor, CCL5, and fibroblast growth factor β were undetectable at baseline and therefore not analysed.

Table 3: **Induced sputum outcomes of participants in the vitamin D_3 and placebo groups**

effects on the course of symptom exacerbation. However, this explanation cannot be confirmed from this study because we did not measure concentrations of these inflammatory mediators in the participants during acute exacerbations.

Our trial has several strengths. Inadequate vitamin D status was highly prevalent in the study population at baseline, and we gave vitamin D_3 using an intermittent bolus dosing regimen, which allowed us to achieve a high degree of compliance with the intervention. The use of prospectively completed daily symptom diaries allowed us to detect unreported exacerbations (ie, those which did not come to medical attention) and to characterise participants' symptoms with precision, allowing us to ascertain the effect of the intervention on symptom severity as well as incidence of exacerbations and upper respiratory infections. Our study complements the trial done by Lehouck and colleagues[6] by providing new data in patients with a wide spectrum of disease severity, recruited from several urban community and hospital centres, for additional outcomes including upper respiratory infection, exacerbation symptoms, markers of lower airway inflammation in induced sputum, and health economic outcomes.

Our trial also has some limitations. We chose a 2-monthly dosing interval on the basis that this is the in-vivo half-life of 25-hydroxyvitamin D.[23] Consequently, the intergroup difference in trough 25-hydroxyvitamin D concentrations at 12 months was smaller than that in Lehouck and colleagues' study,[6] in which doses were given monthly. The 25-hydroxyvitamin D response to an oral bolus of vitamin D_3 peaks 1 week post dose and falls thereafter,[24] so the timing of blood sampling in our trial did not capture the high 25-hydroxyvitamin D levels that are likely to have been observed in participants in the intervention group of the trial in the preceding weeks. That parathyroid hormone concentrations were reduced in the intervention group suggests that our dosing regimen had a physiological effect on the vitamin D status. Median times to first moderate or severe exacerbation and upper respiratory infection were longer than anticipated in the power calculation, possibly as a result of a Hawthorne effect, whereby completion of the study diary improved disease control through enhanced compliance with inhaled corticosteroids.[25]

Another potential limitation relates to our choice of intermittent bolus dosing. Although this can prevent fractures,[26] some have proposed that it might be less

Panel: Research in context

Systematic review

We searched Medline and clinical trials registries (ClinicalTrials.gov, ISRCTN, Australian New Zealand Clinical Trials Registry, and UMIN Clinical Trials Registry) in May, 2009, using the search terms "vitamin D or cholecalciferol or ergocalciferol", "randomised or randomized or randomly or trial", "COPD or bronchitis or emphysema", and "exacerbation or upper respiratory infection or cold or acute respiratory infection". There were no restrictions on language or dates. Our search retrieved one trial, which was ongoing at that time and has since been reported.[6] This trial investigated the effects of a monthly oral dose of 2·5 mg vitamin D_3 (colecalciferol) on exacerbation risk in a cohort of patients with moderate to very severe chronic obstructive pulmonary disease (COPD): no effect of the intervention on the primary outcome was noted in the study population as a whole, but a post-hoc subgroup analysis showed a significantly reduced exacerbation rate in patients with baseline serum 25-hydroxyvitamin D concentrations of less 25 nmol/L in the intervention group.

Interpretation

The results of our trial confirm and extend the findings of the previous study.[6] We enrolled a larger number of patients with a broader spectrum of COPD severity and randomly assigned them to receive a 2-monthly oral dose of 3 mg vitamin D_3 or placebo for 1 year. No effect of vitamin D_3 was noted on the time to first moderate or severe exacerbation or upper respiratory infection in the study population as a whole, but a prespecified subgroup analysis showed a protective effect of vitamin D supplementation against moderate or severe exacerbation in patients with a baseline serum 25-hydroxyvitamin concentration of less than 50 nmol/L. We also noted small reductions in peak symptom severity and symptom score area under the curve for moderate or severe exacerbations irrespective of baseline vitamin D status. For clinicians, consistent findings from the two published trials suggest that correction of vitamin D deficiency in patients with COPD reduces the risk of moderate or severe exacerbation. These promising findings need to be confirmed in randomised controlled trials in which only patients with baseline serum 25-hydroxyvitamin levels of less 50 nmol/L are enrolled.

effective than daily dosing for inducing the non-classical actions of vitamin D.[27–29] However, we have previously shown that administration of intermittent boluses of vitamin D can favourably modulate antimicrobial immune responses.[21,30] Moreover, the fact that both we and Lehouck and colleagues[6] showed positive effects of bolus dosing in patients with vitamin D deficiency suggests that this group at least is responsive to vitamin D_3 administered using such a regimen. Perhaps the effects of the intervention would have been more pronounced had we given vitamin D_3 at daily or weekly intervals. Trials are needed for the direct comparison of the effects of daily versus bolus vitamin D supplementation on clinical outcomes.

Our findings add to the increasing evidence that vitamin D might protect against exacerbations in COPD patients with lower serum levels of 25-hydroxyvitamin D. Randomised controlled trials in patients with baseline concentrations of 25-hydroxyvitamin D of less than 50 nmol/L are needed to confirm the promising findings from our study.

Contributors

ARM, WYJ, NCB, PMT, CJC, CMH, and CJG contributed to the study design. ARM, WYJ, NCB, DAJ, KI, AB, RKR, ABC, DES, and CJC participated in implementation of the trial. CLG, WRM, PMT, TRV, MR, MW, and AD developed and ran laboratory assays. DM validated diary records of health economic outcomes. ARM and RLH contributed to data analysis. ZS did the health economic analysis. ARM wrote the first draft of the manuscript; all other authors critically reviewed it and approved the final version.

Declaration of interests

We declare no competing interests.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Martineau AR, James WY, Hooper RL, et al. Vitamin D_3 supplementation in patients with chronic obstructive pulmonary disease (ViDiCO): a multicentre, double-blind, randomised controlled trial. *Lancet Respir Med* 2014; published online Dec 2. http://dx.doi.org/10.1016/S2213-2600(14)70255-3.

Double-blind multi-centre randomised controlled trial of vitamin D_3 supplementation in COPD (ViDiCO): Web Extra Material

Supplementary Methods

Participants

Adult patients with a medical record diagnosis of COPD, emphysema or chronic bronchitis were identified by searching databases at 60 general practices and at COPD clinics in four Acute National Health Service Trusts in London, UK, and sent a letter inviting them to attend a screening visit. Further patients were invited for screening *via* a poster advertising campaign conducted at participating General Practices. Respondents were excluded from participation in the trial if the ratio of forced expiratory volume in one second (FEV1) to forced or slow vital capacity (VC) after inhalation of 400 micrograms salbutamol was greater than 70%; if they were aged <40 years; if they had a tobacco smoking history <15 pack-years; if they had a medical record diagnosis of asthma, bronchiectasis confirmed on computerised tomography scan, sarcoidosis, hyperparathyroidism, nephrolithiasis, active tuberculosis, renal or hepatic failure, terminal illness or malignancy other than non-melanoma skin cancer not in remission for ≥ 3 years; if they were taking a dietary supplement containing >10 μg vitamin D per day up to 2 months before first dose of study medication; if they were taking a cardiac glycoside, carbamazepine, phenobarbital, phenytoin or primidone; if they were taking a benzothiadiazine derivative at a dose higher than recommended in the British National Formulary (BNF),(1) or in combination with a calcium supplement; if they were using long-term oxygen therapy ≥ 12 hours per day; if they had been treated with any investigational medical product or device up to 4 months before the first dose of study medication; if serum corrected calcium was >2.65 mmol/L; if serum creatinine was >125 μmol/L; if they were unable to use a spirometer; or if they failed to complete the symptom / PEFR diary during the run-in period. Vitamin D supplements taken at a dose ≤ 10 μg (400 IU) per day were permitted during the trial. A sub-group of 50 participants were enrolled in a sputum induction study; additional exclusion criteria for this sub-study were post-bronchodilator FEV1/FVC <40% predicted, and tobacco smoking within the 6 months preceding enrolment. The trial was approved by East London and The City Research Ethics Committee 1 (ref 09/H0703/76) and written informed consent was obtained from all participants before enrolment.

Procedures

Screening visit

Participants attending the screening visit completed the St George's Respiratory Questionnaire (SGRQ)(2) and the EuroQoL EQ-5D questionnaire;(3) they also underwent a baseline clinical assessment including the following: spirometry after inhalation of 400 μg salbutamol *via* a spacer device, performed using a MicroLab ML3500 desktop spirometer (CareFusion GmbH, Hoechberg, Germany) according to American Thoracic Society (ATS) / European Respiratory Society (ERS) recommendations;(4) measurement of height, performed using a Seca 220 Telescopic Measuring Rod (Seca, Hamburg, Germany); measurement of weight, performed using Marsden MMPS-250 column scales (Marsden, Rotherham, UK); and collection of a blood sample for subsequent DNA extraction and determination of full blood count (FBC) and serum concentrations of calcium, albumin, total 25-hydroxyvitamin D (25[OH]D) and parathyroid hormone (PTH). A urine sample was collected from women of childbearing potential for a pregnancy test (SA Scientific, San Antonio, TX USA). A sub-set of 50 participants were invited to undergo sputum induction with hypertonic saline, and their samples were processed to make cytospin slides according to methods described by Pizzichini *et al*.(5) Differential cell counts were performed by one operator (CLG) for all specimens throughout the study; a second operator (WRM) repeated cell counts on a randomly selected sub-set of 20 slides: differential cell counts were highly correlated between operators (for neutrophil count, Spearman's r =0.91, 95% CI 0.79 to 0.97, P<0.001). Induced sputum supernatants were stored at -80ºC pending measurement of concentrations of inflammatory mediators as described below. Quantitative sputum culture was also performed as described by Wilkinson *et al*.(6)

Participants fulfilling eligibility criteria then entered a run-in period of at least 2 weeks, during which they were asked to complete a study diary on a daily basis. This diary (Figure S1) recorded the presence or absence of major COPD symptoms (increase in dyspnoea, sputum volume or sputum purulence as compared with their usual symptoms) and the severity of the following symptoms, scored from 0 (no symptoms) to 3 (symptoms severe enough to interfere with activity or sleep): wheeze, sneezing, sore throat, headache, subjective sensation of fever or chilliness, malaise, nasal congestion, nasal discharge, cough and myalgia. The diary also recorded

medication use, health care use, time off work and out-of-pocket expenses incurred as a result of symptoms of COPD or URI. No specific instructions were given regarding concomitant medication use or management of exacerbations during the trial.

Randomisation

As soon as compliance with diary completion was demonstrated and the screening corrected calcium concentration was available, participants whose eligibility was confirmed were randomly assigned to receive six 2-monthly oral doses of 6 ml Vigantol® oil (Merck Serono, Darmstadt, Germany) containing 3 mg (120,000 IU) vitamin D_3, or 6 ml organoleptically identical placebo (Miglyol® oil, Caesar and Loretz, Hilden, Germany) with allocation ratio 1:1. Randomisation was assigned by permuted blocks of ten and stratified according to a) baseline FEV1 (≥50% predicted *vs.* <50% predicted) and b) inclusion in *vs.* exclusion from the induced sputum sub-study as follows. Before the start of recruitment, Nova Laboratories (Wigston, Leicestershire, UK) prepared 300 packs of study preparation: 150 packs contained vitamin D_3 and 150 packs contained placebo. They then generated a randomisation sequence using a computer program that assigned the term active or placebo to the numbers 1 to 300 by permuted block randomisation with blocks of ten. Each pack was then assigned a randomisation number according to this computer-generated randomisation sequence. On recruitment, study staff enrolling patients classified them into one of four strata based on baseline FEV1 (<50% predicted vs. ≥50% predicted) and participation vs. non-participation in the sputum induction sub-study. Initially each stratum was assigned a batch of ten consecutive randomisation numbers, and each new patient within a given stratum was assigned the next consecutive randomisation number available for that stratum. When all ten randomization numbers in a given stratum had been issued, a new batch of ten consecutive randomisation numbers was assigned to that stratum. Enrolment to the sputum induction sub-study continued until a total of 50 patients had been randomised, and enrolment to the trial as a whole continued until a total of 240 patients had been randomised. Nova Laboratories Ltd (Wigston, UK) bottled study medication according to Good Manufacturing Practice; they had no other involvement in the study. Vitamin D_3 content of a random sample of active medication was determined by high performance liquid chromatography at the end of the study; it was found to contain 99.2% of its original vitamin D_3 content. Treatment allocation was concealed from participants and study staff. Randomised participants were invited to attend a second study visit, at which the first dose of study medication was administered under direct supervision, and a new symptom diary was provided.

Follow-up

Participants completed study diaries daily for the 12 months of study participation. Each diary accommodated up to 12 weeks of data; participants completing follow-up filled 6 diaries in total. Five further doses of study medication were administered at 2-monthly intervals following the first dose: those at 2 and 6 months were directly observed, and those at 4, 8 and 10 months were taken at the time of a telephone call scheduled with a member of the study team. Face-to-face follow-up visits were performed at 2, 6 and 12 months of follow-up, at which spirometry and administration of questionnaires (EQ-5D and SGRQ) were repeated. Returned diaries were checked for completeness, and new diaries were issued as necessary. Additionally, at 2 and 12 months blood samples were taken from all participants, and serum was separated by centrifugation and frozen for subsequent assay of concentrations of 25(OH)D, albumin, calcium and PTH. Serum from 12-month blood samples was also frozen for the same determinations. Sputum induction was also repeated at 2 and 12 months for participants randomised to the sputum sub-study. On completion of the 12 month visit, final diaries were collected and participants were discharged from the study. Details of adverse events arising during the course of the trial were recorded throughout.

Data management and study definitions

All case report form (CRF) and diary data were entered into a database in Microsoft Access 2010. Entries for a 10% subset of participants were checked against source data: error rates of 0.089% and 0.00% were detected for data from diaries / CRF respectively. Diary data were then imported into STATA and episodes of exacerbation and URI were identified using algorithms based on the following definitions. Exacerbation of COPD was defined using criteria proposed by Seemungal *et al*(7) as the occurrence of ≥ 2 major COPD symptoms, or 1 major COPD symptom and ≥ 1 minor COPD symptom, during ≥ 2 consecutive days. Major symptoms were defined as increase in dyspnoea, sputum volume or sputum purulence as compared with their usual symptoms; minor symptoms were defined as increase in nasal congestion or discharge, wheeze, sore throat, or cough. The severity of exacerbation was then categorised as follows. Exacerbations that were not treated with systemic steroids and/or antibiotics were classified as ‘unreported’; those that were treated with systemic steroids and/or antibiotics, but which did not result in hospital admission or a visit to a hospital emergency department were

classified as ‘moderate’; and those resulting in hospital admission or a visit to a hospital emergency department were classified as ‘severe’.(8) A quantitative measure of exacerbation symptom severity was also calculated by coding each of the seven exacerbation symptoms as 0 (symptom absent) or 1 (symptom present), and summing them to give an exacerbation symptom score between 0 and 7, as proposed by Wilkinson *et al*.(9)

URI was defined as a) influenza-like illness, as indicated by the presence of cough, feeling of fever/chilliness and muscle pain,(10) or b) a cold, defined as follows using the Jackson criteria.(11) Scores (from 0-3) for each of 8 Jackson symptoms (sneezing, sore throat, headache, subjective sensation of fever or chilliness, malaise, nasal discharge, nasal obstruction, cough) were summed for each day to generate a total Jackson score. A cold was defined as i) total Jackson symptom score of ≥14 + subjective impression of having a cold, or ii) total Jackson symptom score of ≥14 + increased nasal discharge for at least 3 days, or iii) total Jackson symptom score <14 + subjective impression of having a cold + increase in nasal discharge score above median run-in nasal discharge score for ≥ 3 days.(11) We have previously validated this definition against polymerase chain reaction detection of 11 respiratory viruses in nasopharyngeal swabs in another trial.(12) Body mass index (BMI) was calculated using the formula: BMI = weight (kg) / [height (m)]^2.

Sample size and statistical analysis

Co-primary end points for the trial were time to first moderate / severe COPD exacerbation and time to first URI. Assuming a median time to moderate / severe exacerbation and URI of 60 days(13, 14) we calculated that a total of 192 participants (96 in each group) would need to be randomised in order to detect a 30 day difference in median time to either event between intervention and control groups with 80% power using a 2-sided test at the 5% significance level, assuming a follow-up period for each participant of one year.(15) A difference of this magnitude between groups represents a hazard ratio of 0.67 – a more modest effect size for the effect of vitamin D on exacerbation risk than that previously reported in vitamin D deficient COPD patients by Lehouck *et al* (rate ratio 0.57), (16) and similar to the effect size of vitamin D for prevention of asthma exacerbation recently reported by Castro *et al* (hazard ratio 0.63).(17) We increased this number by 25% to compensate for participant drop-out, giving a total sample size of 240.

Pre-specified secondary endpoints were the proportion of participants experiencing at least one moderate/severe exacerbation or URI; the rate of moderate/severe exacerbation or URI; peak values and areas under the curve for symptom scores during exacerbation / URI; the proportion of moderate / severe exacerbations associated with URI; 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 URI; quality of life, as indicated by SGRQ and EQ5D scores; work absence; health economic outcomes (costs of exacerbations and URI, quality-adjusted life years [QALY] and incremental net benefit over one year); serum concentrations of 25(OH)D, PTH and corrected calcium; and incidence of adverse events. The Benjamini-Hochberg procedure for multiple testing correction was applied to analysis of inflammatory mediators in induced sputum to control the false discovery rate at 20%.(18) Otherwise no formal adjustment was made for the number of secondary endpoints investigated. Pre-specified sub-group analyses were conducted to determine whether the effect of vitamin D_3 supplementation on co-primary outcomes was modified by baseline vitamin D status (serum 25[OH]D <50 nmol/L *vs.* ≥50 nmol/L).

Analyses were performed using STATA/IC (versions 12.1, 2012 and 13, 2013), GraphPad Prism (version 4.03, 2005) and R (version 3.0.2, 2013) software packages. Analysis was by intention-to-treat (ITT): all participants who took at least one dose of study medication were included in both efficacy and safety analyses. Significance was tested at the 5% level. A single pre-specified interim efficacy analysis of time to co-primary outcomes (requiring P<0.001 to stop) was performed after enrolment of 120 participants. Interim safety analyses (n=7) were conducted at 6-monthly intervals throughout the course of the trial. Results of interim analyses were reviewed by the Data Monitoring Committee, who recommended continuation of the trial following each review.

Time-to-event outcomes were analysed using Cox regression adjusted for stratification factors; the assumption of proportional hazards was confirmed for all survival analyses using methods proposed by Grambsch and Therneau.(19) Analyses of proportions used logistic regression adjusted for stratification factors. Quantitative outcomes assessed more than once in the same participant, but not at fixed times, were analysed using linear regression adjusted for stratification factors with random effects of individual. Data for a given episode were considered missing if that episode was incomplete at the end of follow-up. Quantitative outcomes assessed more than once in the same participant at fixed time-points in addition to a baseline assessment were analysed using

linear regression adjusted for stratification factors with random effects of individual, constrained so that there was no treatment effect at baseline, and with a treatment effect estimated at each subsequent time-point. A P-value for allocation-time interaction was used to evaluate evidence for an effect of allocation; where evidence was found ($P<0.05$), P-values for the effect of allocation at individual time-points are reported. Sub-group analyses were performed by repeating primary efficacy analyses with the inclusion of the appropriate interaction term. Interaction effects were summarised as a ratio of hazard ratios with 95% confidence interval and P-value.

Analysis of health economic outcomes was undertaken from a societal perspective. Unit costs for general practitioner (GP) and nurse consultations, outpatient attendances and emergency department attendances were obtained from the Unit Costs of Health and Social Care.(20) Unit costs for hospital admissions were obtained from the Reference Costs Database. (21) Unit drug costs were calculated from the British National Formulary.(1) Participants' costs were obtained from study diaries and included time lost from work due to COPD exacerbation or URI as well as travel expenses and out-of-pocket expenses on prescription drugs and over-the-counter medication incurred as a result of COPD exacerbation or URI. Time lost from work due to COPD exacerbation or URI was valued using age- and sex-adjusted average daily wage rates from the Office for National Statistics.(22) Total health care costs calculated from diary data were validated against those calculated from GP records for 25 randomly selected participants: good correlation between the two estimates was observed (Spearman's r 0.85, 95% CI 0.68 to 0.93, $P<0.001$).

EQ-5D quality of life data were combined with survival data to calculate QALY.(3) Participants' EQ-5D profiles were combined with health state preference values from the UK general population(23) to derive EQ-5D utility index scores at 2, 6 and 12 months of follow-up on a scale anchored at 0 (death) and 1 (perfect health). QALY were calculated for each participant using the weighted average of time spent in the study and quality of life.

Cost effectiveness analysis (CEA) was undertaken to assess the relative cost effectiveness of vitamin D_3 supplementation *vs.* placebo for the prevention of COPD exacerbations and URI. The CEA used bivariate regression methods to allow for correlation between costs and outcomes to report mean values and 95% confidence intervals for incremental costs and QALY of vitamin D_3 supplementation *vs.* placebo at one year, adjusted for stratification factors.

Missing data for health economic analyses were addressed with multiple imputation. The imputation model included stratification factors, and baseline covariates (sex, ethnicity, alcohol use, body mass index and use of inhaled corticosteroids) as predictors. We applied analytical methods in each imputed dataset (n=5) and combined the resultant estimates with Rubin's rules.(24) Incremental net monetary benefits were estimated by valuing incremental QALY at a threshold of £20,000 per QALY and subtracting incremental costs. A cost-effectiveness acceptability curve was calculated by reporting the probability that vitamin D_3 supplementation was cost-effective at different levels of willingness to pay for a QALY gain (£0 to £50,000 per QALY gained).(25)

Laboratory analyses

Serum concentrations of $25(OH)D_2$ and $25(OH)D_3$ were determined by isotope-dilution liquid chromatography–tandem mass spectrometry (26) and summed to give values for total 25(OH)D concentration. Sensitivity for this assay was 10 nmol/l. PTH, albumin and total serum calcium concentrations were determined using an Architect ci8200 analyser (Abbott Diagnostics, Chicago, IL, USA). Calcium concentration was corrected for serum albumin concentration using the formula: corrected calcium (mmol/l) = total calcium (mmol/l) + 0.02 × (40 – albumin [g/l]). Concentrations of 30 inflammatory mediators (IL-1β, IL-1RA, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12 (p40/p70), IL-13, IL-15, IL-17, G-CSF, GM-CSF, IFN-α, IFN-γ, TNF, CXCL8, CXCL9, CXCL10, CCL2, CCL3, CCL4, CCL5, CCL11, EGF, FGF-β, HGF and VEGF) were quantified in induced sputum supernatants obtained at baseline, 2 months and 12 months using a human 30-plex bead immunoassay panel (Invitrogen, Camarillo, CA, USA).

Role of the funding source

The National Institute of Health Research was not involved in study design; in the collection, analysis or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Table S1: **Unreported exacerbation outcomes by allocation**

	Vitamin D (n=122)	**Placebo (n=118)**	**Adjusted hazard ratio / odds ratio / incidence rate ratio / mean difference (95% CI)[1]**	**P**
Time to first unreported exacerbation, days (IQR)	86 (22 to --)	43 (11 to 317)	0.86 (0.64 to 1.16)	0.32
Proportion of participants with ≥1 unreported exacerbation (%)[2]	85/104 (82%)	85/102 (83%)	0.92 (0.44 to 1.90)	0.82
Rate of unreported exacerbations per participant-year	499/112.0 = 4.46	580/107.9 = 5.38	0.86 (0.62 to 1.18)	0.34
Proportion of unreported exacerbations associated with URI (%)	116/499 (23%)	118/580 (20%)	1.56 (0.87 to 2.80)	0.14
Mean peak exacerbation symptom score per unreported exacerbation (s.d.)[3]	4.7 (1.5)	4.5 (1.5)	0.09 (-0.21 to 0.40)	0.54
Mean area under curve per unreported exacerbation, exacerbation symptom score (s.d.)[4]	68.7 (37.8)	70.3 (32.1)	-3.9 (-13.7 to 5.9)	0.43

CI, confidence interval; IQR, inter-quartile range; URI, upper respiratory infection; s.d., standard deviation.

1, adjusted for stratification factors, i.e. baseline % predicted FEV1 (<50% vs. ≥50%) and inclusion in / exclusion from sputum induction sub-study; **2**, these analyses exclude participants who withdrew from the trial without experiencing any unreported exacerbation prior to their date of withdrawal; **3**, exacerbation symptom score calculated by coding seven exacerbation symptoms (increase in dyspnoea, sputum volume, sputum purulence, nasal congestion / discharge, wheeze, sore throat or cough) as 0 (symptom absent) or 1 (symptom present) and summing the scores to give a daily symptom score between 0 and 7. **4**, area under the curve calculated for exacerbation symptom score from 7 days pre-onset of exacerbation to 20 days post-onset; data for 862 unreported exacerbations (407 in the vitamin D arm, 455 in the placebo arm) with complete symptom scores for this period were analysed.

Table S2: **FEV1, FVC and body mass index by allocation**

		Vitamin D (n=122)	**Placebo (n=118)**	**Adjusted mean difference (95% CI)[1]**	**P**
Mean post-bronchodilator FEV1, % predicted (s.d.)	2 mo	62.9 (20.5)	65.5 (22.9)	-1.1 (-2.9 to 0.7)	0.68
	6 mo	60.9 (20.0)	63.5 (21.6)	-0.5 (-2.4 to 1.4)	
	12 mo	63.3 (19.6)	64.2 (21.8)	-0.5 (-2.4 to 1.5)	
Mean post-bronchodilator FVC, % predicted (s.d.)	2 mo	94.5 (17.6)	98.5 (22.4)	-2.6 (-5.4 to 0.3)	0.34
	6 mo	93.8 (18.4)	95.6 (19.5)	-1.1 (-4.0 to 1.9)	
	12 mo	93.4 (18.5)	94.9 (19.6)	-0.5 (-3.6 to 2.6)	
Mean body mass index, kg/m^2 (s.d.)	2 mo	27.9 (6.1)	27.4 (6.5)	0.2 (-0.1 to 0.6)	0.027
	6 mo	27.8 (6.2)	27.6 (6.9)	-0.2 (-0.6 to 0.1)	
	12 mo	28.1 (6.4)	27.3 (6.6)	-0.1 (-0.5 to 0.2)	

FEV1, forced expiratory volume in one second; FVC, forced vital capacity; CI, confidence interval; s.d., standard deviation

1. Adjusted for stratification factors, i.e. baseline % predicted FEV1 (<50% vs. ≥50%) and inclusion in / exclusion from sputum induction sub-study.

Table S3: **Respiratory medication use by allocation**

			Vitamin D (n=122)	**Placebo (n=118)**	**Adjusted hazard ratio / odds ratio / incidence rate ratio / ratio of geometric means (95% CI)[1]**	**P**
Antibiotic use for exacerbation	Median time to first course of antibiotics, days (IQR)		302 (92 to --)	208 (53 to 384)	0.77 (0.55 to 1.08)	0.13
	Proportion of participants taking ≥1 course of antibiotics (%)[2]		62/104 (60%)	74/104 (71%)	0.64 (0.35 to 1.16)	0.14
	Rate of antibiotic courses per participant-year		173/112.0 = 1.55	205/107.9 = 1.90	0.78 (0.56 to 1.09)	0.15
Use of over-the-counter (OTC) medication for URI / exacerbation	Median time to first course of OTC medication, days (IQR)		-- (358 to --)	-- (253 to --)	0.76 (0.47 to 1.23)	0.27
	Proportion of participants taking ≥1 course of OTC medication (%)[2]		30/99 (30%)	37/92 (40%)	0.64 (0.35 to 1.18)	0.15
	Rate of courses of OTC medication per participant-year (IQR)		71/112.0 = 0.63	96/107.9 = 0.89	-0.29 (-0.86 to 0.29)	0.33
Mean number of uses of inhaled relief medication per 24 hours over period since preceding study visit[3]	Median (IQR)	2 months	2.00 (0.81 to 3.60)	2.15 (0.66 to 4.14)	1.00 (0.92 to 1.08)	0.67
		6 months	2.00 (0.50 to 3.51)	2.51 (0.62 to 4.23)	1.06 (0.97 to 1.15)	
		12 months	2.08 (0.81 to 4.01)	2.07 (0.88 to 4.00)	1.04 (0.95 to 1.14)	
Any ICS use[4]	n (%)	2 months	79/118 (67%)	79/111 (71%)	--	--
		6 months	75/110 (68%)	77/105 (73%)	--	
		12 months	66/98 (67%)	65/89 (73%)	--	
Any LABA use	n (%)	2 months	72/118 (61%)	71/111 (64%)	1.57 (0.04 to 59.17)	0.43
		6 months	70/110 (64%)	70/105 (67%)	0.18 (0.00 to 28.18)	
		12 months	61/98 (62%)	59/89 (66%)	0.02 (0.00 to 4.84)	
Any LABA/ICS combination use	n (%)	2 months	61/118 (52%)	63/111 (57%)	1.53 (0.07 to 34.42)	0.76
		6 months	57/110 (52%)	61/105 (58%)	0.28 (0.01 to 7.66)	
		12 months	50/98 (51%)	51/89 (57%)	0.35 (0.01 to 10.08)	
Any long-acting anticholinergic drug use	n (%)	2 months	53/118 (45%)	52/111 (47%)	0.56 (0.02 to 14.56)	0.66
		6 months	51/110 (46%)	49/105 (47%)	3.22 (0.11 to 98.10)	
		12 months	47/98 (48%)	43/89 (48%)	5.33 (0.19 to 151.14)	

CI, confidence interval; IQR, inter-quartile range; OTC, over-the-counter; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist.

1, adjusted for stratification factors, i.e. baseline % predicted FEV1 (<50% vs. ≥50%) and inclusion in / exclusion from sputum induction sub-study; **2**, these analyses exclude participants who withdrew from the trial without having had the relevant outcome; **3**, a small constant (0.5) was added to each value prior to log-transforming for the regression analysis, to avoid taking logs of zero; **4**, results at different time points too closely associated to allow regression model to estimate odds ratios.

Table S4: **Health service use by allocation**

		Vitamin D (n=122)	**Placebo (n=118)**	**Adjusted hazard ratio / odds ratio / incidence rate ratio (95% CI)[1]**	**P**
Unscheduled health care attendance for exacerbation or URI	Median time to first attendance, days (IQR)	353 (93 to --)	330 (101 to --)	1.03 (0.71 to 1.48)	0.87
	Proportion of participants with ≥1 attendance (%)[2]	58/103 (56%)	58/99 (59%)	0.96 (0.55 to 1.70)	0.90
	Rate of attendances per participant-year	131/112.0 = 1.17	123/107.9 = 1.14	0.98 (0.69 to 1.40)	0.92

1, adjusted for stratification factors, i.e. baseline % predicted FEV1 (<50% vs. ≥50%) and inclusion in / exclusion from sputum induction sub-study; **2**, this analysis excludes participants who withdrew from the trial without having had any unscheduled health care attendances for exacerbation / URI.

Table S5: **Quality of life outcomes by allocation**

			Vitamin D (n=122)	**Placebo (n=118)**	**Adjusted mean difference / odds ratio (95% CI)[1]**	**P**
SGRQ	Mean Total score (s.d.)	2 mo	43.6 (18.5)	47.5 (19.7)	0.37 (-2.42 to 3.16)	0.74
		6 mo	44.1 (18.5)	46.6 (19.4)	1.28 (-1.63 to 4.19)	
		12 mo	43.4 (19.0)	45.7 (21.2)	1.45 (-1.55 to 4.45)	
	Mean Symptoms score, (s.d.)	2 mo	52.9 (22.1)	55.0 (24.1)	0.98 (-3.72 to 5.69)	0.95
		6 mo	52.5 (21.2)	54.6 (23.4)	0.41 (-4.51 to 5.34)	
		12 mo	51.5 (22.9)	54.1 (23.5)	-0.70 (-5.79 to 4.39)	
	Mean Activity score, (s.d.)	2 mo	63.9 (24.4)	66.5 (25.6)	1.34 (-2.45 to 5.14)	0.80
		6 mo	63.8 (23.8)	66.5 (25.7)	1.37 (-2.58 to 5.33)	
		12 mo	62.5 (24.5)	64.3 (27.0)	1.87 (-2.21 to 5.94)	
	Mean Impacts score, (s.d.)	2 mo	29.4 (18.6)	34.3 (18.9)	-1.02 (-4.17 to 2.13)	0.60
		6 mo	30.4 (19.2)	32.9 (18.3)	0.91 (-2.38 to 4.20)	
		12 mo	30.1 (18.9)	32.6 (20.7)	1.24 (-2.14 to 4.63)	
EQ5D	Mean index score (s.d.)[2]	2 mo	0.84 (0.21)	0.79 (0.26)	1.43 (0.67 to 3.05)[2]	0.81
		6 mo	0.83 (0.19)	0.78 (0.26)	0.96 (0.43 to 2.05)[2]	
		12 mo	0.86 (0.20)	0.82 (0.24)	1.07 (0.47 to 2.42)[2]	
	Reporting any mobility problem, n (%)	2 mo	37/115 (32%)	44/108 (41%)	0.63 (0.29 to 1.38)	0.72
		6 mo	40/104 (38%)	42/97 (43%)	0.85 (0.38 to 1.92)	
		12 mo	33/96 (34%)	34/89 (38%)	0.86 (0.37 to 2.01)	
	Reporting any self-care problem, n (%)	2 mo	18/115 (16%)	18/108 (17%)	0.87 (0.33 to 2.28)	0.74
		6 mo	15/104 (14%)	17/97 (18%)	0.70 (0.25 to 1.96)	
		12 mo	8/97 (8%)	11/89 (12%)	0.53 (0.15 to 1.83)	
	Reporting any usual activity problem, n (%)	2 mo	24/115 (21%)	28/108 (26%)	0.80 (0.37 to 1.77)	0.80
		6 mo	26/104 (25%)	24/97 (25%)	1.21 (0.53 to 2.75)	
		12 mo	10/97 (10%)	13/89 (15%)	0.71 (0.25 to 2.04)	
	Reporting any pain / discomfort, n (%)	2 mo	28/115 (24%)	38/108 (35%)	0.51 (0.24 to 1.11)	0.25
		6 mo	29/104 (28%)	37/97 (38%)	0.61 (0.27 to 1.34)	
		12 mo	22/97 (23%)	20/89 (22%)	1.10 (0.45 to 2.69)	
	Reporting any anxiety / depression, n (%)	2 mo	24/115 (21%)	27/108 (25%)	0.83 (0.33 to 2.12)	0.97
		6 mo	23/104 (22%)	25/97 (26%)	0.88 (0.33 to 2.34)	
		12 mo	20/97 (21%)	22/89 (25%)	0.82 (0.30 to 2.28)	
	Mean VAS score (s.d.)	2 mo	67.8 (18.2)	63.8 (19.8)	2.85 (-1.31 to 7.02)	0.39
		6 mo	65.2 (19.3)	61.5 (21.0)	2.40 (-1.96 to 6.76)	
		12 mo	64.6 (18.4)	61.1 (20.0)	3.13 (-1.37 to 7.64)	

CI, confidence interval; SGRQ, St George's Respiratory Questionnaire; s.d., standard deviation; mo, months; VAS, visual analogue scale.

1, adjusted for stratification factors, i.e. baseline % predicted FEV1 (<50% vs. ≥50%) and inclusion in / exclusion from sputum induction sub-study; **2**, the distribution of EQ5D index scores was bimodal, with the majority of the sample having a value of exactly 1 and a subgroup with mode around 0.8. Results show odds ratios and P-values from a logistic regression with (EQ5D = 1) as the outcome.

Table S6: **Work absence by allocation**

	Vitamin D (n=122)	**Placebo (n=118)**	**Adjusted hazard ratio / incidence rate ratio / odds ratio (95% CI)[1]**	**P**
Median time to first work absence due to URI / exacerbation, days (IQR)	-- (130 to --)	-- (61 to --)	0.84 (0.57 to 1.24)	0.38
Rate of days of missed work due to URI / exacerbation per participant per year	601/112.0 = 5.4	788/107.9 = 7.3	0.73 (0.38 to 1.40)	0.35
Proportion of participants missing ≥ 1 day of work due to URI / exacerbation (%)[2]	50/102 (49%)	54/100 (54%)	0.84 (0.48 to 1.47)	0.55

1, adjusted for stratification factors, i.e. baseline % predicted FEV1 (<50% vs. ≥50%) and inclusion in / exclusion from sputum induction sub-study; **2**, this analysis excludes participants who withdrew from the trial without having missed a day of work due to ARI/exacerbation.

Table S7: **Total one-year costs, quality-adjusted life years and incremental net benefit per participant by allocation**

		Vitamin D (n=122)[1]	**Placebo (n=118)[1]**	**Adjusted mean difference (95% CI)[2]**	**P**
Study medication, £		35.00 (0.00)	0.00 (0.00)	35.00[3]	-[3]
Exacerbation / URI-related healthcare use, £	Hospitalisation	139.50 (690.38)	128.72 (756.73)	17.62 (-164.38 to 199.62)	0.85
	Emergency dept. attendances	4.72 (19.89)	1.54 (11.80)	3.23 (-0.95 to 7.42)	0.13
	Primary care consultations	37.84 (56.02)	42.27 (69.32)	-3.75 (-19.56 to 12.07)	0.64
	Out-patient chest clinic	1.09 (12.04)	0 (0)	1.13 (-1.05 to 3.31)	0.31
Exacerbation / URI-related prescribed medication use, £	Antimicrobials	4.59 (19.60)	3.15 (5.35)	1.54 (-2.15 to 5.23)	0.41
	Bronchodilators/Corticosteroids	4.65 (9.96)	6.01 (13.73)	-1.23 (-4.23 to 1.77)	0.42
	Other drugs[4]	1.04 (5.49)	0.72 (4.96)	0.37 (-0.96 to 1.70)	0.58
Out-of-pocket costs paid by participant, £	Travel	0.10 (0.81)	0.03 (0.37)	0.07 (-0.09 to 0.23)	0.41
	Over-the-counter medication	1.20 (3.37)	2.62 (7.51)	-1.37 (-2.85 to 0.10)	0.068
	Prescriptions	0.38 (2.18)	0.30 (1.95)	0.10 (-0.42 to 0.63)	0.70
Productivity loss, £		513.40 (1086.75)	670.62 (1856.50)	-142.81 (-528.36 to 242.74)	0.47
Total costs associated with exacerbation / URI over 12 months, £		743.52 (1417.76)	855.98 (2008.37)	-90.09 (-527.67 to 347.48)	0.69
QALYs over 12 months		0.801 (0.190)	0.762 (0.212)	0.035 (-0.017 to 0.087)	0.18
Incremental Net Benefit, £[5]				795.20 (-364.30 to 1954.71)	0.18

CI, confidence interval; URI, upper respiratory infection; QALY, quality-adjusted life-years

1. Mean (standard deviation) are presented. 2, adjusted for stratification factors, i.e. baseline % predicted FEV1 (<50% vs. ≥50%) and inclusion in / exclusion from sputum induction sub-study. 3, 95% CI and P value not presented as medication costs are constant across allocation groups; 4, montelukast, carbocysteine and theophylline preparations; 5, incremental net benefit calculated by multiplying the mean QALY gain by £20,000 and subtracting the incremental cost.

Table S8: **Serious adverse events by allocation[1]**

	Intervention (n=122)	**Control (n=118)**
Cancer diagnosis		
B cell non-Hodgkin's lymphoma	1	0
Bladder carcinoma	1	0
Breast carcinoma	1	0
Lung carcinoma	0	2[2]
Oesophageal carcinoma	0	1
Gastric carcinoma	1[3]	0
Emergency surgical admission		
Epistaxis	0	1
Perforated colon	2[2]	0
Prolapsed intervertebral disc	1	0
Ruptured abdominal aortic aneurysm	1[3]	0
Elective surgery		
CABG	0	1
Cholecystectomy	1	0
Hysterectomy	0	1
ICD insertion	0	1
Knee replacement	0	1
Spinal discectomy	0	1
Elective medical admission		
Catheter ablation for atrial fibrillation	0	1
Pharyngo-oesophagoscopy	1	0
Emergency medical admission		
Acute myocardial infarction	2[3]	0
Acute COPD exacerbation	10	6
Alcohol withdrawal	0	1
Community-acquired pneumonia	2	2[2]
Fall / Decreased mobility	2	3
Lower gastro-intestinal haemorrhage	1	0
Methadone overdose	1[3]	0
Paraspinal abscess	1	0
Right ventricular failure	1	0
Septicaemia	0	1
Unstable angina pectoris	0	1
Death	6	2
Total number of Serious Adverse Events	30	24
Number of participants experiencing any serious adverse event (%)	21	19

1, adverse events were classified as serious if they caused death or were life-threatening, or if they necessitated hospital admission or prolongation of hospital stay; **2**, one resulting in death; **3**, resulting in death

Table S9: **Non-serious adverse events by allocation**

	Vitamin D	**Placebo**
Number of adverse events by system		
Acute respiratory infection (self-reported)	133	136
COPD exacerbation (self-reported)	103	125
Allergy symptoms	5	2
Other ear, nose or throat adverse events	0	0
Hypercalcaemia	0	0
Other biochemical abnormality	3	2
Haematological abnormality	3	1
Cardiovascular adverse events	4	3
Central nervous system / psychiatric adverse events	2	3
Dermatological adverse events	5	4
Falls	3	3
Fractures	1	1
Other musculoskeletal adverse events	7	6
Gastrointestinal adverse events	21	13
Genitourinary adverse events	3	4
Ophthalmic adverse events	2	1
Oral / dental adverse events	2	2
Endocrine / metabolic adverse events	4	1
Other adverse events	22	31
Total number of non-serious adverse events	323	338
Number of adverse events by relatedness to study medication:		
Not related / Doubtful	322	335
Possible	1[1]	3[2]
Probable	0	0
Number of participants discontinuing study medication due to non-serious adverse event	2[3]	1[4]
Number of participants experiencing any non-serious adverse event (%)	94/122 (77%)	104/118 (88%)

1. One report of vomiting after taking study medication
2. Three reports of gastrointestinal symptoms (nausea, vomiting, diarrhoea) after taking IMP
3. Two participants attributed symptoms (excessive thirst, recurrent COPD exacerbations) to IMP and discontinued it
4. One participant attributed symptoms (nausea, vomiting and abdominal discomfort) to IMP and discontinued it

Figure S1: **Study diary**

	DAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY	SUNDAY
Write number	1. Date (day / month / year)							
	2. Reliever inhaler - no. of times used in last 24 hours							
Circle No or Yes	3. More breathless than usual yesterday?	No Yes	No Yes	No Yes	No Yes	No Yes	No Yes	No Yes
	4. Phlegm darker than usual yesterday?	No Yes	No Yes	No Yes	No Yes	No Yes	No Yes	No Yes
	5. Coughing more phlegm than usual yesterday?	No Yes	No Yes	No Yes	No Yes	No Yes	No Yes	No Yes
	6. Cold or 'flu symptoms yesterday?	No Yes	No Yes	No Yes	No Yes	No Yes	No Yes	No Yes
	7. Day off yesterday for cold, 'flu or chest infection?	No Yes	No Yes	No Yes	No Yes	No Yes	No Yes	No Yes
	8. Doctor yesterday for cold, 'flu or chest infection?	No Yes If yes see p26	No Yes If yes see p26	No Yes If yes see p26	No Yes If yes see p26	No Yes If yes see p26	No Yes If yes see p26	No Yes If yes see p26
	9. Steroid tablets, antibiotics or other medicine yesterday?	No Yes If yes see p27	No Yes If yes see p27	No Yes If yes see p27	No Yes If yes see p27	No Yes If yes see p27	No Yes If yes see p27	No Yes If yes see p27
	10. Any costs of cold, 'flu or chest infection yesterday?	No Yes If yes see p28	No Yes If yes see p28	No Yes If yes see p28	No Yes If yes see p28	No Yes If yes see p28	No Yes If yes see p28	No Yes If yes see p28
Symtoms over last 24 hours. Circle • 0 for no symptoms • 1 for mild symtoms • 2 for moderate symptoms • 3 for severe symptoms (interfering with activity or sleep)	11. Wheeze	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
	12. Sneezing	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
	13. Sore throat	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
	14. Headache	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
	15. Chills or fever	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
	16. Feeling generally unwell	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
	17. Blocked nose	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
	18. Runny nose	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
	19. Cough	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3
	20. Muscle aches	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3

Figure S2: Short-acting bronchodilator use by allocation

Mean day-to-day use of short-acting bronchodilator by allocation, presented from the start of the run-in period to the end of the trial. Solid line, vitamin D_3; dotted line, placebo. Arrows indicate timing of administration of study medication. Seven-day moving averages are presented.

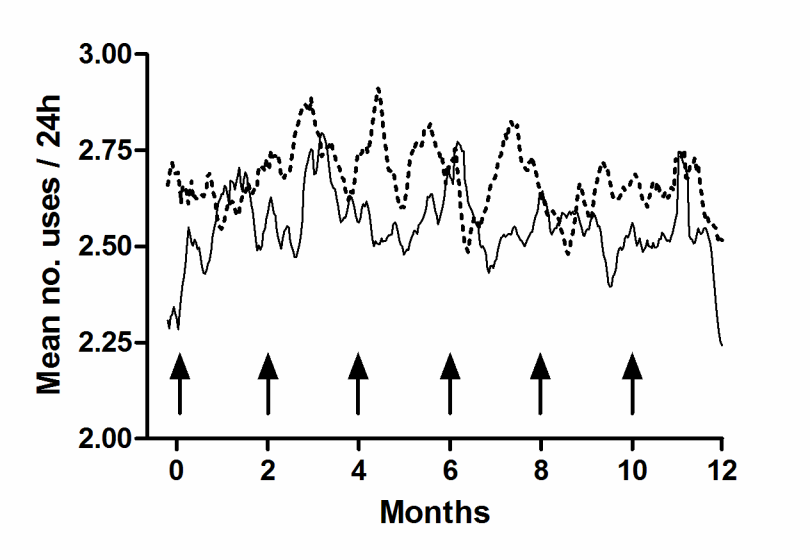
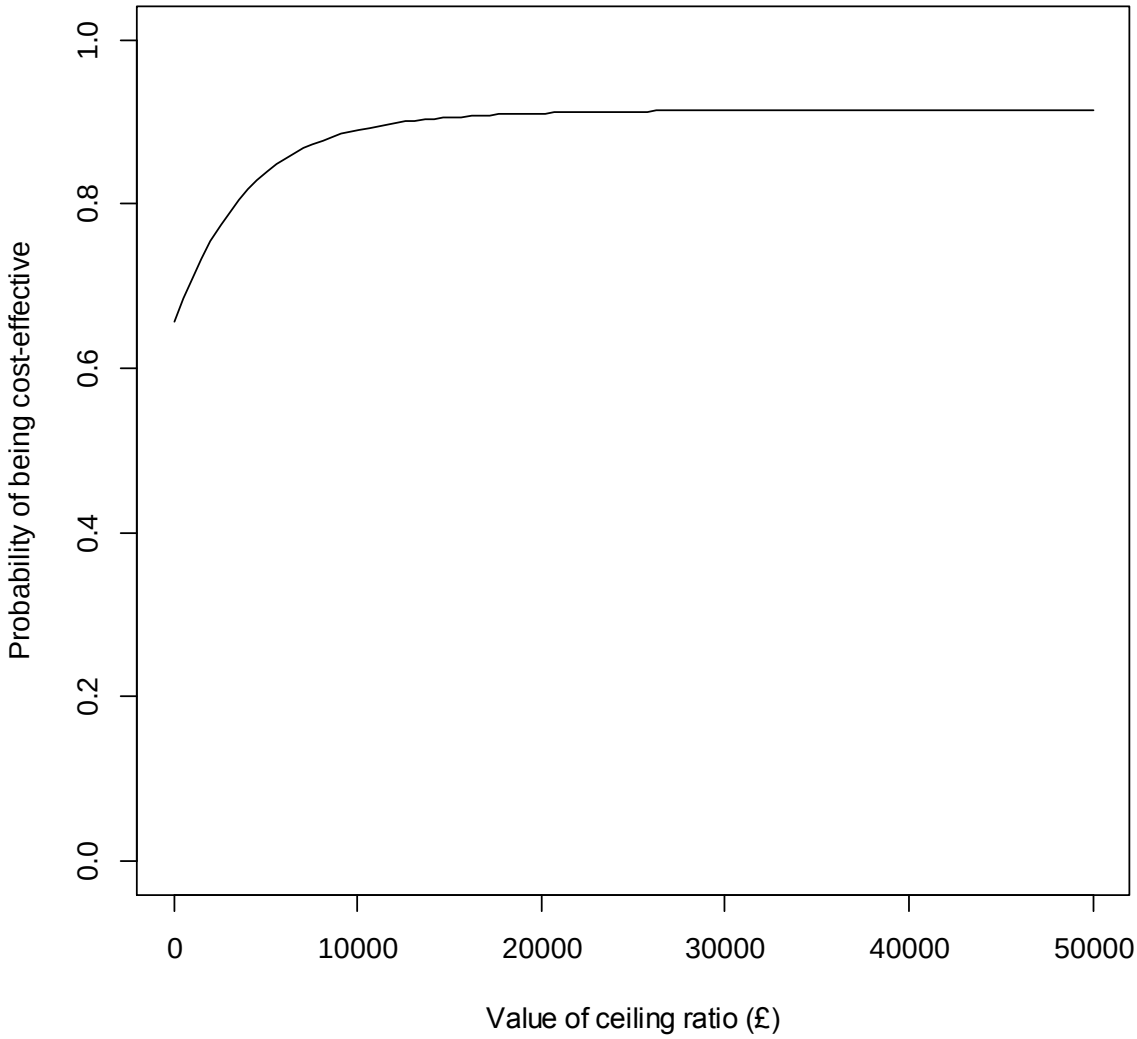


Figure S3: **Probability that vitamin D_3 supplementation is cost effective at alternative levels of willingness to pay for a quality-adjusted life-year (QALY) gain**



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