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Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data

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Summary

Background A previous aggregate data meta-analysis of randomised controlled trials showed that vitamin D supplementation reduces the rate of asthma exacerbations requiring treatment with systemic corticosteroids. Whether this effect is restricted to patients with low baseline vitamin D status is unknown.

Methods For this systematic review and one-step and two-step meta-analysis of individual participant data, we searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science for double-blind, placebo-controlled, randomised controlled trials of vitamin D_3 or vitamin D_2 supplementation in people with asthma that reported incidence of asthma exacerbation, published between database inception and Oct 26, 2016. We analysed individual participant data requested from the principal investigator for each eligible trial, adjusting for age and sex, and clustering by study. The primary outcome was the incidence of asthma exacerbation requiring treatment with systemic corticosteroids. Mixed-effects regression models were used to obtain the pooled intervention effect with a 95% CI. Subgroup analyses were done to determine whether effects of vitamin D on risk of asthma exacerbation varied according to baseline 25-hydroxyvitamin D (25[OH]D) concentration, age, ethnic or racial origin, body-mass index, vitamin D dosing regimen, use of inhaled corticosteroids, or end-study 25(OH)D levels; post-hoc subgroup analyses were done according to sex and study duration. This study was registered with PROSPERO, number CRD42014013953.

Findings Our search identified 483 unique studies, eight of which were eligible randomised controlled trials (total 1078 participants). We sought individual participant data for each and obtained it for seven studies (955 participants). Vitamin D supplementation reduced the rate of asthma exacerbation requiring treatment with systemic corticosteroids among all participants (adjusted incidence rate ratio [aIRR] 0·74, 95% CI 0·56–0·97; p=0·03; 955 participants in seven studies; high-quality evidence). There were no significant differences between vitamin D and placebo in the proportion of participants with at least one exacerbation or time to first exacerbation. Subgroup analyses of the rate of asthma exacerbations treated with systemic corticosteroids revealed that protective effects were seen in participants with baseline 25(OH)D of less than 25 nmol/L (aIRR 0·33, 0·11–0·98; p=0·046; 92 participants in three studies; moderate-quality evidence) but not in participants with higher baseline 25(OH)D levels (aIRR 0·77, 0·58–1·03; p=0·08; 764 participants in six studies; moderate-quality evidence; $p_{interaction}$=0·25). p values for interaction for all other subgroup analyses were also higher than 0·05; therefore, we did not show that the effects of this intervention are stronger in any one subgroup than in another. Six studies were assessed as being at low risk of bias, and one was assessed as being at unclear risk of bias. The two-step meta-analysis did not reveal evidence of heterogeneity of effect (I^2=0·0, p=0·56).

Interpretation Vitamin D supplementation reduced the rate of asthma exacerbations requiring treatment with systemic corticosteroids overall. We did not find definitive evidence that effects of this intervention differed across subgroups of patients.

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Introduction

Asthma affects more than 300 million people worldwide and is estimated to cause almost 400 000 deaths annually.[1,2] Asthma mortality arises primarily during episodes of acute worsening of symptoms, termed exacerbations, which are commonly precipitated by viral upper respiratory infections.[3] Virus-induced asthma exacerbations are associated with increased production of pro-inflammatory cytokines such as interleukin 17A, which exacerbate allergic airway responses.[4] Vitamin D metabolites support antiviral responses in respiratory epithelial cells[5] and inhibit production of interleukin 17A in peripheral blood mononuclear cells isolated from patients with severe asthma.[6] Low circulating concentrations of the major circulating vitamin D metabolite, 25-hydroxyvitamin D (25[OH]D), are associated with increased risk of asthma exacerbation in both children[7] and adults,[8] and eight double-blind,

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Research in context

Evidence before this study

Before doing this study, we searched the PROSPERO International Prospective Register of Systematic Reviews, ClinicalTrials.gov, and MEDLINE for published or ongoing meta-analyses of randomised controlled trials of vitamin D supplementation in people with asthma, without language restrictions, from database inception to Sept 30, 2014, using the search terms "vitamin D" and "asthma". A Cochrane meta-analysis of aggregate data from double-blind, placebo-controlled, randomised controlled trials found that vitamin D supplementation reduced the rate of asthma exacerbations requiring treatment with systemic corticosteroids (rate ratio 0·64, 95% CI 0·46–0·90). Whether this effect is restricted to patients with lower baseline vitamin D status (25-hydroxyvitamin D <25 nmol/L) is not known; an individual participant data meta-analysis could resolve this issue, but this has not previously been done.

Added value of this study

Our meta-analysis of individual participant data from 955 participants in seven randomised controlled trials provides an updated pooled estimate of the protective effects of vitamin D against asthma exacerbations requiring treatment with systemic corticosteroids overall. Uniquely, our meta-analysis also investigates whether the effect of vitamin D on risk of asthma exacerbation varies according to baseline 25-hydroxyvitamin D concentrations.

Implications of all the available evidence

Overall, vitamin D reduced the rate of asthma exacerbations treated with systemic corticosteroids, as compared with placebo (0·30 events per person per year *vs* 0·43 events per person per year; p=0·03). Subgroup analysis revealed that vitamin D reduced the rate of asthma exacerbations treated with systemic corticosteroids in people with a baseline 25-hydroxyvitamin D of less than 25 nmol/L (0·19 events per person per year *vs* 0·42 events per person per year; p=0·046), but vitamin D supplementation did not result in a statistically significant reduction in exacerbation rate in participants with baseline 25-hydroxyvitamin D of 25 nmol/L or higher. We did not find definitive evidence that effects of this intervention differed across subgroups of patients.

placebo-controlled, randomised controlled trials (RCTs)[9–16] have been published investigating the effects of vitamin D supplementation on the risk of asthma exacerbation. So far, six meta-analyses incorporating data from trials of vitamin D for the management of asthma have been done: four reported protective effects of vitamin D supplementation against asthma exacerbation,[17–20] one reported no such effect,[21] and one did not attempt a meta-analysis for the outcome of exacerbation.[22] The most recent of these, a Cochrane systematic review[20] and aggregate data meta-analysis including data from both children and adults and restricted to double-blind, placebo-controlled RCTs found that vitamin D supplementation reduced the rate of asthma exacerbations requiring treatment with systemic corticosteroids by 36%.[20] However, insufficient access to individual participant data (IPD) meant that subgroup analyses could not be done to address the question of whether protective effects of vitamin D supplementation against asthma exacerbation are stronger in individuals with low baseline vitamin D status; the theory being that individuals with the lowest baseline levels of a micronutrient might be expected to derive the greatest benefit from its replacement. In keeping with this hypothesis, protective effects of vitamin D supplementation against acute respiratory infection[23] and acute exacerbations of chronic obstructive pulmonary disease[24,25] have been reported to be strongest in individuals with low circulating 25(OH)D concentrations. We therefore set out to obtain IPD from double-blind, placebo-controlled RCTs investigating the effects of vitamin D supplementation on the risk of asthma exacerbation, and then to meta-analyse the data to obtain an updated estimate of the overall effectiveness of the supplementation and to determine whether the effects of this intervention vary according to baseline vitamin D status.

For the **study protocol** see http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014013953

Methods

Search strategy and selection criteria

The methods for this systematic review and one-step and two-step meta-analysis were described in an outline protocol that was registered with the PROSPERO International Prospective Register of Systematic Reviews. The outline protocol includes populations of people at risk of acute respiratory infection, and people with asthma and chronic obstructive pulmonary disease. This systematic review and meta-analysis of individual participant data focuses on people with asthma. A systematic review and meta-analysis of individual participant data in people with acute respiratory infection has been previously published.[23] Research ethics committee approval was not required in the UK to do this meta-analysis; local ethical permission to contribute de-identified IPD from primary RCTs was required and obtained for studies by Urashima and colleagues[9] and Tachimoto and colleagues[14] (ethics committee of the Jikei University School of Medicine). Findings are reported according to the PRISMA guidelines for IPD meta-analysis.[26]

Double-blind, placebo-controlled RCTs of supplementation with vitamin D_3 or vitamin D_2 in patients with asthma were eligible for inclusion if they had been approved by a research ethics committee and if data on incidence of asthma exacerbation were reported.

Two investigators (DAJ and ARM) searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science using the electronic search strategies described in the appendix (p 1). We regularly updated our searches from database inception up to and including Oct 26, 2016. No language restrictions were imposed. We supplemented these searches by searching review articles and reference lists of trial publications. Collaborators were asked if they knew of any additional RCTs. Three investigators (DAJ, CAC Jr, and ARM) determined which studies met the eligibility criteria.

Data analysis

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 before transfer via email. On receipt, three investigators (DAJ, RLH, and LG) assessed data integrity by doing internal consistency checks and by attempting to replicate results of the analysis for incidence of asthma exacerbations where this 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. Where available, we extracted IPD for certain variables relating to baseline characteristics and follow-up data. Baseline data were requested for age, sex, racial or ethnic origin, weight, height, serum 25(OH) D concentration, study allocation (vitamin D *vs* placebo), and details of stratification variables if applicable. Follow-up data were requested for the total number of asthma exacerbations requiring treatment with systemic corticosteroids, resulting in emergency department attendance or hospital admission, or both, and as defined in the trial protocol; time from first dose of study drug to first asthma exacerbation requiring treatment with systemic corticosteroids; occurrence of serious adverse events and potential adverse reactions to vitamin D supplementation (hypercalcaemia or renal stones); serum 25(OH)D concentration at final follow-up; and duration of participant follow-up.

We used the Cochrane Collaboration Risk of Bias tool[27] 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 or by specifically asking study authors whether all prespecified outcomes were reported. Two investigators (ARM and DAJ) independently assessed study quality, except for the trial by Martineau and colleagues,[12] which was assessed by CAC Jr. Discrepancies were resolved by consensus.

See Online for appendix

The primary outcome of the meta-analysis was incidence of asthma exacerbation requiring treatment with systemic corticosteroids. We selected this outcome on the basis that requirement for systemic corticosteroids is a widely recognised indicator of exacerbation severity.[28] We measured the primary outcome as rate of asthma exacerbations, proportion of participants with at least one exacerbation, and time to first exacerbation. Secondary outcomes were incidence of exacerbations resulting in emergency department attendance or hospital admission, or both; incidence of exacerbations as defined in the protocol of the primary trial; incidence of serious adverse events; incidence of potential adverse reactions to vitamin D (hypercalcaemia and renal stones); and mortality (asthma related and all cause).

Effects of the intervention on event rates, dichotomous outcomes, and time to first event were expressed as rate ratios (RRs), odds ratios (ORs), and hazard ratios (HRs), respectively. LG, DAJ and RLH analysed the data. Our IPD meta-analysis approach followed published guidelines.[29] Initially, all studies were reanalysed separately; the original authors were asked to confirm accuracy of this reanalysis where it had been done previously, and any discrepancies were resolved. Then, for each outcome separately, we did both one-step and two-step IPD meta-analyses. In the one-step approach, IPD from all studies were modelled simultaneously while accounting for the clustering of participants within studies. We used mixed models, with a random effect for study and fixed effects for age and sex, to obtain the pooled intervention effect with a 95% CI. We analysed event rates using mixed-effect Poisson regression; proportions using mixed-effects logistic regression, additionally adjusted for duration of participant follow-up; and survival data using mixed-effects parametric survival models. We did not adjust for other covariates because missing values for some participants would have led to their exclusion from statistical analyses. In the two-step approach, IPD were first analysed for each separate study independently to produce an estimate of the treatment effect for that study. We analysed event rates using Poisson regression, with adjustment for age and sex; proportions using logistic regression with adjustment for age, sex, and duration of participant follow-up; and survival data using parametric survival models, with adjustment for age and sex. We then calculated a weighted average of the individual treatment effect estimates using the DerSimonian and Laird procedure for random-effects meta-analysis.[30] For the two-step IPD meta-analysis, we summarised heterogeneity using the I^2 statistic.

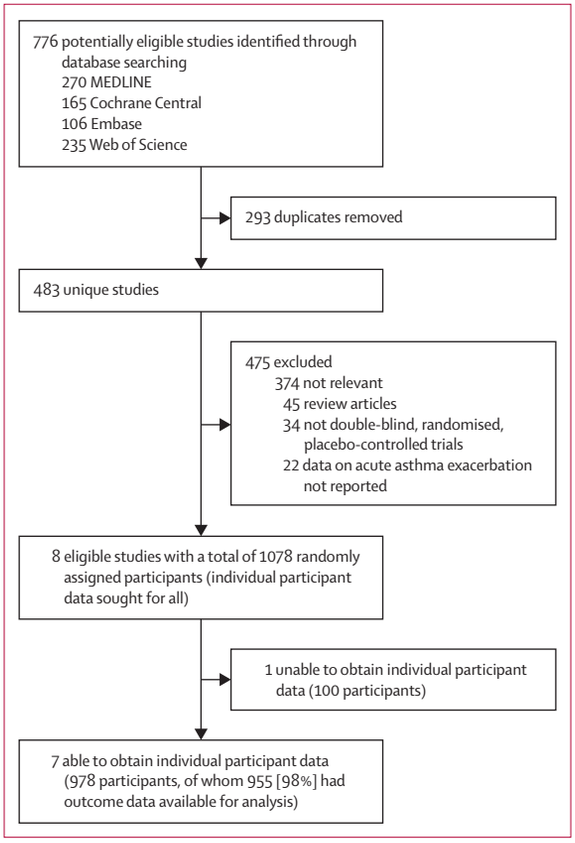

Figure 1: **Study selection**

To investigate the causes of heterogeneity and identify factors modifying the effects of vitamin D supplementation, we did prespecified subgroup analyses by extending the one-step meta-analysis framework to include treatment-covariate interaction terms. Subgroups were defined according to baseline vitamin D status (serum 25[OH]D <25 nmol/L *vs* ≥25 nmol/L), age (<16 years *vs* ≥16 years), ethnic or racial origin (African-American, Afro-Caribbean, or black African origin *vs* Asian origin *vs* white European origin *vs* other or mixed origin), body-mass index (<25 kg/m² *vs* ≥25 kg/m²), vitamin D dosing regimen (daily or weekly administration without bolus dosing *vs* administration of a regimen including at least one bolus dose of at least 30 000 IU vitamin D), dose size (daily equivalent <2000 IU *vs* ≥2000 IU), and concomitant asthma treatment (use of inhaled corticosteroids *vs* not). The 25 nmol/L cutoff for baseline 25(OH)D concentration in the subgroup analyses was selected because it is the threshold for vitamin D deficiency defined by the UK Department of Health[31] and because, below this level, vitamin D supplementation protects most strongly against acute respiratory infection.[23] We also did an exploratory analysis investigating effects in subgroups defined using the 50 nmol/L and 75 nmol/L cutoffs for baseline circulating 25(OH)D concentration because observational studies have reported that less profound states of vitamin D deficiency might associate independently with increased risk of asthma exacerbation.[7,8] We also did exploratory subgroup analyses by sex and study duration (<6 months *vs* ≥6 months) in response to comments from reviewers. Statistical significance was inferred for subgroup effects in which the p value for the treatment-covariate interaction terms was less than 0·05. We did a responder analysis in participants randomly assigned to the intervention arm of included studies for whom end-study 25(OH)D data were available, comparing risk of asthma exacerbations treated with systemic corticosteroids in participants who attained a serum 25(OH)D of 75 nmol/L or higher *vs* participants who did not.

For the primary analysis of rate of exacerbations requiring systemic steroids, the likelihood of publication bias was investigated through the construction of a contour-enhanced funnel plot.[32] We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias)[33] to assess the quality of the body of evidence contributing to the principal analyses of rate of exacerbations requiring systemic steroids, the proportion of participants with at least one exacerbation requiring emergency department attendance or hospital admission, or both, and the proportion of participants with at least one serious adverse event.

Data were analysed using STATA IC, version 12. This study was registered with the PROSPERO, number CRD42014013953.

Role of the funding source

The National Institute of Health Research had no role in study design, data collection, data analysis, or data interpretation, or writing of the report. 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

Our search identified 483 unique studies that we assessed for eligibility, of which eight studies with a total of 1078 randomly assigned participants fulfilled eligibility criteria (figure 1). We sought IPD for all eight studies, which we obtained for seven (total 978 participants); data were not obtained for one study (100 participants) because the corresponding author did not respond to invitations to contribute IPD to this meta-analysis. Outcome data were obtained for 955 (98%) of 978 randomly assigned participants in these seven studies.

The seven analysed RCTs were done in six different countries on three continents, and enrolled participants of both sexes aged 1·6–85·0 years (table 1). Five RCTs with a total of 297 included participants enrolled children, and two RCTs with a total of 658 included participants enrolled adults (table 1). Baseline serum 25(OH)D concentrations were determined in six RCTs, ranging from undetectable to 187·2 nmol/L; table 1). All studies administered oral

vitamin D_3 to participants in the intervention arm: this was given as a bolus dose every 2 months in one study (100 000 IU per bolus); as a daily dose in four studies (ranging from 500 IU/day to 2000 IU/day; and as a combination of bolus and daily doses in two studies (100 000 IU bolus then 400–4000 IU/day). Study durations ranged from 15 weeks to 1 year. Details of the number of asthma exacerbations treated with systemic corticosteroids and the proportion of participants experiencing at least one such event by arm and study are presented in appendix (p 3). In two RCTs,[9,10] no asthma exacerbations requiring treatment with systemic corticosteroids arose, and in one trial,[14] only one asthma exacerbation requiring treatment with systemic corticosteroids arose. Effect estimates could not be calculated for these three studies individually; accordingly, these studies contributed data to the one-step, but not the two-step, meta-analyses.

IPD integrity was confirmed by replication of primary analyses in published papers where applicable. The process of checking IPD revealed two discrepancies with primary reports. In the trial by Urashima and colleagues,[9] the relative risk for asthma exacerbation was calculated using denominators based on the study population as a whole, irrespective of whether or not the participants had asthma (n=334). By contrast, we calculated this figure using denominators based on the number of children with asthma for whom outcome data were available (n=99). In the trial by Castro and colleagues,[11] IPD detailed 14 serious adverse events arising in participants randomly assigned to placebo, as compared with 13 such events reported in the published manuscript.

Details of the risk of bias assessment are provided in appendix (p 4). All RCTs, but one, were assessed as being at low risk of bias for all aspects analysed. The trial by Kerley and colleagues[16] was assessed as being at unclear risk of bias due to its high rate of loss to follow-up (12 of 51 participants), although we found no evidence to suggest differential rates of loss to follow-up between the intervention and control arms (seven of 24 participants *vs* five of 27).

Overall, in the one-step IPD meta-analysis, vitamin D supplementation resulted in a significant reduction in the rate of asthma exacerbations requiring treatment with systemic corticosteroids (adjusted incidence RR [aIRR] 0·74, 95% CI 0·56–0·97; p=0·03; 955 participants in seven studies; table 2). This evidence was assessed as being of high quality (appendix p 5). The two-step IPD meta-analysis revealed a similar effect size among 719 participants in four studies (aIRR 0·69, 0·52–0·92, p=0·01; $p_{heterogeneity}$=0·56; figure 2). In the analyses of the proportion of participants with at least one asthma exacerbation treated with systemic corticosteroids, the effect estimates favoured vitamin D but the differences between groups were not significant, in both the one-step analysis (adjusted OR [aOR] 0·75, 95% CI 0·51–1·09, p=0·13; 955 participants in seven studies) and two-step analysis (aOR 0·69, 0·46–1·02, p=0·06; $p_{heterogeneity}$=0·74;

	Setting	Participants	Age (years)	Male:female	25(OH)D assay; EQA scheme	Baseline 25(OH)D (nmol/L)	Participants with baseline 25(OH)D <25 nmol/L	Intervention: control	Oral dose of vitamin D_3 (intervention arm)	Participants with 25(OH)D ≥75 nmol/L at final follow-up	Control	Study duration	Participants with available outcome data/participants randomly assigned to a group
Urashima et al (2010)[9]	Japan	Schoolchildren with asthma	9·5 (2·1; 6·0–15·0)	56:43	..	Not determined	..	43:56	1200 IU/day	..	Placebo	4 months	99/110 (90%)
Majak et al (2011)[10]	Poland	Schoolchildren with asthma	10·9 (3·3; 6·0–17·0)	32:16	RIA (BioSource Europe); RIQAS	88·9 (38·2; 31·5–184·7)	0/48 (0%)	24:24	500 IU/day	16/24 (67%)	Placebo	6 months	48/48 (100%)
Castro et al (2014)[11]	USA	Adults with asthma	39·2 (12·9; 18·0–85·0)	130:278	CLA (DiaSorin); VDSP	47·0 (16·9; 10·0–74·6)	55/408 (13%)	201:207	100 000 IU bolus then 4000 IU/day	143/174 (82%)	Placebo	28 weeks	408/408 (100%)
Martineau et al (2015)[12]	UK	Adults with asthma	47·9 (14·4; 16·0–78·0)	109:141	LC-MS/MS; DEQAS	49·6 (24·7; 0·0–139·0)	36/250 (14%)	125:125	120 000 IU bolus once every 2 months	40/107 (37%)	Placebo	1 year	250/250 (100%)
Tachimoto et al (2016)[14]	Japan	Schoolchildren with asthma	9·9 (2·3; 6·0–15·0)	50:39	RIA (DiaSorin); CAP	74·9 (24·6; 20·0–187·2)	1/89 (1%)	54:35	800 IU/day, first 2 months	34/54 (63%)	Placebo	6 months	89/89 (100%)
Kerley et al (2016)[16]	Ireland	Schoolchildren with asthma	8·6 (2·8; 5·0–15·0)	24:15	LC-MS/MS; DEQAS	54·4 (17·4; 26·0–92·0)	0/39 (0%)	17:22	2000 IU/day	13/17 (76%)	Placebo	15 weeks	39/51 (76%)
Jensen et al (2016)[15]	Canada	Pre-schoolchildren with asthma	2·9 (1·1; 1·6–5·5)	7:15	LC-MS/MS; DEQAS	64·2 (14·0; 42·0–87·0)	0/22 (0%)	11:11	100 000 IU bolus then 400 IU/day	7/8 (88%)	400 IU vitamin D_3 per day	6 months	22/22 (100%)

Data are mean (SD; range) or n/N (%), unless stated otherwise. 40 IU vitamin D_3 equals 1 μg. 25(OH)D concentrations reported in ng/mL were converted to nmol/L by multiplying by 2·496. 25(OH)D=25-hydroxyvitamin D. EQA=external quality assessment. IU=international unit. RIA=radio-immunoassay. RIQAS=Randox International Quality Assessment Scheme. CLA=chemiluminescent assay. VDSP=Vitamin D Standardisation Program of the Office of Dietary Supplements, National Institutes of Health, USA. LC-MS/MS=liquid chromatography tandem-mass spectrometry. DEQAS=Vitamin D External Quality Assessment Scheme. CAP=College of American Pathologists.

Table 1: **Characteristics of trials and participants included in individual participant data meta-analysis**

	Number of participants; number of trials*	Event rate per participant-year (control group)	Event rate per participant-year (intervention group)	Adjusted incidence rate ratio (95% CI)†	p value	$p_{interaction}$‡
Overall	955; 7	121/284·7 (0·43)	85/286·6 (0·30)	0·74 (0·56–0·97)	0·03	NA
Baseline 25(OH)D (nmol/L)						
<25	92; 3	14/33·0 (0·42)	6/32·2 (0·19)	0·33 (0·11–0·98)	0·046	0·25
≥25	764; 6	107/233·8 (0·46)	79/240·2 (0·33)	0·77 (0·58–1·03)	0·08	..
Age (years)						
<16	290; 5	26/57·6 (0·45)	19/61·8 (0·31)	0·64 (0·34–1·20)	0·16	0·56
≥16	665; 3	95/227·2 (0·42)	66/224·7 (0·29)	0·70 (0·51–0·97)	0·03	..
Sex						
Female	547; 7	80/163·6 (0·49)	47/167·7 (0·28)	0·61 (0·43–0·88)	0·008	0·17
Male	408; 7	41/121·1 (0·34)	38/118·9 (0·32)	0·91 (0·58–1·42)	0·67	..
Ethnic or racial origin						
African-American, Afro-Caribbean, or black African origin	154; 3	28/46·4 (0·60)	14/43·4 (0·32)	0·54 (0·29–1·03)	0·06	0·32
Asian origin	207; 5	6/42·0 (0·14)	4/48·5 (0·08)	0·81 (0·19–3·51)	0·78	..
White European origin	520; 5	80/177·8 (0·45)	59/172·3 (0·34)	0·79 (0·56–1·11)	0·17	..
Other or mixed	74; 3	7/18·6 (0·38)	8/22·3 (0·36)	0·88 (0·31–2·53)	0·81	..
Weight						
Not overweight	381; 7	38/110·5 (0·34)	26/104·5 (0·25)	0·91 (0·55–1·51)	0·71	0·31
Overweight§	574; 7	83/174·3 (0·48)	59/182·0 (0·32)	0·68 (0·49–0·95)	0·02	..
Bolus-dose vitamin D given						
No	275; 4	13/53·8 (0·24)	10/58·9 (0·17)	0·65 (0·26–1·63)	0·36	0·49
Yes	680; 3	108/230·9 (0·47)	75/227·6 (0·33)	0·71 (0·52–0·95)	0·02	..
Daily dose equivalent (IU)						
<2000	258; 4	13/52·1 (0·25)	10/58·6 (0·17)	0·62 (0·26–1·44)	0·26	0·78
≥2000	697; 3	108/232·7 (0·46)	75/228·0 (0·33)	0·73 (0·54–0·98)	0·03	..
Received inhaled corticosteroids						
No	92; 4	1/18·8 (0·05)	4/26·1 (0·15)	1·11 (0·07–18·40)	0·94	0·19
Yes	764; 5	120/248·0 (0·48)	81/246·3 (0·33)	0·71 (0·54–0·95)	0·02	..
Study duration (months)						
<6	138; 2	13/25·0 (0·52)	9/19·4 (0·46)	0·50 (0·18–1·37)	0·18	0·62
≥6	816; 5	108/259·8 (0·42)	76/267·2 (0·28)	0·72 (0·53–0·96)	0·03	..

NA=not applicable. IU=international unit. 25(OH)D=25-hydroxyvitamin D. *Some trials did not contribute data to a given subgroup, either because individuals within that subgroup were not represented or because data relating to the potential effect modifier were not available, accordingly the number of trials represented varies between subgroups. †Adjusted for age and sex. ‡$p_{interaction}$ values are between adjusted rate ratios in the subgroup. §Overweight defined as body-mass index *Z* score of 1·0 or more for participants younger than 19 years and as body-mass index of 25 kg/m² or more for participants aged 19 years or older.

Table 2: **One-step individual participant data meta-analysis of rate of asthma exacerbations requiring treatment with systemic corticosteroids**

719 participants in four studies; appendix p 8). Similarly, for the analyses of time to first exacerbation, the effect estimates favoured vitamin D but the differences between groups were not significant, in both the one-step analysis (adjusted HR [aHR] 0·78, 95% CI 0·55–1·10; p=0·16; 868 participants in five studies) and two-step analysis (aHR 0·74, 0·52–1·05, p=0·09; $p_{heterogeneity}$=0·58; 680 participants in three studies; appendix p 9).

We did subgroup analyses to investigate whether the effects of vitamin D supplementation on rate of asthma exacerbations requiring treatment with systemic corticosteroids differed according to baseline vitamin D status, age, ethnic or racial origin, body-mass index, administration of bolus-dose vitamin D, amount of vitamin D administered, and concomitant use of inhaled corticosteroids (table 2). We also did exploratory post-hoc subgroup analyses by sex and study duration (table 2). Vitamin D supplementation significantly reduced the rate of asthma exacerbations treated with systemic corticosteroids in individuals with baseline circulating 25(OH)D of less than 25 nmol/L (aIRR 0·33, 95% CI 0·11–0·98; 92 participants in three studies; within subgroup p=0·046; table 2). Vitamin D supplementation did not result in a statistically significant reduction in exacerbation rate in participants with baseline 25(OH)D of 25 nmol/L or higher (aIRR 0·77, 0·58–1·03; 764 participants in six studies; within subgroup p=0·08). The treatment-covariate interaction term (ratio of aIRRs) for this subgroup analysis was 0·56 (95% CI 0·20–1·52, $p_{interaction}$=0·25). Quality assessments of these within-

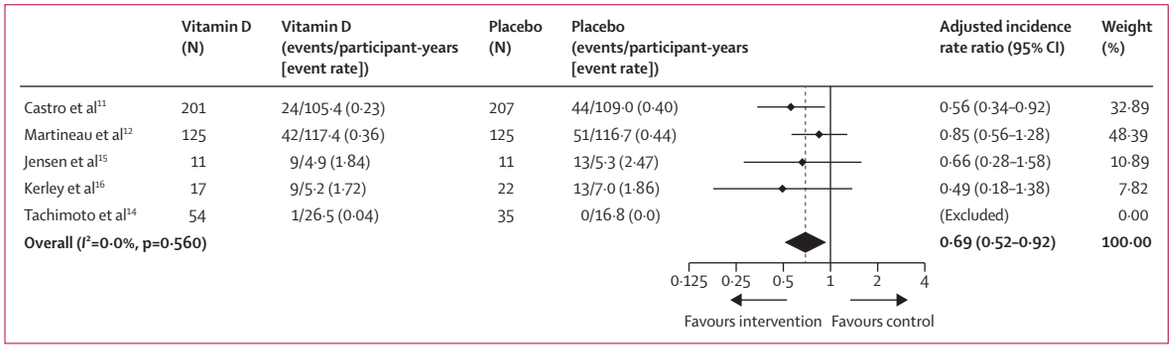

Figure 2: **Two-step individual participant data meta-analysis, event rate for asthma exacerbations requiring treatment with systemic corticosteroids**
Weights are from the random-effects analysis. No asthma exacerbations requiring treatment with systemic corticosteroids arose in the trials by Urashima and colleagues[9] and Majak and colleagues.[10] Only one such event arose in the trial by Tachimoto and colleagues;[14] as such, an adjusted incidence rate ratio could not be calculated for this study.

subgroup effects were downgraded to moderate due to their relative imprecision (appendix p 5).

An exploratory analysis testing the effects of vitamin D supplementation in individuals with baseline 25(OH)D concentrations in the ranges of 25–49·9 nmol/L, 50–74·9 nmol/L, and 75 nmol/L or higher did not reveal evidence of effect modification ($p_{interaction}$=0·40) or significant protective effects of vitamin D supplementation within these subgroups (subgroup with baseline 25[OH]D of 25·0–49·9 nmol/L: aIRR 0·79, 95% CI 0·50–1·23 [306 participants in six studies; within subgroup p=0·29]; subgroup with baseline 25[OH]D of 50·0–74·9 nmol/L: aIRR 0·76, 0·48–1·22 [334 participants in six studies; within subgroup p=0·26]; subgroup with baseline 25[OH]D of 75 nmol/L or higher: aIRR 0·79, 0·37–1·69 [120 participants in five studies; within subgroup p=0·54]; figure 3). p values for interaction for all other subgroup analyses were also higher than 0·05 (table 2; appendix p 7 for end-study 25[OH]D level pairwise analyses).

Results of the one-step IPD meta-analysis of secondary efficacy outcomes are presented in table 3. Vitamin D supplementation reduced the proportion of people with at least one asthma exacerbation resulting in emergency department attendance or hospital admission, or both (aOR 0·46, 95% CI 0·24–0·91; 955 participants in seven studies; p=0·03). No significant effect of vitamin D supplementation was seen on risk of having at least one asthma exacerbation as defined in the protocols of primary RCTs (aOR 0·81, 0·58–1·11; 955 participants in seven studies; p=0·19).

Results of the one-step IPD meta-analysis of safety outcomes are also reported in table 3. No participant had hypercalcaemia or renal stones. Vitamin D supplementation did not affect the risk of having at least one serious adverse event of any cause (aOR 0·87, 95% CI 0·46–1·63; 955 participants in seven studies; p=0·66). Only one trial participant died, which was due to a road traffic accident.

A funnel plot for the outcome of rate of asthma exacerbations treated with systemic corticosteroids did not suggest publication bias in relation to this outcome because the smaller RCTs showed equal spread of results on both sides of the overall adjusted rate ratio (appendix p 10). No relation between effect size and study size was apparent (appendix p 6).

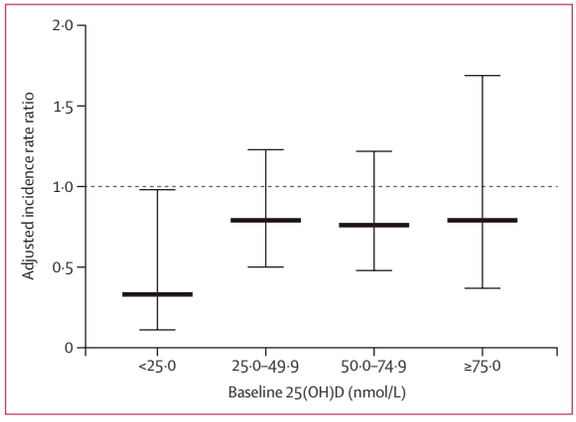

Figure 3: **Effects of vitamin D supplementation on asthma exacerbation rate by baseline circulating 25(OH)D concentration categorised by 25 nmol/L strata**
Shown are the results of one-step individual participant data meta-analysis. The incidence rate ratio is adjusted for age and sex. Mean and 95% CI are presented. 25(OH)D=25-hydroxyvitamin D.

Discussion

We report results of the first IPD meta-analysis of RCTs of vitamin D to reduce the risk of asthma exacerbations. In the study population as a whole, vitamin D supplementation reduced the rate of asthma exacerbations treated with systemic corticosteroids, as compared with placebo (0·30 events per person per year *vs* 0·43 events per person per year; p=0·03), and the proportion of people having at least one exacerbation requiring emergency department attendance or hospital admission, or both (3% *vs* 6%; p=0·03). Subgroup analyses revealed that reductions in exacerbation rate with vitamin D were statistically significant in participants with baseline circulating 25(OH)D concentration levels less than 25 nmol/L, but not in people with baseline levels of 25(OH)D of 25 nmol/L or

	Number of participants; number of trials*	Participants with one or more event (control group)	Participants with one or more event (intervention group)	Adjusted odds ratio (95% CI)*	p value
Asthma exacerbation resulting in emergency department attendance or hospital admission, or both	955; 7	28/480 (6%)	14/475 (3%)	0·46 (0·24–0·91)	0·03
Asthma exacerbation as defined in primary trial	955; 7	123/480 (26%)	105/475 (22%)	0·81 (0·58–1·11)	0·19
Serious adverse event of any cause	955; 7	22/480 (5%)	20/475 (4%)	0·87 (0·46–1·63)	0·66
Hypercalcaemia	955; 7	0/480 (0%)	0/475 (0%)	..	..
Renal stones	955; 7	0/480 (0%)	0/475 (0%)	..	..
Death due to asthma exacerbation	955; 7	0/480 (0%)	0/475 (0%)	..	..
Death due to any cause	955; 7	0/480 (0%)	1/475 (<1%)†	..	..

*Adjusted for age, sex, and duration of participant follow-up. †Death due to road traffic accident.

Table 3: **One-step individual participant data meta-analysis of secondary outcomes**

higher. Vitamin D supplementation was safe at the doses administered: no instances of hypercalcaemia or renal stones were seen, and serious adverse events were evenly distributed between participants randomly assigned to vitamin D versus placebo.

Our findings from analysing the study population as a whole are consistent with those of our recent aggregate data meta-analysis of RCTs of vitamin D for the management of asthma, which reported protective effects against asthma exacerbations treated with systemic corticosteroids of similar magnitude (IRR 0·64, 95% CI 0·46–0·90).[20] The present study represents a significant advance because access to IPD has allowed us to do subgroup analyses to assess whether specific factors modify the effects of vitamin D supplementation on risk of asthma exacerbations. We hypothesised that the protective effects of vitamin D supplementation against asthma exacerbation would be strongest in participants with the lowest baseline vitamin D status, as has been previously reported for the outcome of acute respiratory infection.[23] We saw a statistically significant rate reduction in participants with baseline 25(OH)D of less than 25 nmol/L, but not in participants with 25(OH)D of 25 nmol/L or higher. However, the p value for interaction for this subgroup analysis was non-significant ($p_{interaction}$=0·25); formally, therefore, we have not shown that effects are stronger in one group than in the other. p values for interaction were also higher than 0·05 for subgroup analyses relating to age, sex, racial or ethnic origin, body weight, vitamin D dosing regimen, use of inhaled corticosteroids, and study duration. These factors might not modify the effects of vitamin D supplementation on exacerbation risk; alternatively, we might have lacked statistical power to detect the relevant interactions. Several additional RCTs are ongoing (eg, NCT01419262, NCT01728571, NCT02197702, and NCT02424552), and, in due course, we hope to include IPD from these studies in an updated meta-analysis, increasing the power for subgroup analyses.

Although vitamin D reduced the risk of asthma exacerbations requiring treatment with systemic corticosteroids, no significant effect was seen on the risk of asthma exacerbations as originally defined in the protocols of the primary trials. In the majority of trials, the original definition of exacerbation was broader than the one prespecified for this meta-analysis—eg, encompassing events that resulted in dips in peak expiratory flow rate or FEV_1 that were not treated with systemic corticosteroids.[11,12] Differing efficacies of vitamin D supplementation for these two outcomes might suggest that this intervention specifically reduces risk of more serious exacerbations. Alternatively, less stringent definitions of exacerbation in primary trial protocols might have resulted in a degree of misclassification with a consequent increase in noise: signal ratio that might have obscured a real effect of vitamin D on exacerbation risk.

Our study has several strengths. The included studies were of high quality, and of sufficient duration for steady-state 25(OH)D concentrations to be attained among participants randomly assigned to receive vitamin D_3. The proportion of randomly assigned participants with missing outcome data was small (2·4%), and 25(OH)D concentrations were measured using validated assays in laboratories that participated in external quality assessment schemes. The analysis contained participants with diverse characteristics in multiple settings, incorporating new data from a trial[16] done in children with severe asthma that was published after the date of the final literature search for our previous aggregate data meta-analysis.[20] Our findings therefore have a high degree of internal and external validity.

Our study also has some limitations. We did not obtain IPD for one eligible trial;[13] however, this study was relatively small (n=100) and has previously been assessed as being at high risk of bias.[20] Notably, this study reported strong protective effects of vitamin D against asthma exacerbation;[13] as such, if exclusion of its findings leads to a bias, it is likely to be a bias towards the null. Interpretation of the funnel plot (appendix p 10) is limited by the small number of studies included, but the fact that the smaller RCTs showed an equal spread of results on

both sides of the overall adjusted rate ratio provides some reassurance that publication bias was not a major issue in our meta-analysis; an impression that is reinforced by the absence of an association between effect size and study size (appendix p 6). Power for some subgroup analyses was limited; this is an inescapable problem in view of the small number of published RCTs in this field. Where 95% CI for estimates of effect from subgroup analyses were wide, we downgraded our quality assessment of subgroup findings to moderate (appendix p 5).

In conclusion, our IPD meta-analysis confirms results from our previous aggregate data meta-analysis showing that vitamin D supplementation safely reduces the rate of asthma exacerbations overall. However, we did not find definitive evidence that effects of this intervention differed across subgroups of patients. In view of the low cost of this intervention and the major economic burden associated with asthma exacerbations, vitamin D supplementation represents a potentially cost-effective strategy to reduce this important cause of morbidity and mortality.

Contributors

ARM led the funding application, with input from RLH, CJG, and CAC Jr who were coapplicants. DAJ, CAC Jr, and ARM assessed eligibility of studies for inclusion. DAJ, CJG, CAC Jr, CPK, MEJ, DM, IS, MU, and ARM were all directly involved in the acquisition of data for the Article. RLH designed the statistical analyses in consultation with the authors contributing individual patient data. Statistical analyses were done by LG, DAJ, and RLH. ARM wrote the first draft of the Article. All authors revised the Article critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the Article in ensuring that questions related to the accuracy or integrity of any part of the Article were appropriately investigated and resolved.

Declaration of interests

We declare no competing interests.

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