Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials

David A Jolliffe, Carlos A Camargo Jr, John D Sluyter, Mary Aglipay, John F Aloia, Davaasambuu Ganmaa, Peter Bergman, Heike A Bischoff-Ferrari, Arturo Borzutzky, Camilla T Damsgaard, Gal Dubnov-Raz, Susanna Esposito, Clare Gilham, Adit A Ginde, Inbal Golan-Tripto, Emma C Goodall, Cameron C Grant, Christopher J Griffiths, Anna Maria Hibbs, Wim Janssens, Anuradha Vaman Khadilkar, Ilkka Laaksi, Margaret T Lee, Mark Loeb, Jonathon L Maguire, Paweł Majak, David T Mauger, Semira Manaseki-Holland, David R Murdoch, Akio Nakashima, Rachel E Neale, Hai Pham, Christine Rake, Judy R Rees, Jenni Rosendahl, Robert Scragg, Dheeraj Shah, Yoshiki Shimizu, Steve Simpson-Yap, Geeta Trilok-Kumar, Mitsuyoshi Urashima, Adrian R Martineau

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Barts and The London School of Medicine and Dentistry, and Asthma UK Centre for Applied Research, Queen Mary University of London, London, UK (D A Jolliffe PhD, Prof A R Martineau PhD, Prof C J Griffiths DPhil); **Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA** (Prof C A Camargo Jr MD); **School of Population Health** (J D Sluyter PhD, Prof R Scragg PhD), **and Department of Paediatrics: Child and Youth Health, Faculty of Medical and Health Sciences** (Prof C C Grant PhD), **University of Auckland, Auckland, New Zealand; Department of Pediatrics, St Michael's Hospital, Toronto, ON, Canada** (M Aglipay MSc, Prof J L Maguire MD); **Bone Mineral Research Center, Winthrop University Hospital, Mineola, NY, USA** (Prof J F Aloia MD); **Department of Nutrition, Harvard TH Chan Shool of Public Health, Boston, MA, USA** (D Ganmaa PhD); **Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden** (P Bergman MD); **Department of Geriatric Medicine and Aging Research, University Hospital Zurich, Zurich, Switzerland** (Prof H A Bischoff-Ferrari MD); **Department of Pediatric Infectious Diseases and Immunology, School of Medicine, Pontificia Universidad Católica de Chile,**

Summary

Background A 2017 meta-analysis of data from 25 randomised controlled trials (RCTs) of vitamin D supplementation for the prevention of acute respiratory infections (ARIs) revealed a protective effect of this intervention. We aimed to examine the link between vitamin D supplementation and prevention of ARIs in an updated meta-analysis.

Methods For this systematic review and meta-analysis, we searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, and the ClinicalTrials.gov registry for studies listed from database inception to May 1, 2020. Double-blind RCTs of vitamin D_3, vitamin D_2, or 25-hydroxyvitamin D (25[OH]D) supplementation for any duration, with a placebo or low-dose vitamin D control, were eligible if they had been approved by a research ethics committee, and if ARI incidence was collected prospectively and prespecified as an efficacy outcome. Studies reporting results of long-term follow-up of primary RCTs were excluded. Aggregated study-level data, stratified by baseline 25(OH)D concentration and age, were obtained from study authors. Using the proportion of participants in each trial who had one or more ARIs, we did a random-effects meta-analysis to obtain pooled odds ratios (ORs) and 95% CIs to estimate the effect of vitamin D supplementation on the risk of having one or more ARIs (primary outcome) compared with placebo. Subgroup analyses were done to estimate whether the effects of vitamin D supplementation on the risk of ARI varied according to baseline 25(OH)D concentration (<25 nmol/L *vs* 25·0–49·9 nmol/L *vs* 50·0–74·9 nmol/L *vs* >75·0 nmol/L), vitamin D dose (daily equivalent of <400 international units [IU] *vs* 400–1000 IU *vs* 1001–2000 IU *vs* >2000 IU), dosing frequency (daily *vs* weekly *vs* once per month to once every 3 months), trial duration (≤12 months *vs* >12 months), age at enrolment (<1·00 years *vs* 1·00–15·99 years *vs* 16·00–64·99 years *vs* ≥65·00 years), and presence versus absence of airway disease (ie, asthma only, COPD only, or unrestricted). Risk of bias was assessed with the Cochrane Collaboration Risk of Bias Tool. The study was registered with PROSPERO, CRD42020190633.

Findings We identified 1528 articles, of which 46 RCTs (75 541 participants) were eligible. Data for the primary outcome were obtained for 48 488 (98·1%) of 49 419 participants (aged 0–95 years) in 43 studies. A significantly lower proportion of participants in the vitamin D supplementation group had one or more ARIs (14 332 [61·3%] of 23 364 participants) than in the placebo group (14 217 [62·3%] of 22 802 participants), with an OR of 0·92 (95% CI 0·86–0·99; 37 studies; I^2=35·6%, $p_{heterogeneity}$=0·018). No significant effect of vitamin D supplementation on the risk of having one or more ARIs was observed for any of the subgroups defined by baseline 25(OH)D concentration. However, protective effects of supplementation were observed in trials in which vitamin D was given in a daily dosing regimen (OR 0·78 [95% CI 0·65–0·94]; 19 studies; I^2=53·5%, $p_{heterogeneity}$=0·003), at daily dose equivalents of 400–1000 IU (0·70 [0·55–0·89]; ten studies; I^2=31·2%, $p_{heterogeneity}$=0·16), for a duration of 12 months or less (0·82 [0·72–0·93]; 29 studies; I^2=38·1%, $p_{heterogeneity}$=0·021), and to participants aged 1·00–15·99 years at enrolment (0·71 [0·57–0·90]; 15 studies; I^2=46·0%, $p_{heterogeneity}$=0·027). No significant interaction between allocation to the vitamin D supplementation group versus the placebo group and dose, dose frequency, study duration, or age was observed. In addition, no significant difference in the proportion of participants who had at least one serious adverse event in the vitamin supplementation group compared with the placebo group was observed (0·97 [0·86–1·07]; 36 studies; I^2=0·0%, $p_{heterogeneity}$=0·99). Risk of bias within individual studies was assessed as being low for all but three trials.

Interpretation Despite evidence of significant heterogeneity across trials, vitamin D supplementation was safe and overall reduced the risk of ARI compared with placebo, although the risk reduction was small. Protection was associated with administration of daily doses of 400–1000 IU for up to 12 months, and age at enrolment of 1·00–15·99 years. The relevance of these findings to COVID-19 is not known and requires further investigation.

Funding None.

Introduction

Interest in the potential for vitamin D supplementation to reduce the risk of acute respiratory infections (ARIs) has increased since the emergence of the COVID-19 pandemic.[1] This interest stems from findings of laboratory studies showing that vitamin D metabolites support innate immune responses to respiratory viruses,[2] together with observational studies reporting independent associations between low circulating concentrations of 25-hydroxyvitamin D (25[OH]D), the widely accepted biomarker of vitamin D status, and increased risk of ARI caused by other pathogens.[3,4] Randomised controlled trials (RCTs) of vitamin D supplementation for the prevention of ARI have produced heterogeneous results, with some showing protection, and others reporting null findings. We previously meta-analysed individual participant data from 10 933 participants enrolled in 25 RCTs,[5–29] and showed a protective overall effect of supplementation that was stronger in those with baseline 25(OH)D concentrations of less than 25 nmol/L versus those with baseline 25(OH)D concentrations of 25 nmol/L or higher, and in trials in which vitamin D was administered daily or weekly rather than in less frequent bolus doses.[30] Since the date of the final literature search in this previous meta-analysis (Dec 31, 2015), 21 RCTs involving 64 220 participants who fulfilled the same eligibility criteria have been done (including four with unpublished data [NCT02404623, NCT02046577, NCT01875757, and NCT01758081]).[31–47] We therefore sought data from these more recent studies for inclusion in an updated meta-analysis of stratified aggregate (ie, trial-level) data to establish whether vitamin D supplementation reduced overall ARI risk, and to evaluate whether the effects of vitamin D supplementation on ARI risk varied according to baseline 25(OH)D concentration, dosing regimen (frequency, dose, and trial duration), or age at enrolment.

Methods

Search strategy and selection criteria

In this systematic review and meta-analysis, two investigators (ARM and DAJ) searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, and the ClinicalTrials.gov registry for studies listed from database inception to May 1, 2020. The full list of search terms used are in the appendix (pp 2–4). Randomised, double-blind, trials of supplementation with vitamin D_3, vitamin D_2, or 25(OH)D of any duration, with a placebo or low-dose vitamin D control group, were eligible for inclusion if they had been approved by a research ethics committee, and if data on

Research in context

Evidence before this study

We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, Web of Science, and the ClinicalTrials.gov registry on May 1, 2020, using the search terms listed in the appendix (pp 2–4). We searched for randomised controlled trials and meta-analyses of randomised controlled trials, published in English between database inception and May 1, 2020, evaluating the effectiveness of vitamin D supplementation for the prevention of acute respiratory infections. We identified one meta-analysis of individual participant data from 10 933 participants enrolled in 25 randomised controlled trials of vitamin D supplementation for the prevention of acute respiratory infection. This study showed an overall protective effect of vitamin D supplementation compared with placebo (adjusted odds ratio 0·88 [95% CI 0·81–0·96]). Subgroup analyses revealed that participants with the lowest vitamin D status at baseline who received daily or weekly supplementation benefitted most compared with those who had a higher baseline vitamin D status (aOR 0·30 [0·17–0·53]).

Added value of this study

Our meta-analysis of aggregate data from 48 488 participants enrolled in 43 randomised controlled trials (published between October, 2009, and February, 2021, and two unpublished trials) stratified by baseline 25-hydroxyvitamin D (25[OH]D) concentration, provides an updated estimate of the protective effects of vitamin D supplementation against acute respiratory infection overall, and in subgroups defined by baseline 25(OH)D status, vitamin D dose and dosing frequency, trial duration, age, and the presence versus absence of airway disease.

Implications of all the available evidence

Overall, vitamin D supplementation reduced the risk of having one or more acute respiratory infections, but there was evidence of significant heterogeneity of effect across trials. A funnel plot indicated left-sided asymmetry, which could reflect publication bias, heterogeneity of effect across trials, or both. No significant effect of vitamin D supplementation was observed for any of the subgroups defined by baseline 25(OH)D concentration. However, protective effects were observed in trials in which vitamin D was given using a daily dosing regimen, at daily dose equivalents of 400–1000 IU, for a duration of 12 months or less, and when vitamin D was given to children aged 1·00 to 15·99 years. The relevance of these findings to COVID-19 is not known and requires further investigation.

Santiago, Chile (A Borzutzky MD); **Department of Nutrition, Exercise and Sports, University of Copenhagen, Frederiksberg, Denmark** (C T Damsgaard PhD); **Exercise, Lifestyle and Nutrition Clinic, Edmond and Lily Safra Children's Hospital, Tel Hashomer, Israel** (Prof G Dubnov-Raz MD); **Paediatric Clinic, Department of Medicine and Surgery, University of Parma, Parma, Italy** (Prof S Esposito MD); **Department of Non-Communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK** (C Gilham MSc, C Rake MSc); **Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, CO, USA** (Prof A A Ginde MD); **Saban Pediatric Medical Center, Soroka University Medical Center, Faculty of Health Sciences, Ben-Gurion University, Beer Sheva, Israel** (I Golan-Tripto MD); **Department of Health Research Methods, Evidence and Impact** (E C Goodall PhD), **and Department of Pathology and Molecular Medicine** (Prof M Loeb MD), **McMaster University, Hamilton, ON, Canada; Department of Pediatrics, Case Western Reserve University School of Medicine, Cleveland, OH, USA** (A M Hibbs MD); **University Hospitals Rainbow Babies and Children's Hospital, Cleveland, OH, USA** (A M Hibbs); **Universitair Ziekenhuis Leuven, Leuven, Belgium** (Prof W Janssens MD); **Hirabai Cowasji Jehangir Medical Research Institute, Maharashtra, India** (A V Khadilkar MD); **Faculty of Medicine and Health Technology, University of Tampere, Tampere, Finland** (I Laaksi MD); **Centre for Military Medicine, Helsinki, Finland** (I Laaksi); **Division of Pediatric Hematology, Oncology, and Stem Cell Transplantation, Columbia University Medical Center, New York, NY USA** (M T Lee MD); **Department of Pediatric Pulmonology, Medical University of Lodz, Lodz, Poland** (P Majak MD); **Department of Statistics, The Pennsylvania State University, Hershey, PA, USA**

(Prof D T Mauger PhD); **Department of Public Health, Epidemiology and Biostatistics, Institute of Applied Health Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK** (S Manaseki-Holland PhD); **Department of Pathology, University of Otago, Christchurch, New Zealand** (Prof D R Murdoch MD); **Jikei University School of Medicine, Tokyo, Japan** (A Nakashima MD, Prof M Urashima MD); **Population Health Department, QIMR Berghofer Medical Research Institute, QLD, Australia** (Prof R E Neale PhD, H Pham MPH); **Department of Epidemiology, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA** (J R Rees MD); **Children's Hospital, Pediatric Research Centre, University of Helsinki and Helsinki University Hospital, Helsinki, Finland** (J Rosendahl MD); **Department of Paediatrics, University College of Medical Sciences, Delhi, India** (Prof D Shah MD); **FANCL Research Institute, FANCL Corporation, Yokohama, Japan** (Y Shimizu PhD); **Neuroepidemiology Unit, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, VIC, Australia** (S Simpson-Yap MD); **Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS, Australia** (S Simpson-Yap); **Institute of Home Economics, University of Delhi, New Delhi, India** (Prof G Trilok-Kumar PhD)

Correspondence to: Prof Adrian R Martineau, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London E1 2AT, UK
a.martineau@qmul.ac.uk

or

Dr David A Jolliffe, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London E1 2AT, UK
d.a.jolliffe@qmul.ac.uk

See Online for appendix

the incidence of ARI were collected prospectively and prespecified as an efficacy outcome. We only included studies with ARI as a prespecified efficacy outcome to minimise misclassification bias (ie, prospectively designed instruments to capture ARI events were deemed more likely to be sensitive and specific for this outcome than retrospective analyses). Studies reporting the results of long-term follow-up of primary RCTs were excluded. Database searches were supplemented by searching review articles and the reference lists of trial publications. Collaborators were also asked if they knew of any additional relevant trials. Three investigators (DAJ, CAC, and ARM) decided which trials met the eligibility criteria. Conflicts over study inclusion were resolved by consensus.

Research ethics committee approval for this meta-analysis was not required in the UK; local ethical permission to contribute data from primary trials was required and obtained for studies by Camargo and colleagues[13] (the Ethics Review Committee of the Mongolian Ministry of Health), Murdoch and colleauges[14] (Southern Health and Disability Ethics Committee; URB/09/10/050/AM02), Rees and colleagues[17] (Committee for the Protection of Human Subjects, Dartmouth College, Hanover, NH, USA; protocol 24381), Tachimoto and colleagues[28] (Ethics Committee of the Jikei University School of Medicine; 26–333: 7839), Tran and colleagues[18] (QIMR Berghofer Medical Research Institute Human Research Ethics Committee; P1570), and Urashima and colleagues[6,20] (Ethics Committee of the Jikei University School of Medicine; 26–333: 7839).

Outcomes

The primary outcome of the meta-analysis was the proportion of participants who had one or more ARIs, with the definition of ARI encompassing events classified as upper respiratory infection, lower respiratory infection, and ARI in an unclassified location (ie, infection of the upper or lower respiratory tract, or both). Secondary outcomes were the proportions of participants experiencing one or more of the following outcomes: upper respiratory infection; lower respiratory infection; emergency department attendance for an ARI, hospital admission for an ARI, or both; death due to ARI or respiratory failure; use of antibiotics to treat an ARI; absence from work or school due to an ARI; serious adverse events; death; and potential adverse reactions to vitamin D (hypercalcaemia and renal stones).

Data analysis

Aggregate data from trials that contributed to our previous meta-analysis of individual participant data[30] were extracted from our central database by DAJ and ARM, with permission from the principal investigators of these studies, and aggregate data from newly identified trials were requested from the principal investigators of these studies. On receipt, these data were assessed by DAJ and ARM for consistency with the associated publications. Study authors were contacted to provide missing data and to resolve any queries arising from these consistency checks. Once queries had been resolved, clean summary data were uploaded to the study database, which was held in STATA IC, version 14.2.

We extracted summary data related to the primary outcome (overall and by subgroup) and secondary outcomes (overall only). Data relating to study characteristics were extracted for the following variables: study setting; eligibility criteria; 25(OH)D assay; 25(OH)D concentrations; details of intervention and control regimens; trial duration; case definitions for ARI; and the number of participants contributing data to the primary analysis. Follow-up summary data were extracted for the proportions of participants who had one or more ARIs during the trial, overall and stratified by baseline serum 25(OH)D concentration, when this information was available. We also extracted summary data on the proportions of participants who had one or more of the following events during the trial: upper respiratory infection; lower respiratory infection; emergency department attendance for an ARI, hospital admission for an ARI, or both; death due to an ARI or respiratory failure; use of antibiotics to treat an ARI; absence from work or school due to an ARI; serious adverse events; death due to any cause; and potential adverse reactions to vitamin D (hypercalcaemia and renal stones).

We used the Cochrane Collaboration Risk of Bias tool[48] to assess the following variables: sequence generation; allocation concealment; masking of participants, personnel, and outcome assessors; completeness of outcome data; evidence of selective outcome reporting; and other potential factors that might affect validity. Study quality was assessed independently by two investigators (ARM and DAJ), except for the six trials for which DAJ or ARM were investigators, which were assessed by CAC and JDS. Any discrepancies were resolved by consensus.

Data were analysed by DAJ and the results were checked and verified by JDS. Our meta-analysis approach followed published guidelines.[49] The primary comparison was of participants randomly assigned to a vitamin D supplementation group (intervention) versus a placebo group; this comparison was done for all of the aforementioned outcomes. For trials that included higher-dose, lower-dose, and placebo groups, data from higher-dose and lower-dose groups were pooled for analysis of the primary comparison. A secondary comparison of participants randomly assigned to higher versus lower doses of vitamin D was done for the primary outcome only. A log odds ratio (OR) and its SE was calculated for each outcome within each trial from the proportion of participants who had one or more events in the intervention group versus the control group. These were meta-analysed in a random-effects model using the metan package[50] within STATA IC (version 14.2) to obtain a pooled OR with a 95% CI, and a measure of heterogeneity summarised by the I^2 statistic with the corresponding p value.

To explore reasons for heterogeneity of effect of the intervention between trials we stratified analyses according to baseline serum 25(OH)D concentration (<25·0 nmol/L *vs* 25·0–49·9 nmol/L *vs* 50·0–74·9 nmol/L *vs* ≥75·0 nmol/L) and according to age at baseline (<1·00 years *vs* 1·00–15·99 years *vs* 16·00–64·99 years *vs* ≥65·00 years). We also performed subgroup analyses according to vitamin D dosing regimen (administration of daily *vs* weekly *vs* once per month to once every 3 months), dose (daily equivalent of <400 international units [IU] *vs* 400–1000 IU *vs* 1001–2000 IU *vs* >2000 IU), trial duration (≤12 months *vs* >12 months), and presence versus absence of airway disease (trials restricted to participants with asthma *vs* those restricted to participants with chronic obstructive pulmonary disease *vs* those in which participants without airway disease were eligible). The thresholds for baseline 25(OH)D concentration used in subgroup analyses were selected a priori because they represent cutoffs that are commonly used to distinguish profound vitamin D deficiency (25[OH]D concentrations of <25 nmol/L), moderate vitamin D deficiency (25–49·9 nmol/L), and suboptimal vitamin D status (50–74·9 nmol/L).[51] We also did an exploratory analysis restricted to studies involving children aged 1·00–15·99 years with a duration of 12 months or less that compared the effects of daily vitamin D at a dose of 400–1000 IU/day versus placebo.

To investigate factors associated with heterogeneity of effect between subgroups of trials, we did multivariable meta-regression analysis on trial-level characteristics, namely, dose, dose frequency, trial duration, and age at enrolment to produce an adjusted OR (95% CI) and p value for interaction for each factor. Independent variables were dichotomised to create a more parsimonious model (baseline serum 25[OH]D concentration of <25 nmol/L *vs* ≥25 nmol/L; administration of daily *vs* non-daily doses; administration of daily equivalent of ≤1000 IU *vs* >1000 IU vitamin D; trial duration of ≤12 months *vs* >12 months; and participant age at enrolment of <16·00 years *vs* ≥16·00 years). The meta-regression analysis excluded data from two placebo-controlled trials (Tran and colleagues[18] and NCT02046577) that included higher-dose, lower-dose, and placebo groups, because participants in the higher-dose and lower-dose groups were given vitamin D doses that spanned the 1000 IU/day cutoff, and four placebo-controlled trials that enrolled participants aged younger and older than the age cutoff of 16 years.[9,20,26,36] These study characteristics rendered these trials unclassifiable for the purposes of the meta-regression analysis.

For the primary analysis, the likelihood of publication bias was investigated by constructing a contour-enhanced funnel plot, confirmed with an Egger's regression test.[52,53] We used the five considerations of the Grading of Recommendations, Assessment, Development and Evaluations framework (study limitations, consistency of effect, imprecision, indirectness, and publication bias)[54] to assess the quality of the body of evidence contributing to analysis of the primary efficacy outcome and major secondary outcomes of our meta-analysis.

We did three exploratory sensitivity analyses for the primary comparison of the primary outcome: one analysis excluded RCTs in which the risk of bias was assessed as being unclear; the second analysis excluded RCTs in which the incidence of ARI was not the primary or co-primary outcome; and the third analysis substituted diary-defined ARI events for survey-defined ARI events.

The methods used in this study were prespecified in a protocol, registered with the PROSPERO international prospective register of systematic reviews (CRD42020190633).

For the **study protocol** see https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=190633

Role of the funding source

There was no funding source for this study.

Results

Our search identified a total of 1528 unique studies that were assessed for eligibility, of which 46 studies, including 75 541 randomised participants, fulfilled study eligibility criteria (figure 1). Studies for which the full texts were reviewed before exclusion due to ineligibility are listed in the appendix (p 8). Of the 46 eligible studies identified, 35 studies (including NCT01875757 and NCT01758081)[5–17,19,20,22,23,25–28,31,33,36,38,39,41–47] compared the effects of one vitamin D regimen with placebo only, five studies (including NCT02046577)[18,21,24,40] compared higher-dose vitamin D, lower-dose vitamin D, and placebo groups, and six studies (including NCT02404623)[29,32,34,35,37] compared the effects of higher-dose vitamin D with lower-dose vitamin D regimens only. Stratified aggregate data were sought and obtained for all but three eligible studies (Ducharme and colleagues,[47] NCT01875757, and NCT01758081). Data for the primary outcome were obtained for 48 488 (98·1%) of 49 419 participants across 43 studies, which included 41 published trials[5–29,31–46] and two completed but as yet unpublished clinical trials (NCT02404623 and NCT02046577).

Characteristics of the 43 studies contributing data to this meta-analysis and the participants are presented in table 1. The trials were done in 23 different countries spanning five continents, and enrolled both male and female participants from birth to age 95 years. Baseline serum 25(OH)D concentrations were ascertained in 35 of 43 trials; mean baseline 25(OH)D concentrations ranged from 18·9–90·9 nmol/L. 42 studies administered oral vitamin D_3 to participants in the intervention group, whereas one study administered oral 25(OH)D. Vitamin D was given as bolus doses once per month to once every 3 months in 13 studies; as weekly doses in six studies; as daily doses in 22 studies; and as a combination of bolus and daily doses in two studies. Trial durations ranged from 8 weeks to 5 years. The incidence of ARI was a primary or co-primary outcome in 23 studies, and a secondary outcome in 20 studies.

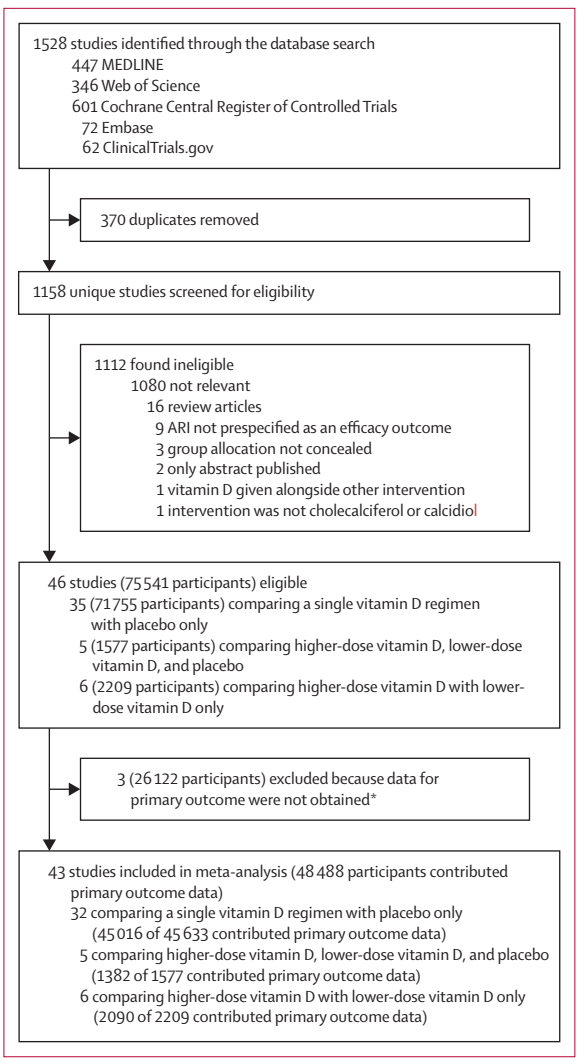

Figure 1: **Study selection**
Data for the primary outcome were the proportion of participants with one or more ARIs. ARI=acute respiratory infection. *All three studies compared a single vitamin D regimen with placebo only.

For the primary comparison of vitamin D supplementation versus placebo control, a significantly lower proportion of participants taking a vitamin D supplement had one or more ARIs (14 332 [61·3%] of 23 364 participants) compared with those taking placebo (14 217 [62·3%] of 22 802 participants), with an OR of 0·92 (95% CI 0·86–0·99; 37 studies; table 2, figure 2; and the Cates plot in the appendix [p 13]). Heterogeneity of the effect was moderate (I^2=35·6%, $p_{heterogeneity}$=0·018).

For the secondary comparison of higher-dose versus lower-dose vitamin D supplementation, we observed no significant difference in the proportion of participants who had at least one ARI between the higher dose (1052 [68·2%] of 1544) and lower-dose groups (971 [64·6%] of 1503), with an OR of 0·87 (95% CI 0·73–1·04; 11 studies; I^2=0·0%, $p_{heterogeneity}$=0·50; appendix p 14).

To investigate reasons for the observed heterogeneity of effect for the primary comparison of vitamin D supplementation versus placebo control, we stratified this analysis by two participant-level factors (baseline 25[OH]D concentration and age), and by four trial-level factors (dose, dose frequency, trial duration, and presence *vs* absence of airway disease). Four of these factors (baseline 25[OH]D concentration, dose, dose frequency, and trial duration) were pre-specified in the study protocol, and two of them (age and presence *vs* absence of airway disease) were exploratory analyses. Compared with participants who received a placebo control, no significant effect of vitamin D supplementation on the risk of having one or more ARIs was observed in participants with baseline 25(OH)D concentrations of less than 25 nmol/L (OR 0·81 [95% CI 0·57–1·15]; 3777 participants in 20 studies; I^2=44·5%, $p_{heterogeneity}$=0·017), 25–49·9 nmol/L (1·04 [0·94–1·15]; 9896 participants in 29 studies; I^2=0·0%, $p_{heterogeneity}$=0·49), 50–74·9 nmol/L (0·88 [0·76–1·02]; 6283 participants in 30 studies; I^2=9·3%, $p_{heterogeneity}$=0·32), or 75 nmol/L or higher (1·00 [0·85–1·18]; 3416 participants in 26 studies; I^2=0·0%, $p_{heterogeneity}$=0·78; table 2; appendix p 15). A significant protective effect of vitamin D supplementation on the risk of having one or more ARIs was observed in participants aged 1·00–15·99 years (0·71 [0·57–0·90]; 11 871 participants in 15 studies; I^2=46·0%, $p_{heterogeneity}$=0·027), but not in participants aged younger than 1 year (0·95 [0·82–1·10]; 5697 participants in five studies; I^2=18·7%, $p_{heterogeneity}$=0·30), 16·00–64·99 years (0·97 [0·93–1·09]; 9603 participants in 21 studies; I^2=11·5%, $p_{heterogeneity}$=0·31), or 65·00 years or older (0·96 [0·90–1·02]; 19 140 participants in 17 studies; I^2=0·0%, $p_{heterogeneity}$=0·73; table 2; appendix p 19).

With regard to dosing frequency, a significant protective effect of vitamin D supplementation on the risk of having one or more ARIs compared with a placebo control was observed in trials in which vitamin D was given daily (OR 0·78 [95% CI 0·65–0·94]; 6162 participants in 19 studies; I^2=53·5%, $p_{heterogeneity}$=0·003), but not in trials in which vitamin D was given weekly (0·97 [0·88–1·06]; 12 756 participants in six studies; I^2=0·0%, $p_{heterogeneity}$=0·48), or as bolus doses once per month to once every 3 months (0·98 [0·93–1·03]; 27 248 participants in 12 studies; I^2=0·0%, $p_{heterogeneity}$=0·57; table 2; appendix p 16). Significant protective effects of the intervention were also observed in trials in which vitamin D was administered at a daily dose equivalent of 400–1000 IU (0·70 [0·55–0·89]; 2305 participants in ten studies; I^2=31·2%, $p_{heterogeneity}$=0·16), but not in those in which the daily dose equivalent was less than 400 IU (0·65 [0·31–1·37]; 2308 participants in two studies; I^2=46·3%, $p_{heterogeneity}$=0·007), 1001–2000 IU (0·97 [0·93–1·02]; 33 859 participants in 16 studies; I^2=0·0%, $p_{heterogeneity}$=0·51), or more than 2000 IU (1·05 [0·84–1·31]; 6906 participants in seven studies; I^2=37·1%, $p_{heterogeneity}$=0·15; table 2;

	Participants (sex); mean age at baseline, years (SD; range)	Number of participants in intervention and control groups	25(OH)D assay; EQA scheme	Mean baseline 25(OH)D concentrations, nmol/L (SD)	Number of participants with baseline 25(OH)D concentrations of <25 nmol/L of the total number assessed (%)	Oral dose of vitamin D_3 in the intervention group	Control group	Trial duration	Mean attained 25(OH)D concentrations in intervention group, nmol/L (SD)	ARI definition	ARI outcome	Number of participants with ARI outcome data of the total number randomised (%)
Li-Ng et al (2009);[5] USA	162 healthy adults (34 male, 128 female); 57·9 (13·6; 21·4–80·6)	Intervention=84; control=78	RIA (DiaSorin), DEQAS	63·7 (25·5)	3/150 (2·0%)	50 µg daily *vs* placebo	Placebo	3 months	88·5 (23·2)	URI: ≥2 URI symptoms in absence of allergy symptoms	Primary	157/162 (96·9%)
Urashima et al (2010);[6] Japan	430 school children (242 male, 188 female); 10·2 (2·3; 6·0–15·0)	Intervention=217; control=213	NA	NM	NM	30 µg daily	Placebo	4 months	NM	URI: influenza A or B diagnosed by RIDT or RIDT-negative influenza-like illness	Primary	334/430 (77·7%)
Manaseki-Holland et al (2010);[7] Afghanistan	453 pre-school children with pneumonia (257 male, 196 female); 1·1 (0·8; 0·1–3·3)	Intervention=224; control=229	NA	NM	NM	One 2500 µg bolus	Placebo	3 months	NM	LRI: repeat episode of pneumonia or age-specific tachypnoea without wheeze	Secondary	453/453 (100%)
Laaksi et al (2010);[8] Finland	164 male military conscripts; 19·1 (0·6; 18·0–21·0)	Intervention=80; control=84	EIA (IDS OCTEIA)	75·9 (18·7)	0	10 µg daily	Placebo	6 months	71·6 (22·9)	ARI: medical record diagnosis	Primary	164/164 (100%)
Majak et al (2011);[9] Poland	48 children with asthma (24 male, 24 female); 10·9 (3·3; 6·0–17·0)	Intervention=24; control=24	RIA (BioSource), RIQAS	88·9 (38·2)	0	12·5 µg daily	Placebo	6 months	37·6 (13·1)	ARI: self-reported	Secondary	48/48 (100%)
Kumar et al (2011);[10] India	2079 low birthweight infants (970 male, 1109 female); 0·1 (0·0; 0·0–0·3)	Intervention=1039; control=1040	NR	NM	NM	35 µg weekly	Placebo	6 months	55·0 (22·5)	ARI: medical record diagnosis of events leading to hospital admission	Secondary	2064/2079 (99·3%)
Lehouck et al (2012);[11] Belgium	182 adults with COPD (145 male, 37 female); 67·9 (8·3; 48·0–86·0)	Intervention=91; control=91	RIA (DiaSorin), DEQAS	49·8 (29·2)	31/182 (17·0%)	2500 µg bolus monthly	Placebo	1 year	130·0 (44·7)	URI: self-report	Secondary	175/182 (96·2%)
Manaseki-Holland et al (2012);[12] Afghanistan	3046 infants (1591 male, 1455 female); 0·5 (0·3; 0·0–1·0)	Intervention=1524; control=1522	NR	NM	NM	2500 µg bolus once every 3 months	Placebo	1·5 years	32·7 (17·1)	LRI: pneumonia confirmed by chest radiograph	Primary	3011/3046 (98·9%)
Camargo et al (2012);[13] Mongolia	247 third or fourth grade school children (129 male, 118 female); 10·0 (0·9; 7·0–12·7)	Intervention=143; control=104	LC-MS/MS, DEQAS	18·9 (9·7)	192/245 (78·4%)	7·5 µg daily	Placebo	7 weeks	49·1 (15·1)	ARI: parent-reported "chest infections or colds"	Secondary	244/247 (98·8%)

(Table 1 continues on next page)

	Participants (sex); mean age at baseline, years (SD; range)	Number of participants in intervention and control groups	25(OH)D assay; EQA scheme	Mean baseline 25(OH)D concentrations, nmol/L (SD)	Number of participants with baseline 25(OH)D concentrations of <25 nmol/L of the total number assessed (%)	Oral dose of vitamin D_3 in the intervention group	Control group	Trial duration	Mean attained 25(OH)D concentrations in intervention group, nmol/L (SD)	ARI definition	ARI outcome	Number of participants with ARI outcome data of the total number randomised (%)
(Continued from previous page)												
Murdoch et al (2012);[14] New Zealand	322 healthy adults (81 male, 241 female); 48·1 (9·7; 18·0–67·6)	Intervention=161; control=161	LC-MS/MS, DEQAS	72·1 (22·1)	5/322 (1·6%)	5000 µg bolus monthly for the first 2 months, followed by 2500 µg bolus monthly thereafter	Placebo	1·5 years	123·6 (27·5)	URI: assessed with symptom score	Primary	322/322 (100%)
Bergman et al (2012);[15] Sweden	140 adults with increased susceptibility to ARI (38 male, 102 female); 53·1 (13·1; 20·0–77·0)	Intervention=70; control=70	CLA (DiaSorin), DEQAS	49·3 (23·2)	15/131 (11·5%)	100 µg daily	Placebo	1 year	94·9 (38·1)	URI: assessed with symptom score	Secondary	124/140 (88·6%)
Marchisio et al (2013);[16] Italy	116 children with recurrent acute otitis media (64 male, 52 female); 2·8 (1·0; 1·3–4·8)	Intervention=58; control=58	CLA (DiaSorin)	65·3 (17·3)	2/116 (1·7%)	25 µg daily	Placebo	6 months	90·3 (21·1)	URI: doctor-diagnosed acute otitis media	Primary	116/116 (100%)
Rees et al (2013);[17] USA	759 adults with previous colorectal adenoma (438 male, 321 female);* 61·2 (6·6; 47·1–77·9)	Intervention=399; control=360	RIA (IDS OCTEIA), DEQAS	62·5 (21·3)	0	25 µg daily	Placebo	13 months (average)	186·9 (455·1)	URI: assessed from daily symptom diary	Secondary	759/759 (100%)
Tran et al (2014);[18] Australia	644 healthy older adults (343 male, 301 female); 71·7 (6·9; 60·3–85·2)	Intervention group 1=215; intervention group 2=215; control=214	CLA (DiaSorin), DEQAS	41·7 (13·5)	66/643 (10·3%)	Intervention group 1: 750 µg bolus monthly; intervention group 2: 1500 µg bolus monthly	Placebo	1 year	71·0 (19·6)	URI: self-reported common cold	Secondary	594/644 (92·2%)
Goodall et al (2014);[19] Canada	600 healthy university students (218 male, 382 female); 19·6 (2·2; 17·0–33·0)	Intervention=300; control=300	NA	NM	NM	250 µg weekly (2 × 2 factorial with gargling)	Placebo	8 weeks	NM	URI: self-reported common cold	Primary	492/600 (82·0%)
Urashima et al (2014);[20] Japan	247 high school students (162 male, 85 female); 16·5 (1·0; 15·0–18·0)	Intervention=148; control=99	NA	NM	NM	50 µg daily	Placebo	2 months	NM	URI: influenza A diagnosed by RIDT or RIDT-negative influenza-like illness	Primary	247/247 (100%)

(Table 1 continues on next page)

	Participants (sex); mean age at baseline, years (SD; range)	Number of participants in intervention and control groups	25(OH)D assay; EQA scheme	Mean baseline 25(OH)D concentrations, nmol/L (SD)	Number of participants with baseline 25(OH)D concentrations of <25 nmol/L of the total number assessed (%)	Oral dose of vitamin D_3 in the intervention group	Control group	Trial duration	Mean attained 25(OH)D concentrations in intervention group, nmol/L (SD)	ARI definition	ARI outcome	Number of participants with ARI outcome data of the total number randomised (%)
(Continued from previous page)												
Grant et al (2014);[21] New Zealand	249 infants (121 male, 128 female); unborn at baseline	Intervention group 1=83; intervention group 2=81; control=85	LC-MS/MS, DEQAS	54·8 (25·8)	30/200 (15·0%)	Intervention group 1: 10 µg daily; intervention group 2: 20 µg daily	Placebo	6 months	85·2 (34·7) in intervention group 1 and 101·1 (46·8) in intervention group 2	ARI: doctor-diagnosed ARI precipitating primary care consult	Secondary	236/260 (90·8%)
Martineau et al (2015);[22] ViDiCO trial; UK	240 adults with COPD (144 male, 96 female); 64·7 (8·5; 40·0–85·0)	Intervention=122; control=118	LC-MS/MS, DEQAS	46·1 (25·7)	50/240 (20·8%)	3000 µg bolus once every 2 months	Placebo	1 year	67·3 (27·5)	URI: assessed from daily symptom diary	Co-primary	240/240 (100%)
Martineau et al (2015);[23] ViDiAs trial; UK	250 adults with asthma (109 male, 141 female); 47·9 (14·4; 16·0–78·0)	Intervention=125; control=125	LC-MS/MS, DEQAS	49·6 (24·7)	36/250 (14·4%)	3000 µg bolus once every 2 months	Placebo	1 year	69·4 (21·0)	URI: assessed from daily symptom diary	Co-primary	250/250 (100%)
Martineau et al (2015);[24] ViDiFlu trial; UK	240 older adults and their carers (82 male, 158 female); 67·1 (13·0; 21·4–94·0)	Intervention=137; control=103	LC-MS/MS, DEQAS	42·9 (23·0)	60/240 (25·0%)	Older adults, 2400 µg bolus once every 2 months plus 10 µg daily; carers, 3000 µg once every 2 months	Older adults, placebo plus 10 µg vitamin D_3 daily; carers, placebo	1 year	84·8 (24·1)	URI and LRI: both assessed from daily symptom diary	Co-primary	240/240 (100%)
Simpson et al (2015);[25] Australia	34 healthy adults (14 male, 20 female); 32·2 (12·2; 18·0–52·0)	Intervention=18; control=16	LC-MS/MS, DEQAS	67·9 (23·0)	0	500 µg weekly	Placebo	17 weeks	NM	ARI: assessed with symptom score	Primary	34/34 (100%)
Dubnov-Raz et al (2015);[26] Israel	54 adolescent swimmers with vitamin D insufficiency (34 male, 20 female); 15·2 (1·6; 12·9–18·6)	Intervention=27; control=27	RIA (DiaSorin), DEQAS	60·4 (11·9)	0	50 µg daily	Placebo	12 weeks	73·7 (16·6)	URI: assessed with symptom score	Primary	25/54 (46·3%)
Denlinger et al (2016);[27] USA	408 adults with asthma (130 male, 278 female); 39·2 (12·9; 18·0–85·0)	Intervention=201; control=207	CLA (DiaSorin), VDSP	47·0 (16·9)	55/408 (13·5%)	One 2500 µg bolus then 100 µg daily	Placebo	28 weeks	104·3 (32·4)	URI: assessed with symptom score	Secondary	408/408 (100%)
Tachimoto et al (2016);[28] Japan	89 children with asthma (50 male, 39 female); 9·9 (2·3; 6·0–15·0)	Intervention=54; control=35	RIA (DiaSorin), CAP	74·9 (24·6)	1/89 (1·1%)	20 µg daily for the first 2 months	Placebo	6 months	85·7 (24·5)	URI: assessed with symptom score	Secondary	89/89 (100%)

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	Participants (sex); mean age at baseline, years (SD; range)	Number of participants in intervention and control groups	25(OH)D assay; EQA scheme	Mean baseline 25(OH)D concentrations, nmol/L (SD)	Number of participants with baseline 25(OH)D concentrations of <25 nmol/L of the total number assessed (%)	Oral dose of vitamin D_3 in the intervention group	Control group	Trial duration	Mean attained 25(OH)D concentrations in intervention group, nmol/L (SD)	ARI definition	ARI outcome	Number of participants with ARI outcome data of the total number randomised (%)
(Continued from previous page)												
Gupta et al (2016);[31] India	324 children with pneumonia (226 male, 98 female); 1·4 (1·1; 0·5–5·0)	Intervention=162; control=162	RIA (Immunotech SAS or DiaSorin), EQA scheme NR	43·9 (33·4)	104/312 (33·3%)	One 2500 µg bolus	Placebo	6 months	64·1 (43·9)	ARI: physician-confirmed recurrent pneumonia	Co-primary	314/324 (96·9%)
Ginde et al (2017);[29] USA	107 institutionalised older adults (45 male, 62 female); 80·7 (9·9; 60·0–95·0)	Intervention=55; control=52	LC-MS/MS, VDSP	57·3 (22·7)	12/107 (11·2%)	2500 µg bolus monthly plus ≤25 µg per day equivalent	Placebo plus 10–25 µg vitamin D_3 per day equivalent	1 year	NM	ARI: medical record diagnosis	Primary	107/107 (100%)
Aglipay et al (2017);[32] Canada	703 healthy children (404 male, 296 female); 2·7 (1·5; 1·0–5·0)	Intervention=349; control=354	CLA (Roche Elecsys), EQA scheme NR	90·9 (20·9)	1/703 (0·1%)	50 µg daily	10 µg vitamin D_3 daily	4–8 months (mean 6·3 months)	50 µg group 121·6 (2·2); 10 µg group 91·9 (1·7)	URI: laboratory-confirmed	Primary	699/703 (99·4%)
Hibbs et al (2018);[34] USA	300 African American preterm infants (166 male, 133 female);† offspring unborn at baseline	Intervention=153; control=147	RIA (supplier NR), EQA scheme NR	55·4 (22·2)	0	10 µg daily, regardless of dietary intake	10 µg vitamin D_3 daily, only if dietary intake was <5 µg vitamin D_3 daily	1 year	95·0 (21·2)	ARI: self-reported URI or LRI	Secondary	300/300 (100%)
Lee et al (2018);[35] USA	62 children and young adults with sickle cell disease (30 male, 32 female); 9·9 (3·9; 3·0–20·0)	Intervention=31; control=31	LC-MS/MS, DEQAS	35·7 (16·5)	18/62 (29·0%)	2500 µg bolus monthly	300 µg vitamin D_3 monthly	2 years	92·4 (23·7)	Self-reported respiratory events, including ARI	Primary	62/62 (100%)
Rosendahl et al (2018);[37] Finland	987 healthy infants (495 male, 492 female); offspring unborn at baseline	Intervention=492; control=495	CLA (IDS-iSYS), VDSP	81·5 (25·9)	0	30 µg daily	10 µg vitamin D_3 daily	2 years	117·7 (26·1)	Parent-reported infections, including ARI	Co-primary	897/987 (90·9%)

(Table 1 continues on next page)

	Participants (sex); mean age at baseline, years (SD; range)	Number of participants in intervention and control groups	25(OH)D assay; EQA scheme	Mean baseline 25(OH)D concentrations, nmol/L (SD)	Number of participants with baseline 25(OH)D concentrations of <25 nmol/L of the total number assessed (%)	Oral dose of vitamin D_3 in the intervention group	Control group	Trial duration	Mean attained 25(OH)D concentrations in intervention group, nmol/L (SD)	ARI definition	ARI outcome	Number of participants with ARI outcome data of the total number randomised (%)
(Continued from previous page)												
Shimizu et al (2018);[38] Japan	252 healthy adults (82 male, 170 female); 53·1 (6·7; 45·0–74·0)	Intervention=126; control=126	RIA (DiaSorin), EQA scheme NR	48·9 (13·5)	1/214 (0·5%)	10 µg daily‡	Placebo	4 months	114·6 (32·7)	URI: self-reported	Primary	215/252 (85·3%)
Arihiro et al (2019);[33] Japan	237 adults with diagnosis of inflammatory bowel disease (146 male, 91 female); 44·5 (13·2; 18·0–82·0)	Intervention=119; control=118	RIA (DiaSorin), EQA scheme NR	58·6 (22·0)	5/223 (2·2%)	12·5 µg daily	Placebo	6 months	80·4 (21·5)	ARI: laboratory-confirmed influenza	Primary	223/237 (94·1%)
Aloia et al (2019)[39]; USA	260 healthy African American women aged >60 years; 69·0 (5·3; 65·4–72·5)	Intervention=130; control=130	LC-MS/MS, NIST	54·4 (16·7)	9/258 (3·5%)	50 µg daily	Placebo	3 months	117·0 (28·0)	ARI: self-reported common cold or influenza	Secondary	260/260 (100%)
Loeb et al (2019);[36] Vietnam	1300 healthy children and adolescents (621 male, 679 female); 8·5 (4·0; 3·0–17·0)	Intervention=650; control=650	CLA (DiaSorin), DEQAS	65·5 (16·8)	5/1153 (0·4%)	350 µg weekly	Placebo	8 months	91·8 (23·6)	ARI: RT-PCR confirmed influenza A or B	Primary	1153/1300 (88·7%)
Hauger et al (2019);[40] Denmark	130 healthy children (61 male, 69 female); 6·6 (1·5; 4·0–8·0)	Intervention group 1=43; intervention group 2=44; control=43	LC-MS/MS, DEQAS	56·8 (12·5)	0	Intervention group 1: 20 µg daily; intervention group 2: 10 µg daily	Placebo	5 months	20 µg group, 75·8 (11·5); 10 µg group, 61·8 (10·6)	ARI: self-reported	Secondary	118/130 (90·8%)
Bischoff-Ferrari et al (2020);[41] Switzerland, France, Germany, Portugal, and Austria	2157 older adults (826 male, 1331 female); 74·9 (4·4; 70·0–95·0)	Intervention=1076; control=1081	LC-MS/MS, DEQAS	55·9 (21·0)	143/2140 (6·7%)	50 µg daily (2 × 2 × 2 factorial with omega-3 fatty acid supplementation and strength training exercise)	Placebo	3 years	93·8 (28·2)	ARI: self-reported and verified by independent physician	Co-primary	2157/2157 (100%)

(Table 1 continues on next page)

	Participants (sex); mean age at baseline, years (SD; range)	Number of participants in intervention and control groups	25(OH)D assay; EQA scheme	Mean baseline 25(OH)D concentrations, nmol/L (SD)	Number of participants with baseline 25(OH)D concentrations of <25 nmol/L of the total number assessed (%)	Oral dose of vitamin D_3 in the intervention group	Control group	Trial duration	Mean attained 25(OH)D concentrations in intervention group, nmol/L (SD)	ARI definition	ARI outcome	Number of participants with ARI outcome data of the total number randomised (%)
(Continued from previous page)												
Camargo et al (2020);[42] New Zealand	5110 older adults (2935 male, 2121 female); 66·4 (8·3; 50·0–84·0)	Intervention=2558; control=2552	LC-MS/MS, DEQAS	63·4 (23·6)	89/5056 (1·8%)	One 5000 µg bolus loading dose, then 2500 µg bolus monthly	Placebo	3 years	135·0 (39·9)	ARI: self-reported common cold or influenza	Secondary	5056/5110 (98·9%)
Ganmaa et al (2020);[43] Mongolia	8851 healthy school children (4485 male, 4366 female); 9·4 (1·6; 6·0–13·0)	Intervention=4418; control=4433	EIA (BioMerieux), DEQAS	29·7 (10·5)	2813/8851 (31·8%)	350 µg weekly	Placebo	3 years	77·4 (22·7)	ARI: self-reported	Secondary	8851/8851 (100%)
Mandlik et al (2020);[44] India	285 healthy children (158 male, 127 female); 8·1 (1·2: 6·0–12·0)	Intervention=135; control=150	EIA (DLD Diagnostics), EQA scheme NR	58·9 (10·9)	0	25 µg daily plus 500 000 µg calcium	Placebo	6 months	80 (23·3)	URI: self-reported	Secondary	244/285 (85·6%)
Pham et al (2021);[45] Australia	16 000 older adults (8678 male, 7322 female); 69·3 (5·5; 60·0–86·0)	Intervention=8000; control=8000	LC-MS/MS, VDSP	NM	NM	1500 µg bolus monthly	Placebo	5 years	114·8 (30·3)§	ARI: self-reported	Secondary	16 000/16 000 (100%)
Rake et al (2020);[46] England	787 healthy older adults (408 male, 379 female); 72·2 (4·9; 65·0–84·0)	Intervention=395; control=392	CLA (Cobas 6000, Roche), EQA scheme NR	50·2 (27·1)	127/787 (16·1%)	2500 µg bolus monthly	Placebo	2 years	109·2 (33·9)	URI or LRI: general practitioner-recorded	Secondary	787/787 (100%)
NCT02404623; Israel	50 prematurely born infants (21 male, 29 female); 0 (0)	Intervention=25; control=25	CLA (DiaSorin), EQA scheme NR	33·6 (29·7)	19/46 (41·3%)	20 µg daily	10 µg vitamin D_3 daily	1 year	20 µg group, 78·0 (75·0); 10 µg group, 81·0 (73·0)	ARI: general practitioner-recorded	Secondary	25/50 (50·0%)
NCT02046577; Chile	303 healthy preschool children (168 male, 135 female); 2·2 (0·5; 1·3–3·3)	Intervention group 1=99; intervention group 2=103; control=101	LC-MS/MS, EQA scheme NR	62·2 (15·5)	1/194 (0·5%)	Intervention group 1: 140 µg weekly; intervention group 2: 280 µg weekly	Placebo	6 months	140 µg group, 82·4 (24·5); 280 µg group, 104·6 (52·9)	ARI: self-reported	Primary	194/303 (64·0%)

25(OH)D=25-hydroxyvitamin D. ARI=acute respiratory infection. CAP=College of American Pathologists. CLA=chemiluminescent assay. COPD=chronic obstructive pulmonary disease. DEQAS=Vitamin D External Quality Assessment Scheme. EIA=enzyme immunoassay. EQA=external quality assessment. LC-MS/MS=liquid chromatography with tandem mass spectrometry. LRI=lower respiratory infection. NA=not applicable. NIST=National Institute for Standards and Technology. NM=not measured. NR=not reported. RIA=radioimmunoassay. RIDT=rapid influenza diagnostic test. RIQAS=Randox International Quality Assessment Scheme. URI=upper respiratory infection. VDSP=Vitamin D Standardisation Program of the Office of Dietary Supplements, National Institutes of Health, USA. *Sex was missing for two participants randomly assigned to the intervention group; they were subsequently excluded from the analysis due to missing outcome data. †Sex was missing for one participant. ‡Equivalent to 30 ug vitamin D_3[55] (1 µg vitamin D_3 is equivalent to 40 international units; 25[OH]D concentrations reported in ng/ml were converted to nmol/L by multiplying by 2·496). §In a subset of 4441 participants randomly assigned to the intervention group; for comparison, mean 25(OH)D concentrations at follow-up in a subset of participants randomly assigned to the placebo group was 77·5 nmol/L (SD 25·2).

Table 1: **Characteristics of the 43 eligible trials and their participants**

	Number of trials	Proportion of participants in the intervention group with one or more ARIs	Proportion of participants in the control group with one or more ARIs	Odds ratio (95% CI)	I^2	p value for heterogeneity
Overall	37	14 332/23 364 (61·3%)	14 217/22 802 (62·3%)	0·92 (0·86–0·99)	35·6%	0·018
Baseline 25(OH)D concentration, nmol/L*						
<25·0	20	1395/1879 (74·2%)	1433/1898 (75·5%)	0·81 (0·57–1·15)	44·5%	0·017
25·0–49·9	29	3662/5022 (72·9%)	3569/4874 (73·2%)	1·04 (0·94–1·15)	0·0%	0·49
50·0–74·9	30	1929/3279 (58·8%)	1829/3004 (60·9%)	0·88 (0·76–1·02)	9·3%	0·32
≥75·0	26	1072/1742 (61·5%)	1029/1674 (61·5%)	1·00 (0·85–1·18)	0·0%	0·78
Dosing frequency						
Daily	19	1703/3210 (53·1%)	1672/2952 (56·6%)	0·78 (0·65–0·94)	53·5%	0·003
Weekly	6	4482/6421 (69·8%)	4447/6335 (70·2%)	0·97 (0·88–1·06)	0·0%	0·48
Once per month to once every 3 months	12	8147/13 733 (59·3%)	8098/13 515 (59·9%)	0·98 (0·93–1·03)	0·0%	0·57
Daily dose equivalent, IU†						
<400	2	482/1175 (41·0%)	511/1133 (45·1%)	0·65 (0·31–1·37)	86·3%	0·007
400–1000	10	656/1236 (53·1%)	627/1069 (58·7%)	0·70 (0·55–0·89)	31·2%	0·16
1001–2000	16	10 593/16 961 (62·5%)	10 674/16 898 (63·2%)	0·97 (0·93–1·02)	0·0%	0·51
>2000	7	2291/3462 (66·2%)	2250/3444 (65·3%)	1·05 (0·84–1·31)	37·1%	0·15
Trial duration, months						
≤12	29	1977/4887 (40·5%)	1866/4368 (42·7%)	0·82 (0·72–0·93)	38·1%	0·021
>12	8	12 355/18 477 (66·9%)	12 351/18 434 (67·0%)	0·99 (0·95–1·04)	0·0%	0·95
Age, years*						
<1·00	5	875/2901 (30·2%)	839/2796 (30·0%)	0·95 (0·82–1·10)	18·7%	0·30
1·00–15·99	15	4297/5994 (71·7%)	4303/5877 (73·2%)	0·71 (0·57–0·90)	46·0%	0·027
16·00–64·99	21	3137/4876 (64·3%)	3087/4727 (65·3%)	0·97 (0·93–1·09)	11·5%	0·31
≥65·00	17	6023/9665 (62·3%)	6004/9475 (63·4%)	0·96 (0·90–1·02)	0·0%	0·73
Airway disease						
Asthma only	4	203/404 (50·2%)	202/391 (51·7%)	0·73 (0·36–1·49)	71·7%	0·014
Chronic obstructive pulmonary disease only	2	106/208 (51·0%)	104/207 (50·2%)	1·01 (0·68–1·51)	0·0%	0·71
Unrestricted	31	14 023/22 752 (61·6%)	13 911/22 204 (62·7%)	0·92 (0·86–0·99)	33·0%	0·040

Data are n/N (%), unless otherwise specified. ARI=acute respiratory infection. 25(OH)D=25-hydroxyvitamin D. IU=international units. *The number of trials in each category for this variable adds up to more than 36 because this is a participant-level variable (ie, some trials contributed data from participants who were included in more than one category). †Data from two trials (Tran and colleagues[18] and NCT02046577) that included higher-dose, lower-dose, and placebo groups were excluded from this subgroup analysis because the higher-dose and lower-dose groups spanned the 1000 IU/day cutoff, making them unclassifiable.

Table 2: **Number of participants in randomised placebo-controlled trials with at least one ARI, overall and stratified by potential effect-modifiers**

appendix p 17). Significant protective effects of vitamin D supplementation were also observed in trials that were 12 months or less in duration (0·82 [0·72–0·93]; 9255 participants in 29 studies; I^2=38·1%, $p_{heterogeneity}$=0·021) but not in those that were more than 12 months in duration (0·99 [0·95–1·04]; 36 911 participants in eight studies; I^2=0·0%, $p_{heterogeneity}$=0·95; table 2; appendix p 18).

Finally, significant protective effects of vitamin D supplementation on the risk of having one or more ARIs compared with a placebo control were also observed in trials that were not restricted to participants with asthma or chronic obstructive pulmonary disease (OR 0·92 [95% CI 0·86–0·99]; 44 956 participants in 31 studies; I^2=33·0%, $p_{heterogeneity}$=0·040), but not in trials that exclusively enrolled participants with asthma (0·73 [0·36–1·49]; 795 participants in four studies; I^2=71·7%, $p_{heterogeneity}$=0·014), or chronic obstructive pulmonary disease (1·01 [0·68–1·51]; 415 participants in two studies; I^2=0·0%, $p_{heterogeneity}$=0·71; table 2; appendix p 20).

An exploratory analysis restricted to five placebo-controlled trials that investigated the effects of daily vitamin D dosing at 400–1000 IU/day in children aged from 1·00 to 15·99 years, were 12 months or less in duration, and in which mean baseline 25[OH]D concentrations ranged from 56·8 nmol/L to 88·9 nmol/L, showed that a significantly lower proportion of participants had one or more ARIs compared with placebo (OR 0·56 [95% CI 0·38–0·82]; 608 participants in five studies; I^2=0·0%, $p_{heterogeneity}$=0·44; appendix pp 13, 21).

Multivariable meta-regression analysis of trial-level subgroups did not identify a significant interaction between allocation to a vitamin D supplementation group versus a placebo group and dose, dose frequency, trial duration, or participant age (appendix p 10).

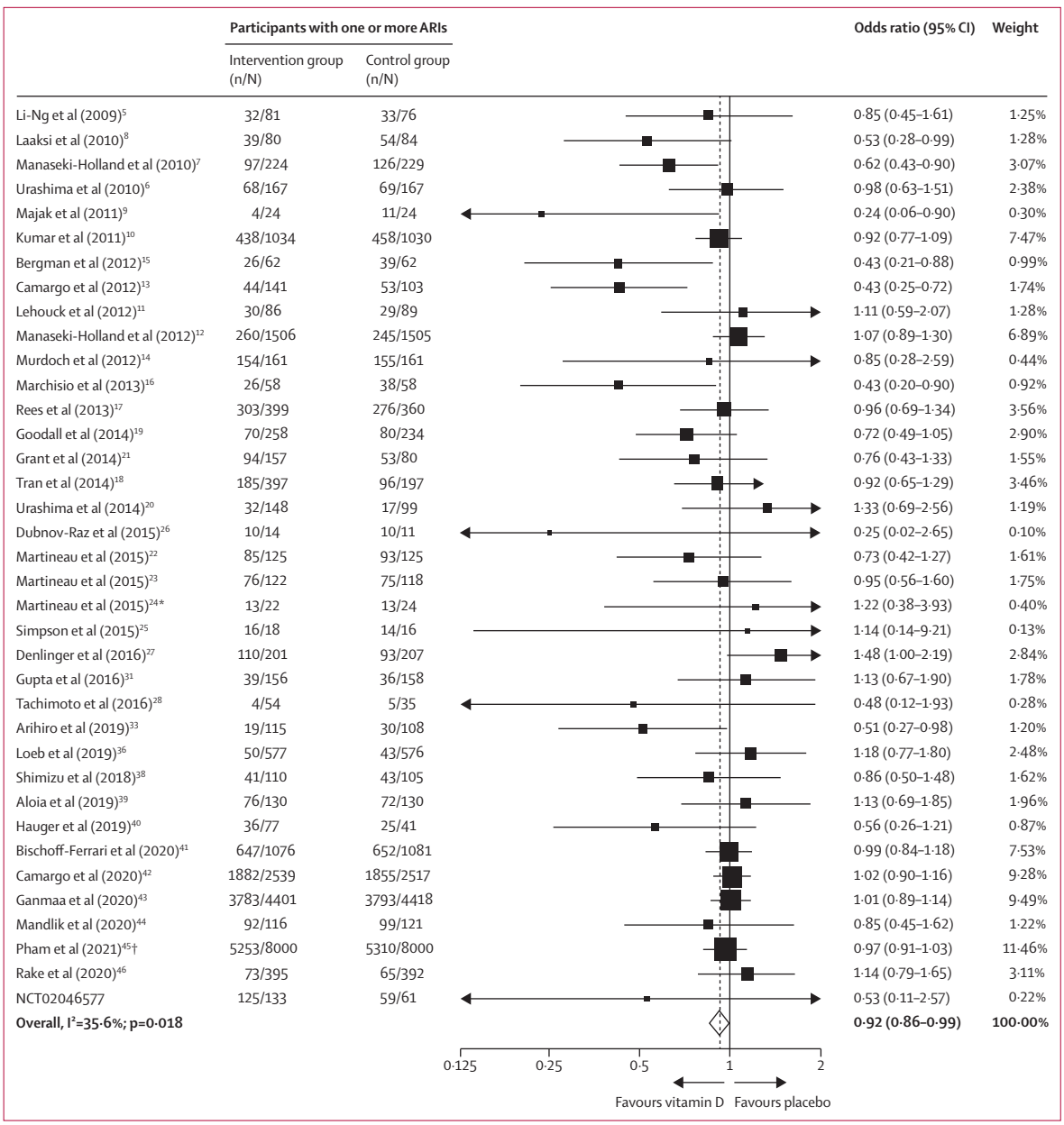

Figure 2: **Random-effects meta-analysis of randomised, placebo-controlled trials reporting the proportion of participants with one or more ARIs**
ARI=acute respiratory infection. n=number of participants with one or more ARI. N=total number of participants in the intervention or control group. *Analysis includes data from the subset of ViDiFlu trial[24] participants who were randomly assigned to vitamin D versus placebo control. †In this trial, participants were asked to report the occurrence of ARI in the preceding month before each annual survey was completed (a maximum of five surveys per participant was completed). The numerator is the number of participants who reported an ARI in at least one survey. ARI outcomes in participants who completed fewer than five surveys and who did not report an ARI (2239 [14%] of 16 000) were estimated based on the proportion of participants who had one or more ARIs among those who completed all five surveys (12 152 [76%]).

The meta-analysis of secondary outcomes was done with the results of placebo-controlled trials only (table 3). Overall, without considering participant-level or trial-level factors, vitamin D supplementation did not have a significant effect on the proportion of participants who had one or more upper respiratory infections or lower respiratory infections, had used antibiotics to treat an ARI, had been absent from work or school due to ARI, had been admitted to hospital or had attended the emergency department due to an ARI, had had a serious adverse event of any cause, had died due to an ARI or respiratory failure, had died due to any cause, or had episodes of hypercalcaemia or renal stones compared with placebo.

Details of the risk of bias assessment are provided in the appendix (p 9). Four trials were assessed as having

	Number of trials	Proportion of participants in the intervention group with one or more events	Proportion of participants in the control group with one or more events	Odds ratio (95% CI)	I^2	p value for heterogeneity
Efficacy outcomes						
Upper respiratory infection*	29	8578/14 569 (58·9%)	8475/14 115 (60·0%)	0·96 (0·91–1·02)	1·2%	0·45
Lower respiratory infection*	15	3930/13 243 (29·7%)	3956/13 108 (30·2%)	0·98 (0·93–1·04)	0	0·63
Emergency department attendance, hospital admission due to an ARI, or both	19	139/10 963 (1·3%)	149/10 850 (1·4%)	0·90 (0·71–1·14)	0	1·00
Death due to ARI or respiratory failure	34	14/14 688 (0·1%)	11/14 139 (0·1%)	1·04 (0·61–1·77)	0	1·00
Use of antibiotics to treat an ARI*	14	2056/8638 (23·8%)	2109/8504 (24·8%)	0·92 (0·83–1·01)	9·0%	0·35
Absence from work or school due to ARI	10	378/1527 (24·7%)	364/1044 (34·9%)	0·91 (0·69–1·20)	35·3%	0·13
Safety outcomes						
Serious adverse event of any cause*	36	567/14 937 (3·8%)	585/14 407 (4·1%)	0·97 (0·86–1·07)	0	0·99
Death due to any cause	35	129/14 930 (0·9%)	110/14 374 (0·8%)	1·13 (0·88–1·44)	0	1·00
Hypercalcaemia	22	51/10 370 (0·5%)	41/10 000 (0·4%)	1·18 (0·80–1·74)	0	1·00
Renal stones	21	117/12 616 (0·9%)	136/12 219 (1·1%)	0·85 (0·67–1·11)	0	1·00

Data are n/N (%), unless otherwise specified. ARI=acute respiratory infection. *Analysis includes a subset of participants in the trial by Pham and colleagues,[45] who completed symptom diaries.

Table 3: **Secondary outcomes in randomised placebo-controlled trials**

an unclear risk of bias due to high loss to follow-up (ie, >30% loss to follow-up). In the trial by Laaksi and colleagues,[8] 60 (37%) of 164 randomised participants were lost to follow-up. In the trial by Dubnov-Raz and colleagues,[26] 29 (52%) of 54 participants did not complete all symptom diaries. In the unpublished trial NCT02046577, loss to follow-up ranged from 33% to 37% across the three study groups (194 [64%] of 303 participants were lost to follow-up overall), and in the ongoing trial NCT02404623, 25 (50%) of 50 participants were lost to follow-up. All other trials were assessed as being at low risk of bias for all seven aspects assessed.

A funnel plot for the proportion of participants who had one or more ARIs showed left-sided asymmetry, confirmed with an Egger's regression test[53] (p=0·007; appendix p 22). This left-sided asymmetry might reflect heterogeneity of effect across trials, or publication bias arising from omission of small trials showing non-protective effects of vitamin D supplementation from the meta-analysis.[56] Given the possibility of publication bias arising from the omission of these small trials showing non-protective effects, the quality of the body of evidence contributing to analyses of the primary efficacy outcome and major secondary outcomes was downgraded to moderate (appendix p 11).

The results of exploratory sensitivity analyses are presented in the appendix (p 12). The meta-analysis of the proportion of participants in placebo-controlled trials who had one or more ARIs, excluding three studies assessed as having an unclear risk of bias (including NCT02046577),[8,26] showed protective effects of vitamin D supplementation consistent with the main analysis (OR 0·93 [95% CI 0·87–1·00]; 45 783 participants in 34 studies; I^2=34·7%, $p_{heterogeneity}$=0·026). Sensitivity analysis for the same outcome, excluding 18 placebo-controlled trials that investigated incidence of ARI as a secondary outcome, did not show a significant protective effect of vitamin D supplementation over placebo (0·92 [0·82–1·03]; 9694 participants in 19 studies; I^2=12·6%, $p_{heterogeneity}$=0·30). A sensitivity analysis for the same outcome, substituting symptom diary-defined ARI events (available for 2598 participants) for survey-defined ARI events (available for 16 000 participants) in the trial by Pham and colleagues,[45] revealed protective effects of vitamin D supplementation consistent with the main analysis (0·91 [0·84–0·99]; 32 764 participants in 37 studies; I^2=35·5%, $p_{heterogeneity}$=0·019).

Discussion

This updated meta-analysis of RCTs of vitamin D supplementation for the prevention of ARIs includes data from an additional 18 studies completed since December 2015, when the final literature search for our previous meta-analysis of individual participant-level data was done.[30] For expediency during the COVID-19 pandemic, we used a trial-level approach for this update, which includes data from a total of 48 488 participants across 43 trials. Overall, we report a small but significant protective effect of vitamin D supplementation on the risk of having one or more ARIs compared with placebo (OR 0·92 [95% CI 0·86–0·99). As expected, there was significant heterogeneity across trials (I^2=35·6%, $p_{heterogeneity}$=0·018), which might have led to underestimation of the protective effect of vitamin D supplementation and contributed to the asymmetry observed in the funnel plot.[56] Alternatively, left-sided asymmetry in the funnel plot might reflect publication bias, which could have led

to overestimation of the protective effect. In contrast to the findings of our previous meta-analysis,[30] we did not observe enhanced protection in participants with the lowest 25(OH)D concentrations at baseline. However, there was evidence from an analysis of potential effect-modifiers that the efficacy of vitamin D supplementation varied according to dosing regimen, trial duration, and participant age at enrolment, with protective effects associated with daily administration of doses of 400–1000 IU vitamin D taken for 12 months or less, and being aged 1·00–15·99 years at enrolment. An exploratory analysis restricted to data from five trials fulfilling these design criteria revealed a larger protective effect of vitamin D supplementation over placebo (OR 0·56 [95% CI 0·38–0·82) compared with the main analysis, without significant heterogeneity across trials (I^2=0·0%, $p_{heterogeneity}$=0·44).

The magnitude of the overall protective effect of vitamin D supplementation on the risk of ARI observed in the current analysis (OR 0·92 [95% CI 0·86–0·99]) is small, and similar to the value reported in our previous meta-analysis of individual participant-level data (adjusted OR 0·88 [95% CI 0·81–0·96]).[30] Consistent with our previous study, the point estimate for this effect was lower among participants with baseline 25(OH)D concentrations of less than 25 nmol/L than in those with baseline concentrations higher than 25 nmol/L. However, in contrast to our previous finding, a significant protective effect of vitamin D was not observed in participants with the lowest 25(OH)D concentrations at baseline. This difference reflects the inclusion of null data from four new RCTs, in which vitamin D was given at daily dose equivalents of 2000 IU/day or more at weekly or monthly intervals over 2–5 years.[42,43,45,46] The null results of these studies contrast with the protective effects reported in earlier trials, in which smaller daily doses of vitamin D were given over shorter time-periods.[8,9,13,16] These differing findings suggest that the frequency, dose, and duration of vitamin D supplementation might be key determinants of its protective effects against ARIs. Consistent with this hypothesis, significant protective effects of vitamin D supplementation over placebo were observed in our meta-analysis of trials in which vitamin D was given daily, at doses of 400–1000 IU/day, and for 12 months or less. The greater protective effects of lower versus higher doses of vitamin D might reflect the deleterious effects of higher-dose vitamin D on its own metabolism or on host responses to respiratory pathogens. Head-to-head mechanistic studies in individuals randomised to different regimens of vitamin D supplementation are needed to investigate this issue.

The current study has several strengths. We included the most recent RCT data available in this fast-moving field, including findings from four large phase 3 trials published in 2020,[41–43,45] as well as from some as yet unpublished studies (NCT02404623 and NCT02046577). The inclusion of additional studies allowed us to analyse the results of placebo-controlled studies versus those comparing high-dose and low-dose vitamin D groups separately, and gave us the power to investigate reasons for heterogeneity of effect observed across trials. For instance, we could distinguish the effects of daily versus weekly dosing; data from trials employing daily versus weekly dosing were pooled in our previous meta-analysis.[30]

Our work also has some limitations. Given the need to generate a rapid update of our previous work in the context of the COVID-19 pandemic, we meta-analysed aggregate trial-level data rather than individual participant-level data, which allowed us to proceed rapidly and without the delays introduced by the need to establish multiple data sharing agreements. However, we did contact authors to obtain unpublished estimates of effect that were stratified by predefined baseline 25(OH)D concentrations, harmonised across studies. Therefore, we were able to provide accurate data for the major participant-level effect-modifier of interest. Despite the large number of trials overall, only eleven compared the effects of lower-dose versus higher-dose vitamin D supplementation; the power for this secondary comparison was therefore less than for the primary comparison. We did not have the individual participant-level data to investigate race or ethnicity and obesity as potential effect-modifiers. We also could not account for other factors that might influence the protective effect of vitamin D supplementation in the prevention of ARIs (eg, taking the supplement with or without food), or secular trends that would influence trials, such as the increased societal use of vitamin D supplements;[57] concurrent use of standard dose vitamin D supplements or multivitamins in the placebo group would effectively render these as high-dose versus low-dose vitamin D trials and potentially drive results toward the null. Another limitation relates to the funnel plot, which suggested that the overall effect size might have been over-estimated due to publication bias. We mitigated this risk of publication bias by including obtainable data from unpublished studies identified by searching ClinicalTrials.gov. Finally, we acknowledge that additional RCTs investigating the effects of vitamin D on the risk of ARIs are ongoing or have not yet been published (NCT01875757 and NCT01758081). We hope to include data from these studies in future meta-analyses.

In summary, this updated meta-analysis of data from RCTs of vitamin D supplementation for the prevention of ARIs showed a significant overall protective effect of this intervention compared with a placebo control. The protective effect was heterogenous across trials, and might have been overestimated due to publication bias. In contrast to findings of our previous meta-analysis of individual participant-level data, we did not see a protective effect of vitamin D supplementation among participants with the lowest baseline 25(OH)D

concentrations. The vitamin D dosing regimen of most benefit was daily and used standard doses (400–1000 IU) for up to 12 months. The relevance of these findings to COVID-19 is not known and requires further investigation.

Contributors

DAJ and ARM wrote the study protocol and designed the statistical analyses. DAJ, CAC, and ARM assessed the eligibility of studies for inclusion in this analysis. DAJ, ARM, CAC, and JDS assessed risk of bias. DAJ and ARM had access to, and verified, the underlying data from all original research articles. Statistical analyses were done by DAJ; the results were checked and verified by JDS. DAJ and ARM wrote the first draft of the report. All authors critically revised the report for important intellectual content, gave final approval of the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. ARM had final responsibility to submit for publication.

Declaration of interests

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Data sharing

The study dataset can be requested from d.a.jolliffe@qmul.ac.uk.

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