Vitamin D supplementation to prevent acute respiratory infection: Updated systematic review and meta-analysis of aggregate data

Study Protocol

Version 1

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Full Title

Vitamin D supplementation to prevent acute respiratory infections: Updated systematic review and meta-analysis of aggregate data

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1 Glossary of terms and abbreviations

25(OH)D	25-hydroxyvitamin D
ARI	Acute Respiratory Infection
URI	Upper Respiratory Infection
LRI	Lower Respiratory Infection
GP	General Practitioner
NICE	National Institute for Health Care and Excellence
Participant	An individual who takes part in a randomised clinical trial
PI	Principal Investigator
RCT	Randomised Controlled Trial
URI	Upper Respiratory Infection
ADMA	Aggregate Data Meta-analysis
IPDMA	Individual Participant Data Meta-analysis
CI	Confidence Interval
OR	Odds ratio
COVID-19	Coronavirus disease 2019
PICO	Population Intervention Comparator Outcome
RIDT	Rapid Influenza Diagnostic Test

2 Summary

Short Title	Vitamin D Supplementation to Prevent Acute Respiratory Infection (ARI): Aggregate Data Meta-Analysis of Randomised Controlled Trials
Methodology	Aggregate data meta-analysis of randomised controlled trials
Research Site	Centre for Primary Care and Public Health, Barts and The London School of Medicine and Dentistry
Primary Objective	To determine whether vitamin D supplementation influences the proportion of participants experiencing at least one ARI
Secondary Objectives	1. To determine whether vitamin D supplementation influences the proportion of participants experiencing at least one ARI, in sub-groups categorised by baseline vitamin D status, size of vitamin D dose administered, frequency of vitamin D administration and duration of supplementation 2. To determine whether there is an effect of allocation to vitamin D vs. placebo on the following secondary outcomes: • Proportion with at least one Upper Respiratory Infection (URI) • Proportion with at least one Lower Respiratory Infection (LRI) • Proportion with at least one school/work absence due to ARI • Proportion taking at least one course of antibiotics for ARI • Proportion with at least one hospital admission or emergency department attendance due to ARI • Proportion with at least one serious adverse event of any cause • Proportion dying of ARI • Proportion dying of any cause • Proportion experiencing at least one episode of hypercalcaemia • Proportion experiencing at least one episode of renal stones
Number of Trials and Participants	38 trials with 29,476 randomised participants
Main Inclusion Criteria	Studies will be eligible to contribute primary data to this meta-analysis if they are: • Randomised controlled trials of vitamin D or calcidiol in which data relating to incidence of ARI have been prospectively collected as an efficacy outcome • Approved by a research ethics committee
Statistical Methodology and Analysis (if applicable)	The effectiveness of vitamin D supplementation vs. control will be assessed by calculation of odds ratios and standard errors from aggregate data for each outcome, within each trial, and subsequent meta-analysis using a random effects model to produce a pooled estimate of effect size and a measure of trial heterogeneity.

	Heterogeneity will be interrogated by sub-group analysis of trial-level characteristics and by multivariate meta-regression analysis, to produce an adjusted estimate of effect size and a p value for interaction.

3 Introduction

Acute respiratory infections (ARI) are major causes of morbidity and health service use that impose significant human and economic costs (1). Although vaccines are available for some of the pathogens responsible for ARI, their protective efficacy is limited by poor uptake, narrow spectrum of protection and failure to induce protection in some groups, e.g. older adults. New interventions offering a broader spectrum of protection, higher degree of patient-acceptability and lower cost are urgently needed.

A growing body of evidence suggests that vitamin D supplementation might prevent ARI by inducing protective innate immune responses to a wide range of viral and bacterial respiratory pathogens (2-4). These findings have led to a significant number of randomised controlled trials (RCTs) of vitamin D supplementation for protection against ARI, which our group meta-analysed in 2017 (5). Twenty-five RCTs provided individual participant data (IPD) from n=10,933 subjects for this analysis, which showed that vitamin D supplementation reduced the odds of having ≥1 ARI in all participants (adjusted odds ratio [aOR] 0.88; 95% confidence interval [CI] 0.81 to 0.96) and that this protective effect was greater in participants with profound vitamin D deficiency at baseline (serum 25[OH]D concentration <25 nmol/L; aOR 0.58, 95% CI 0.40 to 0.82). Our analysis also found that within profoundly deficient participants, the protective effects of vitamin D were seen in those administered a daily or weekly dosing regimen (aOR 0.30, 95% CI 0.17 to 0.53), but not in those who received a bolus monthly or two-monthly regimen of vitamin D supplementation (aOR 0.82, 95% CI 0.51 to 1.33). Taken together, these subgroup findings point towards a dosing strategy for improved ARI protection, however our analysis did not offer insights into an optimal vitamin D dose size or duration of supplementation.

In the past 3 years a significant number of new RCTs have come into the fold, including two vitamin D “mega trials” (n>5,000 participants). In light of the amount of new data and their potential to address any attendant power issues we may have encountered with previous sub-group analyses, together with the potential relevance of this research theme to the emergent COVID-19 pandemic, we endeavoured to update our meta-analysis by synthesis of aggregate level data in order to provide a rapid answer to the following question:

“Does vitamin D supplementation influence the proportion of participants who experience acute respiratory infections?”.

Our consortium comprises principal investigators from 38 primary trials of vitamin D supplementation for prevention of ARI, giving us access to aggregate data from over 29,000 participants. This approach gives us adequate power to generate valid, reliable answers to the questions above.

4 Aims and objectives

The primary aim of the proposed project is to determine whether vitamin D supplementation influences the proportion of participants who experience at least one ARI.

Our secondary aims are 1. To determine whether vitamin D supplementation influences the proportion of participants who experience at least one ARI, in sub-groups categorised according to the following potential effect-modifiers:

i) Baseline vitamin D status
ii) Size of vitamin D dose administered
iii) Frequency of vitamin D administration
iv) Duration of supplementation

and 2. To determine whether vitamin D supplementation influences the following efficacy or safety outcomes:

i) Proportion with at least one Upper Respiratory Infection (URI)
ii) Proportion with at least one Lower Respiratory Infection (LRI)
iii) Proportion with at least one school/work absence due to ARI
iv) Proportion taking at least one course of antibiotics for ARI
v) Proportion with at least one hospital admission or emergency department attendance due to ARI
vi) Proportion with at least one serious adverse event of any cause
vii) Proportion dying of ARI
viii) Proportion dying of any cause
ix) Proportion experiencing at least one episode of hypercalcaemia
x) Proportion experiencing at least one episode of renal stones

5 Methodology

We will conduct an aggregate data meta-analysis of proportional data from each trial, and then summarise the evidence by synthesising the data whilst preserving the randomisation and clustering of patients within studies. The 'PICO' structured question addressed in our project is summarised in Table 1 below.

Table 1. 'PICO' structured question for aggregate data meta-analysis of trials of vitamin D supplementation for prevention of acute respiratory infection

Population	Males and females of any age and any race/ethnic origin with and without vitamin D deficiency at baseline
Intervention	Supplementation with vitamin D (either vitamin D_3 [cholecalciferol], vitamin D_2 [ergocalciferol] or 25-hydroxyvitamin D [calcidiol]) administered at any dose with any frequency via any route
Comparator	Placebo or alternate dose of vitamin D
Primary Outcome	Proportion of participants experiencing one or more ARI

5.1 Eligibility Criteria

Studies will be eligible to contribute summary data to the proposed aggregate data meta-analysis if they are:

- Randomised controlled trials of vitamin D supplementation in which data relating to incidence of ARI have been prospectively collected using a directed, closed question routinely directed at all participants

- Approved by a research ethics committee

Table 2: Trials to be included in the proposed aggregate data meta-analysis, by date of publication

Study first author, year	Setting	Participants	Mean baseline 25(OH)D, nmol/L (s.d.)	Baseline 25(OH)D <25 nmol/L (%)	Intervention: control	Oral dose of vitamin D_3, intervention arm	Study duration	ARI definition
Li-Ng 2009 (6)	USA	Healthy adults	63.7 (25.5)	3/150 (2.0)	84:78	50 µg daily	3 mo	URI: ≥2 URI symptoms in absence of allergy symptoms
Urashima 2010 (7)	Japan	Schoolchildren	Not determined	--	217:213	30 µg daily	4 mo	URI: influenza A/B diagnosed by RIDT or RIDT-negative ILI
Manaseki-Holland 2010 (8)	Afghanistan	Pre-school children with pneumonia	Not determined	--	224:229	2.5 mg bolus once	3 mo	LRI: repeat episode of pneumonia – age-specific tachypnoea without wheeze
Laaksi 2010 (9)	Finland	Military conscripts	75.9 (18.7)	0/73 (0.0)	80:84	10 µg daily	6 mo	ARI: medical record diagnosis
Majak 2011 (10)	Poland	Children with asthma	88.9 (38.2)	0/48 (0.0)	24:24	12.5 µg daily	6 mo	ARI: self-report
Trilok-Kumar 2011 (11)	India	Low birthweight infants	Not determined	Not determined	1,039:1,040	35 µg weekly	6 mo	ARI: medical record diagnosis of events causing hospitalisation
Lehouck 2012(12)	Belgium	Adults with COPD	49.8 (29.2)	31/182 (17.0)	91:91	2.5 mg bolus monthly	1 yr	URI: self-report
Manaseki-Holland 2012 (13)	Afghanistan	Infants	Not determined	Not determined	1524:1522	2.5 mg bolus 3-monthly	1.5 yr	LRI: pneumonia confirmed by chest radiograph
Camargo 2012 (14)	Mongolia	3rd/4th grade schoolchildren	18.9 (9.7)	192/245 (78.4)	143:104	7.5 µg daily	7 wk	ARI: parent-reported 'chest infections or colds'
Murdoch 2012 (15)	New Zealand	Healthy adults	72.1 (22.1)	5/322 (1.6)	161:161	2 x 5 mg bolus monthly then 2.5 mg bolus monthly	1.5 yr	URI: assessed with symptom score
Bergman 2012 (16)	Sweden	Adults with increased susceptibility to ARI	49.3 (23.2)	15/131 (11.45)	70:70	100 µg daily	1 yr	URI: assessed with symptom score
Marchisio 2013 (17)	Italy	Children with recurrent acute otitis media	65.3 (17.3)	2/116 (1.7)	58:58	25 µg daily	6 mo	URI: doctor-diagnosed acute otitis media
Rees 2013 (18)	USA	Adults with previous colorectal adenoma	62.5 (21.3)	0/759 (0.0)	399:360	25 µg daily	13 mo (average)	URI: assessed from daily symptom diary
Tran 2014 (19)	Australia	Healthy older adults	41.7 (13.5)	66/643 (10.3)	430:214	0.75 mg bolus *vs.* 1.5 mg bolus monthly	1 yr	URI: self-reported cold
Goodall 2014 (20)	Canada	Healthy university students	Not determined	--	300:300	0.25 mg weekly (factorial with gargling)	8 wk	URI: self-reported cold
Urashima 2014 (21)	Japan	High school students	Not determined	--	148:99	50 µg daily	2 mo	URI: influenza A diagnosed by RIDT or RIDT-negative ILI
Grant 2014 (22)	New Zealand	Pregnant women and offspring	54.8 (25.8)	30/200 (15.0)	173:87 (mothers) 164:85 (offspring)	Mothers: 25 µg *vs.* 50 µg daily Infants: 10 µg *vs.* 20 µg daily	9 mo (3 mo in pregnancy + 6 mo in infancy)	ARI: doctor-diagnosed ARI precipitating primary care consult
Martineau 2015a (23) [ViDiCO]	UK	Adults with COPD	46.1 (25.7)	50/240 (20.8)	122:118	3 mg bolus 2-monthly	1 yr	URI: assessed from daily symptom diary
Martineau 2015b (24) [ViDiAs]	UK	Adults with asthma	49.6 (24.7)	36/250 (14.4)	125:125	3 mg bolus 2-monthly	1 yr	URI: assessed from daily symptom diary
Martineau 2015c (25) [ViDiFlu]	UK	Older adults and their carers	42.9 (23.0)	60/240 (25.0)	137:103	Older adults: 2.4 mg bolus 2-monthly + 10 µg daily Carers: 3 mg 2-monthly	1 yr	URI & LRI, both assessed from daily symptom diary

Study first author, year	Setting	Participants	Mean baseline 25(OH)D, nmol/L (s.d.)	Baseline 25(OH)D <25 nmol/L (%)	Intervention: control	Oral dose of vitamin D_3, intervention arm	Study duration	ARI definition
Simpson 2015 (26)	Australia	Healthy adults	67.9 (23.0)	0/33 (0.0)	18:16	0.5 mg weekly	17 wk	ARI assessed with symptom score
Dubnov-Raz 2015 (27)	Israel	Adolescent swimmers with vitamin D insufficiency	60.4 (11.9)	0/54 (0.0)	27:27	50 µg daily	12 wk	URI assessed with symptom score
Denlinger 2016 (28)	USA	Adults with asthma	47.0 (16.9)	55/408 (13.5)	201:207	2.5 mg bolus then 100 µg daily	28 wk	URI assessed with symptom score
Tachimoto 2016 (29)	Japan	Children with asthma	74.9 (24.6)	1/89 (1.1)	54:35	20 µg daily, first 2 mo.	6 mo	URI: assessed with symptom score
Ginde, 2016 (30)	USA	Institutionalised older adults	57.3 (22.7)	12/107 (11.2)	55:52	2.5 mg bolus monthly + ≤25 µg per day equivalent	1 yr	ARI: medical record diagnosis
Gupta 2016 (31)	India	Children with pneumonia	--	--	162:162	2.5 mg bolus, single dose	6 mo	Physician confirmed recurrent pneumonia
Arihiro 2018 (32)	Japan	Adults with diagnosis of ulcerative colitis or Crohns disease	58.6 (22.0)	--	108:115	12.5 µg daily	6 mo	Lab confirmed influenza; physician confirmed URI
Hibbs 2018 (33)	USA	Healthy infants	Median (IQR): 47.7 (38.4-69.9) intervention; 52.4 (42.4-62.4) control	--	153:147	10 µg daily	1 yr	ARI: self-reported URI/LRI
Lee 2018 (34)	USA	Sickle cell disease	35.7 (--)	--	31:31	2.5 mg bolus monthly	1 yr	Self-reported respiratory events, including ARI
Loeb 2018 (35)	Vietnam	Healthy children and adolescents	65.5 (16.8)	6/1300 (0.4)	650:650	50 µg weekly	8 mo	Lab confirmed influenza; lab confirmed non-influenza respiratory virus
Rosendahl 2018 (36)	Finland	Healthy infants	81.5 (25.9)	--	495:492	30 µg daily	2 yrs	Parent reported infections, including ARI
Shimizu 2018 (37)	Japan	Healthy adults	48.9 (13.5)	--	126:126	10 µg daily	4 mo	URI: self-reported
Aloia 2019 (38)	USA	Healthy older adults	54.4 (16.7)	--	130:130	50 µg daily	3 mo	ARI: self-reported cold/flu
Camargo 2019 (39)	New Zealand	Healthy older adults	63.0 (24.0)	--	2558:2552	5 mg bolus loading dose; then 2.5mg bolus monthly	3 yrs	ARI: self-reported cold/flu
Hauger 2019 (40)	Denmark	Healthy children	56.7 (12.3)	--	40/38:41	20 µg /10 µg daily	5 mo	ARI: self-reported
Mandlik 2020 (41)	India	Healthy children	58.4 (10.3)	--	120:124	25 µg daily	8 mo	URI: self-reported
Rake 2020 (42)	England	Healthy older adults	50.2 (--)	127/787 (16.1)	395:392	2.5 mg bolus monthly	2 yrs	URI/LRI: GP recorded
Ganmaa, unpublished	Mongolia	Healthy school children	29.7 (10.5)	2813/8851 (31.8)	4418:4433	0.35 mg weekly	3 yrs	ARI: self-reported

5.2 Data collection, entry and checking and study quality

Where necessary, datasets will be re-analysed to identify the proportion of participants experiencing ARI re-defined using diagnostic criteria that are harmonised between trials.

A shell table requesting the proportion of participants per arm, for each outcome will be provided to authors for populating. All data supplied will be subjected to range and consistency checks. This will ensure that all randomised patients are included; that all non-randomised patients are excluded; that data are as accurate as possible; and that intention-to-treat analysis is performed for all analyses. Any missing data, obvious errors, inconsistencies will be queried and rectified as necessary through input from the original authors.

The quality of each study will also be assessed at this stage, in order to evaluate the integrity of the randomisation and follow-up procedure for each trial. The Risk of Bias tool developed by the Cochrane Collaboration will be used to score the quality of each study (43).

5.3 Study procedures

Procedures for individual studies are documented in original trial reports (6-9, 11-15, 17, 19-21, 23-25, 27, 31-37, 39-42, 44-52) and individual study protocols.

5.4 Statistical analysis

5.4.1 Summarising overall effect of vitamin D supplementation

Our aggregate data meta-analytical approach will follow existing guidelines (53). For each analysis, we will include all participants ever randomised and will base analysis on the intention-to-treat principle.

From the proportion of events in the intervention vs. control arm for each outcome, within each trial, we will calculate a log odds ratio and its standard error, which will be meta-analysed in a random effects model using the metan package within STATA IC v14.2 (College Station, TX) to obtain a pooled odds ratio with a 95% confidence interval and a measure of heterogeneity summarized by the I^2 statistic and its corresponding p value.

Analyses of the effectiveness of vitamin D supplementation *vs.* placebo will be performed on the combined ARI study population for the following outcomes:

a) Proportion of participants who experience at least one ARI, incorporating URI (including colds, influenza-like illness, ear infections, acute rhinosinusitis) and LRI (including pneumonia); URI and LRI may be analysed separately or together.

b) Proportion of participants with at least one hospital attendance, defined as Emergency Department attendance / hospital admission for ARI

c) Proportion of participants taking at least one course of antimicrobials for treatment of ARI

d) Proportion of participants with at least one work/school absence due to ARI

e) Proportion of participants experiencing at least one adverse event including hypercalcaemia, renal stones, drop-out/withdrawal rates, serious adverse events (both ARI-related and total) and mortality (both ARI-related and total).

A separate analysis of the effectiveness of high dose vitamin D *vs.* low vitamin D control will be performed on relevant trials, for the primary outcome only.

Original authors will be asked to confirm accuracy of this reanalysis, and any discrepancies will be resolved.

5.4.2 Examining heterogeneity and potential sub-group effects

To consider the causes of heterogeneity and factors that may modify the effects of vitamin D supplementation, we will perform pre-specified sub-group analyses according to:

i) Baseline vitamin D status (serum 25[OH]D <25 *vs.* 25-49.9 *vs.* 50-74.5 *vs.* ≥75 nmol/L);
ii) Size of vitamin D dose administered (daily equivalents ≤400 IU *vs.* 401-1000 IU *vs.* 1001-2000 IU *vs.* >2,000 IU);
iii) Frequency of vitamin D administration (daily *vs.* weekly *vs.* monthly or less frequently);
iv) Duration of supplementation (<6 months *vs.* 6-12 months *vs.* >12 months)

The 25 nmol/L threshold for baseline 25(OH)D concentration in sub-group analyses was selected on the grounds that it is the threshold for vitamin D deficiency defined by the UK Department of Health (54), and the level below which participants in clinical trials have experienced the most consistent benefits of supplementation (55). Thresholds of 50 nmol/L and 75 nmol/L were selected on the grounds that observational studies have reported that less profound states of vitamin D deficiency may also associate independently with increased risk of ARI (56, 57).

Examination of sub-group effects will be undertaken by multivariate meta-regression analysis on trial-level characteristics, namely, dose frequency, dose size and dose duration, to produce an adjusted odds ratio, a 95% confidence interval and a p value for interaction for each factor.

5.4.3 Exploration of sources of bias, unavailable data and publication bias

For the analyses detailed above, we will explore the potential for, and possible impact of, publication bias according to recent guidelines (58), through the construction of contour-enhanced funnel plots and appropriate statistical tests for ‘small-study effects’ (59); that is, the tendency for smaller studies to provide more positive findings. We recognise that, especially where heterogeneity exists, publication bias may be one of a number of reasons for any small study effects identified.

6 Ethics

Individual trials contributing summary data to this aggregate data meta-analysis will all be approved by Research Ethics Committees in the countries where they took place. No participant-level data will be used in this analysis.

7 Dissemination of findings and manuscript authorship

Findings of this study will be presented at scientific conferences and submitted for publication in peer-reviewed journals. Any publication of results of this meta-analysis will include one PI for each trial whose data are included in that meta-analysis as a named co-author. Other investigators named on this protocol who have made a substantive contribution to the meta-analysis, but who are not PIs for individual studies, may also be named co-authors on manuscripts arising from this study.

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