Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data

Supplementary Material

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Search Strategies

A. Medline

Cochrane Highly Sensitive Search Strategy for identifying randomised controlled trials

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

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

#3. #1 NOT #2

Terms specific to vitamin D

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

Terms specific to acute respiratory tract infection

#5. Acute Respiratory Infection OR Upper Respiratory Infection OR Lower Respiratory Infection OR Respiratory Tract Infection OR Common Cold OR Sinusitis OR Pharyngitis OR Laryngitis OR Laryngotracheobronchitis OR Tonsillitis OR peritonsillar abscess OR Croup OR Epiglottitis OR supraglottitis OR Otitis Media OR Pneumonia OR Bronchopneumonia OR Bronchitis OR Pleurisy OR Pleuritis

Combination of terms to identify randomised controlled trials of vitamin D for the prevention of acute respiratory infection

#3 AND #4 AND #5

B. EMBASE

Terms for identifying randomised controlled trials

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

Terms specific to vitamin D

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

Terms specific to acute respiratory tract infection

#5. acute AND respiratory AND infection OR upper AND respiratory AND infection OR lower AND respiratory AND infection OR respiratory AND tract AND infection OR common AND cold OR sinusitis OR pharyngitis OR laryngitis OR laryngotracheobronchitis OR tonsillitis OR peritonsillar AND abscess OR croup OR epiglottitis OR supraglottitis OR otitis AND media OR pneumonia OR bronchopneumonia OR bronchitis OR pleurisy OR pleuritis

Combination of terms to identify randomised controlled trials of vitamin D for the prevention of acute respiratory tract infection

#3 AND #4 AND #5

C. Cochrane Central

Terms specific to vitamin D

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

Terms specific to acute respiratory tract infection

#2. Acute Respiratory Infection OR Upper Respiratory Infection OR Lower Respiratory Infection OR Respiratory Tract Infection OR Common Cold OR Sinusitis OR Pharyngitis OR Laryngitis OR Laryngotracheobronchitis OR Tonsillitis OR peritonsillar abscess OR Croup OR Epiglottitis OR supraglottitis OR Otitis Media OR Pneumonia OR Bronchopneumonia OR Bronchitis OR Pleurisy OR Pleuritis

Combination of terms to identify randomised controlled trials of vitamin D for the prevention of acute respiratory tract infection

#1 AND #2

D. Web of Science

TS =(Vitamin D OR vitamin D2 OR vitamin D3 OR cholecalciferol OR ergocalciferol OR alphacalcidol OR alfacalcidol OR calcitriol OR paricalcitol OR doxerocalciferol) AND TS =(Acute Respiratory Infection OR Upper Respiratory Infection OR Lower Respiratory Infection OR Respiratory Tract Infection OR Common Cold OR Sinusitis OR Pharyngitis OR Laryngitis OR Laryngotracheobronchitis OR Tonsillitis OR peritonsillar abscess OR Croup OR Epiglottitis OR supraglottitis OR Otitis Media OR Pneumonia OR Bronchopneumonia OR Bronchitis OR Pleurisy OR Pleuritis) AND TS =(placebo* or random* or clinical trial* or double blind* or single blind* or rct)

E. ClinicalTrials.gov and ISRCTN Registry

Vitamin D AND respiratory AND infection

Sources of support for participating trials

The trial by Ginde and colleagues was supported by NIH/NIA grant K23AG040708, NIH/NCATS Colorado CTSA Grant UL1TR001082, and the American Geriatrics Society Jahnigen Career Development Scholars Award

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The trial by Simpson and colleagues was supported by the Royal Hobart Hospital Research Foundation.

The trial by Trilok Kumar and colleagues was supported by the Department of Biotechnology, Government of India (ref BT/PR-PR7489/PID/20/285/2006), Nutrition Third World and Sight and Life.

The trial by Rees and colleagues was supported by the National Cancer Institute at the National Institutes of Health (grant numbers CA098286 and CA098286-S).

The trial by Tran and colleagues was supported by the National Health and Medical Research Council of Australia, grant 613655.

Results

Table S1: Participants' baseline characteristics by study arm

	Control group (n=5,225)	Intervention group (n=5,708)
Sex		
Male, N (%)	2,564 (49.1)	2,871 (50.3)
Female, N (%)	2,659 (50.9)	2,836 (49.7)
Age, years		
≤1	2744 (52.5)	2827 (49.5)
1.1-15.9	513 (9.8)	566 (27.9)
16-65	1459 (27.9)	1592 (27.9)
>65	509 (9.7)	723 (12.7)
25(OH)D, nmol/L		
<25	249 (4.8)	289 (5.1)
≥25	1639 (31.4)	1995 (35.0)
Not recorded	3337 (63.9)	3424 (60.0)
Body mass index, kg/m^2		
<25	1943 (37.2)	2074 (36.3)
≥25	1039 (19.9)	1235 (21.6)
Not recorded	2243 (42.9)	2399 (42.0)
Co-morbidity: Asthma		
No	1008 (19.3)	1101 (19.3)
Yes	534 (10.2)	542 (9.5)
Not recorded	3683 (70.5)	4065 (71.2)
Co-morbidity: COPD		
No	763 (14.6)	791 (13.9)
Yes	230 (4.4)	238 (4.2)
Not recorded	4232 (81.0)	4679 (82.0)
Influenza vaccination		
No	373 (7.1)	407 (7.1)
Yes	779 (14.9)	826 (14.5)
Not recorded	4073 (78.0)	4475 (78.4)

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; COPD, Chronic Obstructive Pulmonary Disease

Table S2: Risk of Bias Assessment

	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Li-Ng 2009[1]	✓	✓	✓	✓	✓	✓	✓
Urashima 2010[2]	✓	✓	✓	✓	✓	✓	✓
Manaseki-Holland 2010[3]	✓	✓	✓	✓	✓	✓	✓
Laaksi 2010[4]	✓	✓	✓	✓	?	✓	✓
Majak 2011[5]	✓	✓	✓	✓	✓	✓	✓
Trilok-Kumar 2011[6]	✓	✓	✓	✓	✓	✓	✓
Lehouck 2012[7]	✓	✓	✓	✓	✓	✓	✓
Manaseki-Holland 2012[8]	✓	✓	✓	✓	✓	✓	✓
Camargo 2012[9]	✓	✓	✓	✓	✓	✓	✓
Murdoch 2012[10]	✓	✓	✓	✓	✓	✓	✓
Bergman 2012[11]	✓	✓	✓	✓	✓	✓	✓
Marchisio 2013[12]	✓	✓	✓	✓	✓	✓	✓
Rees 2013[13]	✓	✓	✓	✓	✓	✓	✓
Tran 2014[14]	✓	✓	✓	✓	✓	✓	✓
Goodall 2014[15]	✓	✓	✓	✓	✓	✓	✓
Urashima 2014[16]	✓	✓	✓	✓	✓	✓	✓
Grant 2014[17]	✓	✓	✓	✓	✓	✓	✓
Martineau 2015a[18] [ViDiCO]	✓	✓	✓	✓	✓	✓	✓
Martineau 2015b[19] [ViDiAs]	✓	✓	✓	✓	✓	✓	✓
Martineau 2015c[20] [ViDiFlu]	✓	✓	✓	✓	✓	✓	✓
Simpson 2015[21]	✓	✓	✓	✓	✓	✓	✓
Dubnov-Raz 2015[22]	✓	✓	✓	✓	?	✓	✓
Denlinger 2016[23]	✓	✓	✓	✓	✓	✓	✓
Tachimoto 2016[24]	✓	✓	✓	✓	✓	✓	✓
Ginde 2016[25]	✓	✓	✓	✓	✓	✓	✓

✓ = low risk of bias; ? = unclear risk of bias;

Table S3: Summary of Findings Table

Vitamin D_3 compared to placebo for prevention of acute respiratory tract infection (ARTI)

Population: children and adults of any age, sex or ethnic origin, with or without co-morbidity
Setting: fourteen countries on four continents (Asia, Australasia, Europe, North America)
Intervention: oral vitamin D_3 (cholecalciferol) supplementation
Comparison: oral placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	**Risk with Vitamin D**			
Proportion with at least one ARTI, all participants	422 per 1,000	391 per 1,000 (371 to 412)	**OR 0.88** (0.81 to 0.96)	10933 (25 RCTs)	⊕⊕⊕⊕ HIGH
Proportion with at least one ARTI, baseline 25(OH)D <25 nmol/L	408 per 1,000	299 per 1,000 (237 to 364)	**OR 0.62** (0.45 to 0.83)	871 (15 RCTs)	⊕⊕⊕⊕ HIGH
Proportion with at least one ARTI, daily or weekly vitamin D (no boluses)	496 per 1,000	444 per 1,000 (415 to 473)	**OR 0.81** (0.72 to 0.91)	5133 (15 RCTs)	⊕⊕⊕⊕ HIGH
Proportion with serious adverse event, any cause	40 per 1,000	39 per 1,000 (32 to 48)	**OR 0.98** (0.80 to 1.20)	11224 (25 RCTs)	⊕⊕⊕⊕ HIGH

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

CI: Confidence interval; **OR:** Odds ratio

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

Table S4: Exploratory one-step individual participant data meta-analysis, proportion of participants experiencing at least one acute respiratory tract infection by baseline vitamin D status categorised by 25 nmol/L strata

Baseline 25(OH)D (nmol/L)	Number of Trials	Proportion with ≥1 ARTI, control group (%)	Proportion with ≥1 ARTI, intervention group (%)	Adjusted odds ratio (95% CI)[1]	P value	P value for interaction
<25	14	137/249 (55.0)	117/289 (40.5)	0.58 (0.40, 0.82)	0.002	0.77
25 to 49.9	19	385/671 (57.4)	459/821 (55.9)	0.98 (0.79, 1.23)	0.89	
50 to 74.9	19	405/631 (64.2)	472/778 (60.7)	0.91 (0.71, 1.16)	0.44	
≥75	16	237/337 (70.3)	248/396 (62.6)	0.68 (0.46, 0.99)	0.05	

1, adjusted for age, sex and study duration. Abbreviations: 25(OH)D, 25-hydroxyvitamin D; ARTI, acute respiratory tract infection; CI, confidence interval.

Table S5: One-step IPDMA, ARTI event rate: sub-group analyses by baseline vitamin D status and dosing regimen.

	N Trials	N Individuals	Rate of ARTI per participant-year, control group	Rate of ARTI per participant-year, intervention group	Adjusted incidence rate ratio (95% CI)[1]	P value	P value for Interaction
Baseline 25(OH)D (nmol/L)							
<25	14	509	2.15	1.67	0.78 (0.66, 0.93)	0.004	0.02
≥25	19	3458	2.12	1.91	0.95 (0.90, 1.00)	0.04	
Dosing Regimen Type							
Bolus dose ≥30,000 IU given	10	5595	0.73	0.76	0.99 (0.94 to 1.05)	0.83	0.11
Bolus dose not given	15	5133	2.23	2.09	0.93 (0.88 to 0.98)	0.008	

1, adjusted for age, sex and study duration. Abbreviations: 25(OH)D, 25-hydroxyvitamin D; ARTI, acute respiratory tract infection; CI, confidence interval.

Table S6: One-step IPDMA, time to first ARTI: sub-group analyses by baseline vitamin D status and dosing regimen.

	N Trials	N Individuals	Median time to first ARTI, control group, days (IQR)	Median time to first ARTI, intervention group, days (IQR)	Adjusted hazard ratio (95% CI)[1]	P value	P value for Interaction
Baseline 25(OH)D (nmol/L)							
<25	10	229	159 (56 to --)	172 (74 to --)	0.92 (0.66 to 1.28)	0.62	0.61
≥25	12	2231	104 (41 to 280)	110 (40 to 328)	0.97 (0.88 to 1.06)	0.48	
Dosing Regimen Type							
Bolus dose ≥30,000 IU given	8	4795	-- (121 to --)	-- (117 to --)	0.98 (0.89 to 1.08)	0.74	0.30
Bolus dose not given	10	4313	138 (57 to 331)	153 (61 to 351)	0.91 (0.84 to 0.99)	0.04	

1, adjusted for age, sex and study duration. Abbreviations: --, these values cannot be defined; 25(OH)D, 25-hydroxyvitamin D; ARTI, acute respiratory tract infection; CI, confidence interval.

Table S7: Responder analysis, one-step IPDMA

	N trials	Proportion with >=1 ARTI, (%)	Adjusted odds ratio (95% CI)[1]	P value
Intervention, end-study 25(OH)D < 75 nmol/L	18	542/1120 (48.4)	1	--
Intervention, end-study 25(OH)D ≥ 75 nmol/L	18	784/1291 (60.7)	0.96 (0.78, 1.18)	0.68
	N trials	**Median time to first ARTI, days (IQR)**	**Adjusted hazard ratio (95% CI)**	**P value**
Intervention, end-study 25(OH)D < 75 nmol/L	11	190 (63, --)[2]	1	--
Intervention, end-study 25(OH)D ≥ 75 nmol/L	12	102 (39, 312)	1.02 (0.88, 1.19)	0.76
	N trials	**Rate of ARTI per participant-year**	**Adjusted incidence rate ratio (95% CI)**	**P value**
Intervention, end-study 25(OH)D < 75 nmol/L	18	1.51	1	--
Intervention, end-study 25(OH)D ≥ 75 nmol/L	18	2.04	1.01 (0.94, 1.10)	0.72

1, adjusted for age, sex and study duration. 2, 75th centile for time to first ARTI in this group cannot be defined. Abbreviations: 25(OH)D, 25-hydroxyvitamin D; ARTI, acute respiratory tract infection; CI, confidence interval; IQR, inter-quartile range.

Figure S1: Cates plots illustrating reduction in risk of acute respiratory tract infection with vitamin D supplementation, irrespective of dosing frequency, in A) all participants, irrespective of baseline vitamin D status, B) participants with baseline serum 25(OH)D concentration <25 nmol/L, and C) participants receiving daily or weekly vitamin D supplementation regimens without any additional bolus doses.

A.

B.

C.

Figure S2: Mean baseline serum 25(OH)D concentration at enrolment by dosing regimen. ‘Bolus’, studies in which a bolus dose of ≥30,000 IU vitamin D was given in the intervention arm; ‘No bolus’, studies in which vitamin D was administered daily or weekly without administration of such a bolus dose of vitamin D.

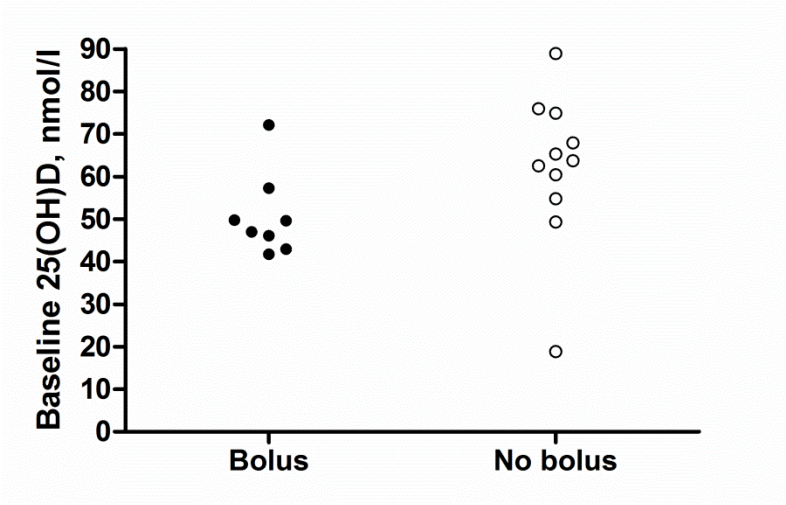


Figure S3: Mean age at enrolment by dosing regimen. ‘Bolus’, studies in which a bolus dose of ≥30,000 IU vitamin D was given in the intervention arm; ‘No bolus’, studies in which vitamin D was administered daily or weekly without administration of such a bolus dose of vitamin D.

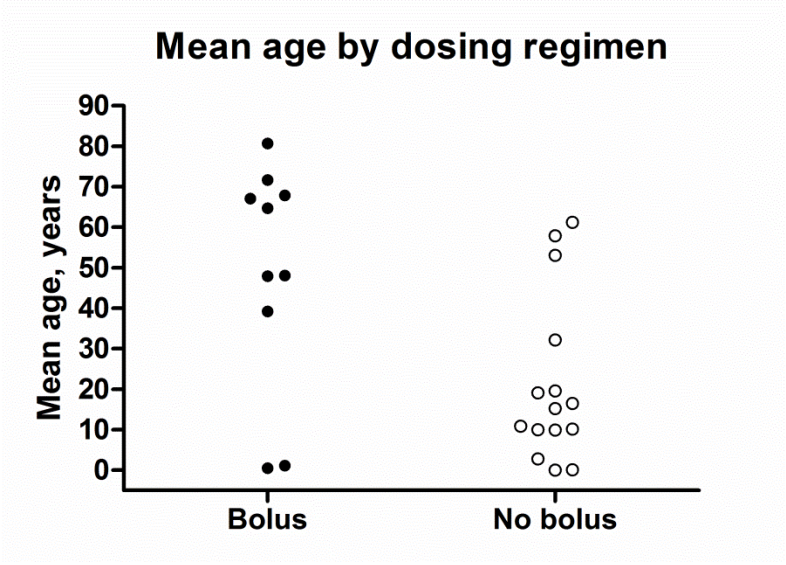
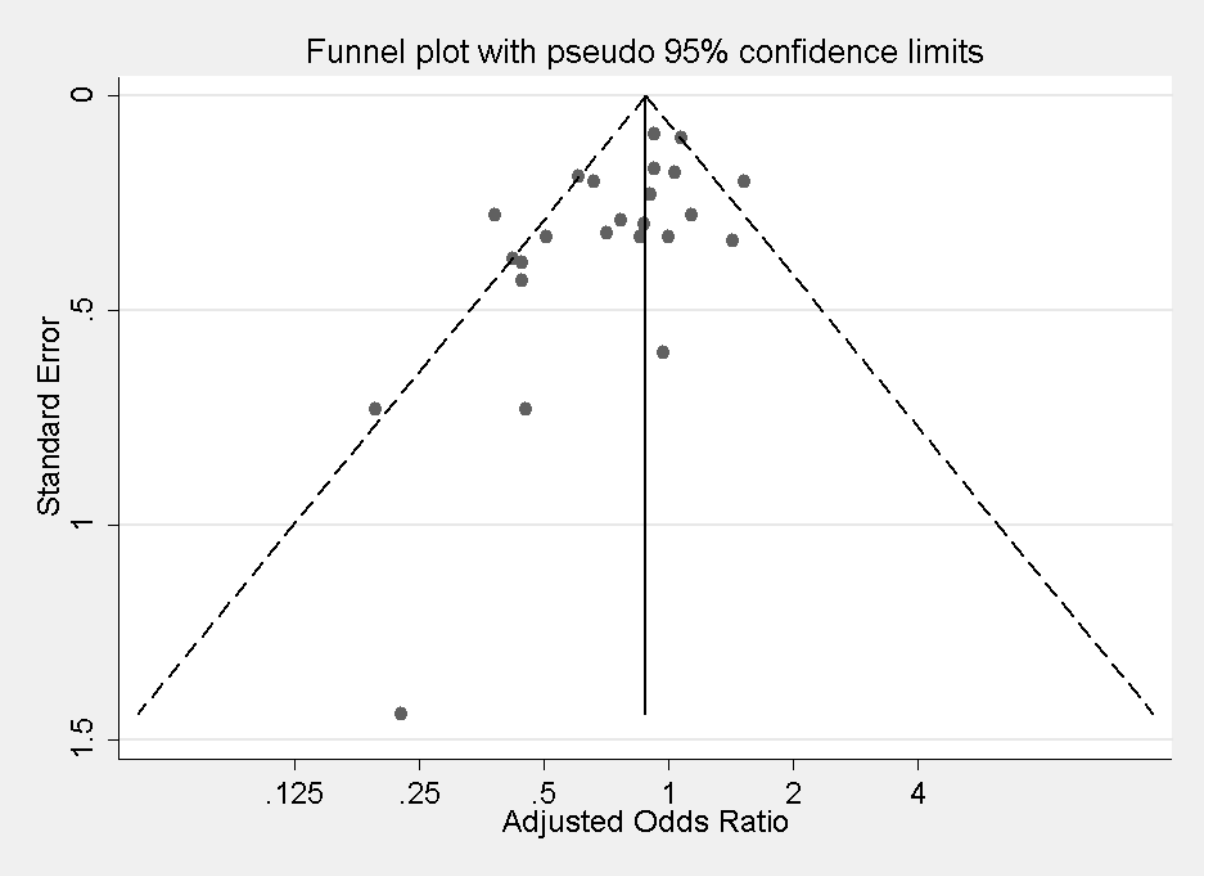


Figure S4: Cates plot illustrating reduction in risk of acute respiratory tract infection with daily/weekly vitamin D supplementation without additional bolus doses in A) participants with baseline serum 25(OH)D concentration <25 nmol/L, and B) participants with baseline serum 25(OH)D concentration ≥25 nmol/L.

A.

B.

Figure S5: Funnel plot for individual patient data meta-analysis of proportion of participants experiencing at least one acute respiratory tract infection



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