Scientific Advisory Committee on Nutrition

Rapid review:
Vitamin D and acute respiratory tract infections

June 2020

Contents

Introduction

1. Current government advice on vitamin D relates to the protection of musculoskeletal health and is based on the recommendations of the Scientific Advisory Committee on Nutrition (SACN) following publication of its report on Vitamin D and Health (SACN, 2016).

2. Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a coronavirus known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since the COVID-19 outbreak, media reports and some academic publications have suggested that vitamin D supplementation (particularly high doses) could reduce the risk of COVID-19.

3. A systematic review and meta-analysis (Martineau et al, 2017) of randomised controlled trials (RCTs), reporting that vitamin D supplementation reduces the risk of acute respiratory tract infections (ARTI), has been widely cited as evidence to support this suggestion.

4. In this context, SACN agreed to conduct a rapid review of the scientific evidence on vitamin D and ARTI risk published after the SACN report on Vitamin D and Health (2016).

5. The term ARTI refers to any infection of the sinuses, throat, airways or lungs. Upper RTIs (URTI) include tonsillitis, laryngitis and the common cold. Lower RTIs (LRTIs) include bronchitis and pneumonia. Influenza affects both upper and lower respiratory tracts.

Objective

6. The purpose of this review was to:
    - assess evidence from RCTs on vitamin D and risk of ARTIs published since the SACN report on Vitamin D and Health (2016).
    - consider if evidence on vitamin D and ARTIs published since the SACN report (2016) changes its previous conclusions on vitamin D and ARTIs

7. This review did not include consideration of evidence on vitamin D and COVID-19 risk. An evidence review of Vitamin D and COVID-19 risk has been conducted by the National Institute for Health and Care Excellence (NICE). Emerging evidence on COVID-19 and obesity is being considered by Public Health England (PHE) separately (PHE, 2020).

Background

SACN's remit

8. SACN's remit is to assess risks and benefits of nutrients/foods to health by evaluating published scientific evidence and, based on its assessment, make dietary recommendations for the UK general healthy population including any vulnerable (at risk) groups which have been identified (see SACN Code of Practice).

SACN advice on vitamin D

9. In its report on Vitamin D and Health (2016), SACN carried out a comprehensive assessment of the evidence on vitamin D and a wide range of musculoskeletal and non-musculoskeletal health outcomes (including infection). Evidence on vitamin D and non-musculoskeletal outcomes was considered insufficient to draw any firm conclusions or to inform the setting of recommendations for vitamin D. Musculoskeletal health was the basis for setting recommendations for vitamin D.

10. SACN concluded that the evidence suggested overall that the risk of poor musculoskeletal health is increased at serum 25-hydroxyvitamin D (25(OH)D) concentrations below 25 nmol/L. Serum 25(OH)D concentration is an indicator of exposure to vitamin D from skin synthesis and dietary intake. The reference nutrient intake (RNI) for vitamin D was set to maintain serum 25(OH)D concentration ≥25 nmol/L.

11. SACN set a RNI for vitamin D of 10 µg/d (400 IU/d) for the UK population (aged 4 years and above). This is the average daily amount of vitamin D (from natural food sources, fortified foods or supplements) needed by the majority (97.5%) of the population to maintain a serum 25(OH)D concentration ≥ 25 nmol/L when UVB sunshine exposure is minimal.

12. The RNI of 10 µg/d (400 IU/d) includes pregnant and lactating women and population groups at increased risk of having a serum 25(OH)D concentration < 25 nmol/L. Population groups at increased risk include those from minority ethnic groups with dark skin; those with minimal sunshine exposure as a result of not spending time outdoors (such as frail and institutionalised people) or those habitually wearing clothing that covers most of the skin while outdoors.

13. Data were insufficient to set RNIs for infants and children aged under 4 years. As a precaution, a 'safe intake' of vitamin D was recommended for these ages: in the range 8.5 to 10 µg/d (340 to 400 IU/d) for ages 0 up to 1 year (including exclusively breastfed and partially breastfed infants, from birth); and 10 µg/d (400 IU/d) for ages 1 up to 4 years.

Summary of SACN's previous assessment on vitamin D and ARTIs (2016)

14. The following studies on vitamin D and ARTI risk were considered in the SACN report on Vitamin D and Health (2016): 3 systematic reviews and meta-analyses (Bergman et al, 2013; Charan et al, 2012; Mao and Huang, 2013); 1 systematic review (Joliffe et al, 2013); and 7 RCTs published after the systematic reviews and meta-analyses.

15. All 5 RCTs in Charan et al (2012) were included in Bergman et al (2013) (11 RCTs, 4 in patient groups; n=5660), which reported that vitamin D supplementation significantly reduced risk of ARTI (Odds ratio (OR), 0.64; 95% CI, 0.49 to 0.84; p=0.001). There was significant heterogeneity between studies ($p < 0.0001$; I^2=72%) and evidence of publication bias. The protective effect was significant in trials with daily vitamin D supplementation but not in those which administered bolus doses once per month or less. There was no modifying effect of baseline 25(OH)D concentration on supplementation outcome.

16. Mao & Huang (2013) (7 RCTs, n=4827) included the same RCTs that were in Bergman et al (2013) but excluded the 4 RCTs in patient groups. There was no difference in ARTI risk between the supplemented and control groups (Risk ratio (RR), 0.98; 95% CI, 0.93 to 1.03; p=0.45). Vitamin D dosing regimen, age and length of follow-up did not affect risk and there was no evidence of publication bias.

17. The systematic review by Jolliffe et al (2013) (14 RCTs) reported conflicting results: 7 trials reported a protective effect of vitamin D supplementation against ARTIs, 6 reported null effects and 1 reported adverse effects of vitamin D supplementation on risk of pneumonia recurrence.

18. Out of 7 RCTs published after these meta-analyses: 5 reported that vitamin D supplementation did not reduce ARTI risk (Rees et al, 2013; Goodall et al, 2014; Urashima et al, 2014; Dubnov-Raz et al, 2015; Simpson et al, 2015); 1 reported that vitamin D supplementation significantly increased URTI risk (Martineau et al, 2015); and 1 reported beneficial effects at higher (20 µg/day) but not lower (10 µg/day) doses of vitamin D (Grant et al, 2015).

19. SACN concluded that the evidence on vitamin D supplementation and infection risk (ARTIs and tuberculosis) was inconsistent and generally did not show a beneficial effect of vitamin D supplementation on infectious disease risk.

Review of evidence on vitamin D and ARTI published since the SACN report (2016)

20. The following evidence was considered:
    - the systematic review and meta-analysis of individual participant data (IPD) on vitamin D supplementation and ARTIs by Martineau et al (2017) (which covered RCTs published up to December 2015 and included those published after the SACN, 2016 report)
    - systematic reviews and meta-analyses of RCTs on vitamin D and ARTIs published after the systematic review and meta-analysis by Martineau et al (2017)
    - RCTs on vitamin D and ARTIs published after the search period covered by the systematic review and meta-analysis by Martineau et al (2017).

Methods

Literature search for evidence published since 1 January 2016

21. A comprehensive search of online databases was conducted to identify systematic reviews, meta-analyses, pooled analyses of randomised trials, RCTs and controlled trials looking at the effect of vitamin D supplementation on the incidence of ARTIs in children and adults. The search was conducted on 22 April 2020 with a limit of '2016-current' to identify papers published after the systematic review search dates covered by Martineau et al (2017).

22. Studies considered were those that examined whether vitamin D reduced ARTI risk in general healthy populations rather than its effect as a therapeutic agent in pre-existing disease.

23. Details of the literature search, including the inclusion and exclusion criteria (Table 1), the databases searched and the search terms (Table 2) are outlined in Annex 1.

Selection of evidence

24. The search identified 2078 records. After removal of duplicates, 746 were screened for eligibility independently by 2 reviewers by title and abstract. Differences were resolved by discussion. Of these, full-texts of 33 potentially relevant publications were screened by 2 reviewers.

25. No systematic reviews and meta-analyses, published after Martineau et al (2017), were identified. However, 1 systematic review and meta-analysis (Vuichard Gysin et

al, 2016) was included for further assessment because it included only RCTs with healthy populations.

26. Five RCTs were identified: Aloia et al (2019); Camargo et al (2018); Jung et al (2018); Loeb et al (2019); and Shimzu et al (2018).

27. In total, 6 papers (1 systematic review and 5 RCTs) were included for assessment.

28. Annex 1 includes a list of the studies that were excluded after full text screening with the reasons for their exclusion (Table 3) and a flow diagram of the study selection process (figure 1).

29. Due to the rapid nature of this review it was not possible, within the required timeframe, to grade the evidence.

Assessment of evidence

Systematic review and meta-analysis (Martineau et al, 2017)

30. The systematic review and meta-analysis of IPD by Martineau et al (2017) assessed the effect of vitamin D supplementation on incidence of ARTI. It included 25 RCTs (11 321 participants from 14 countries, aged 0 to 95 years). Out of the 25 included RCTs, 10 were in populations with pre-existing respiratory disease and considered whether vitamin D reduced severity or duration of symptoms.

31. Study duration ranged from 7 weeks to 1.5 years. Mean baseline serum 25(OH)D concentrations (reported in 19/25 trials; 4172 participants) ranged from 19 to 89 nmol/L. All trials administered oral vitamin D3 in the intervention arm. IPD was obtained for 10 933 participants.

32. A 1-step and 2-step IPD analysis was performed for each outcome, using a random-effects model adjusted for age, sex and study duration to obtain the pooled intervention effect with a 95% confidence interval. In the 1-step approach, IPD was modelled from all studies simultaneously while accounting for clustering of participants within studies. In the 2-step approach, IPD were analysed first for each study independently to produce an estimate of the treatment effect for that study before synthesis of the data.

33. Subgroup analyses were conducted to investigate whether effects of vitamin D supplementation on ARTI risk differed according to baseline 25(OH)D concentration, dosing frequency, dose size, age, body mass index, and the presence or absence of comorbidity (asthma, or chronic obstructive pulmonary disease). Subgroup analysis by race or ethnicity was not conducted because data for this variable were missing for 34% of participants and power for subgroup analyses was limited by small numbers in many racial or ethnic subgroups.

34. Overall results:
    - in 1-step meta-analysis, vitamin D supplementation reduced the proportion of participants experiencing at least 1 ARTI (OR, 0.88; 95% CI, 0.81 to 0.96; p=0.003; p for heterogeneity <0.001; 25 RCTs, 10 933 participants)
    - in 2-step meta-analysis, vitamin D supplementation reduced the proportion of participants experiencing at least 1 ARTI (OR, 0.80; 95% CI, 0.69 to 0.93; p=0.004; I^2=53.3%, p= for heterogeneity 0.001; 24 RCTs, 10 899 participants).

35. Subgroup analyses: protective effects of vitamin D supplementation were reported in:
    - those with baseline 25(OH)D concentration <25 nmol/L (OR 0.58, 95% CI, 0.40 to 0.82, p=0.002; 14 RCTs; 538 participants) but not in those with 25(OH)D >25 nmol/L (OR, 0.89; 95% CI, 0.77 to 1.04; p=0.15; 19 RCTs; 3634 participants)
    - participants receiving daily or weekly vitamin D supplements (OR, 0.81; 95% CI, 0.72 to 0.91; p<0.001; 15 RCTs, 5133 participants) but not bolus doses (OR, 0.97; 95% CI, 0.86 to 1.10; p=0.67; 10 RCTs, 5800 participants).

36. Further analysis within the subgroup receiving daily or weekly vitamin D supplementation, stratified by baseline 25(OH)D concentration > or < 25 nmol/L, reported a larger reduction in participants who experienced at least 1 ARTI with baseline 25(OH)D concentration < 25 nmol/L (OR, 0.30, 95% CI, 0.17 to 0.53; p<0.001; 6 RCTs; 234 participants) than those with baseline 25(OH)D >25 nmol/L (OR, 0.75, 95% CI, 0.60 to 0.95; p=0.02; 6 RCTs, 1603 participants).

37. Although the IPD meta-analysis by Martineau et al (2017) was very thorough and of high quality, the authors noted that there was considerable variation in baseline vitamin D status and use of bolus doses between studies. They suggested that the high degree of heterogeneity between trials might be partly attributable to these factors. Other limitations identified by the authors included: evidence of publication bias; lack of data relating to adherence; and diverse definitions of ARTI, which were not medically confirmed in most studies.

38. In addition to those highlighted by the authors, the following limitations were identified:
    - although the inclusion criteria specified trials that collected data on incidence of ARTI prospectively and prespecified as an efficacy outcome, 2 of the included trials collected data retrospectively from RCTs in which ARTI risk was not a prespecified outcome
    - in 2 studies, the control group also received a lower dose of vitamin D (no placebo or no treatment group)
    - out of the 7 trials that reported vitamin D reduced ARTI risk: 4 were in populations with pre-existing respiratory conditions; and 1 had a high number of dropouts (37%)

- various methods were used across RCTs to measure serum 25(OH)D concentration which can vary considerably (15 to 20%) depending on the type of assay used (SACN, 2016).

Systematic reviews and meta-analyses published since January 2016

Vuichard Gysin et al (2016)

39. The systematic review and meta-analysis by Vuichard Gysin et al (2016) assessed the effect of vitamin D supplementation on ARTI and laboratory-confirmed ARTI. It included 15 RCTs of healthy individuals (7053 participants from 10 countries; aged 0 to 84 years). Study duration ranged from 7 weeks to 3 years. Mean baseline serum 25(OH)D concentrations (reported in 11/15 trials) ranged from 17 to 83 nmol/L. All studies administered oral vitamin D3 (frequency ranged from daily to 3-monthly; average daily dose, 37.5 µg). Further details of this systematic review are provided in Annex 2 (Table 4).

40. Subgroup analyses were conducted to investigate whether effects of vitamin D supplementation on ARTI risk differed according to baseline 25(OH)D concentration (< 50 compared to > 50 nmol/L) (subgroup analysis at the 25 nmol/L threshold was not conducted) and different administration intervals (daily/weekly compared monthly/3-monthly).

41. Results:
    - no evidence of a difference in ARTI risk between vitamin D and comparator groups (RR, 0.94; 95% CI, 0.88 to 1.00; p=0.06; I^2=57%; random-effects model, 14 RCTs, 6985 participants)
    - no evidence of a difference between groups in first laboratory confirmed ARTI (RR, 0.90; 95% CI, 0.68 to 1.21; p=0.5; I^2 = 66%; random-effects model; 4 RCTs; 1392 participants).

42. Subgroup analyses: no differences were reported for participants with baseline 25(OH)D concentration <50 vs >50 nmol/L (RR, 0.94; 95% CI, 0.87 to 1.01; p=0.10; 10 RCTs, 5581 participants) or those receiving daily/weekly vs monthly/3-monthly (RR, 0.94; 95% CI, 0.88 to 1.00; p=0.06; 14 RCTs, 6985 participants).

43. Study limitations: although this systematic review and meta-analysis included only RCTs of healthy populations, the authors identified similar limitations to those noted for the Martineau et al (2017) systematic review: major differences across studies with respect to settings, vitamin D dosing regimens and definitions and assessment of outcomes.

44. Three of the RCTs were not included in the systematic review and meta-analysis by Martineau et al (2017). Out of these, 1 (Neale et al, 2013) was a post-hoc analysis of a pilot study and was published only as an abstract; 1 (Aloia et al, 2007) was a post-

hoc analysis of a previous RCT (Aloia et al, 2005) in which limited information about URTIs (participants asked 'have you had any colds or influenza') was recorded as an adverse event; and 1 (De Gruijl et al, 2012) did not include a placebo group (comparator groups were sunbed exposure or no treatment).

Randomised controlled trials published since January 2016

45. The 5 eligible RCTs were from 5 countries (Japan, New Zealand, South Korea, Vietnam, USA) and included participants of both sexes aged between 3 and 84 years. Sample sizes ranged from 25 to 5100 participants and study duration ranged from 4 weeks to 3 years. Mean baseline serum 25(OH)D concentrations ranged from 31 to 65.5 nmol/L.

46. Four studies supplemented with vitamin D3 in the intervention arm and 1 supplemented with 25(OH)D. Vitamin D supplementation regimens were:
    - daily, 3 RCTs – (1) 125 µg; (2) mean dose 87 µg/d) (D3); (3) 10 µg (25(OH)D)
    - bolus dose, 2 RCTs - (1) weekly - 350 µg (D3); (2) initial dose of 5000 µg at study start, then monthly, 2500 µg (D3).

47. Outcomes were self-reported in 4 studies and clinically confirmed in 1 study.

48. The 5 RCTs are summarised below. Additional details are provided in Annex 2 (Table 5).

Aloia et al (2019) (US) (duration, 3 years)

49. Participants (260 African American women; average age, 68 years) received vitamin D3 (dose adjusted every 3 months to maintain serum 25(OH)D concentration >75 nmol/L: mean dose 87±37 µg/day) or placebo. A questionnaire about ARTIs was administered by a research coordinator every 3 months.

50. There was no difference between groups in occurrence of ARTIs. Overall, the ARTI rate did not change significantly from baseline (slope, –0.008; p=0.232 for time effect) and was not different between groups over time (slope, 0.003; p=0.775).

Camargo et al (2019) (New Zealand) (duration, 1.6 years)

51. Participants (5110 adults; mean age, 66 years) received vitamin D3 (initial bolus dose of 5000 µg then 2500 µg/month) or placebo. ARTIs were reported monthly through a mailed questionnaire.

52. There was no difference between groups in occurrence of at least 1 ARTI (adjusted HR for vitamin D vs placebo, 1.01; 95% CI, 0.94 to 1.07; p=0.85). In a subgroup analysis of participants with baseline 25(OH)D concentration <50 nmol/L, there was

also no difference between groups in occurrence of ARTI (HR, 1.08; 95% CI, 0.95 to 1.23; p=0.27).

Jung et al (2018) (South Korea) (duration, 4 weeks)

53. Participants (25 male taekwondo athletes undergoing high intensity and endurance training 5 times/week; mean age, 20 years) received vitamin D3 (125 µg/day) or placebo. URTI symptoms (runny nose, sneezing, cough) were self-reported daily by questionnaire.

54. URTI symptoms (score/day) were significantly lower in the vitamin D compared to the placebo group (7.7±1.06 vs 13.0 ±1.60; p=0.011).

Loeb et al (2019) (Vietnam) (duration, 8 months)

55. Participants (1300 children and adolescents; mean age, 8.5 years) received vitamin D3 (350 µg/week) or placebo. Symptoms of influenza and non-influenza respiratory viral infections were assessed twice weekly by health workers and an oropharyngeal swab was obtained (for clinical confirmation) from participants with >1 symptom.

56. There was no significant difference between vitamin D and placebo for influenza infections (HR, 1.18; 95% CI, 0.79 to 1.77; p=0.64). For non-influenza virus infections, a significant reduction was reported in the vitamin D compared to the placebo group (HR, 0.76; 95% CI, 0.61 to 0.94; p=0.01). For all respiratory viral infections, there was a significant reduction in the vitamin D compared to placebo group (HR, 0.81; 95% CI, 0.66 to 0.99; p=not reported).

Shimzu et al (2018) (Japan) (duration, 16 weeks)

57. Participants (252 adults; mean age, 53 years) received 25(OH)D (10 µg/day) or placebo. Incidence of URTI were self-reported by questionnaire.

58. There was no significant difference between groups in the incidence of URTI: (37.3% in the 25(OH)D group and 41.0% in the placebo group; p=0.675). A subgroup analysis of participants with 25(OH)D concentration <50 nmol/L (n=121) also reported no difference between groups.

Summary of evidence from RCTs

59. Out of the 5 RCTs:
    - 3 (including the largest, n=5110) reported no evidence of difference in ARTI risk between the vitamin D and placebo groups
    - 1 reported URTI symptoms were significantly lower in the vitamin D group

- 1 reported no difference between groups for influenza infections but a significantly greater reduction in the vitamin D group for non-influenza virus infections.

60. Out of the 2 RCTs that reported significant reductions in the vitamin D group: 1 (Jung et al, 2018) was very small in size (n=25) with a very particular population (male athletes undergoing intense training); the other (Loeb et al, 2019) included only children and adolescents and a potential mechanism for the differential effect by type of viral infection (vitamin D reduced non-influenza virus infections but not influenza) is unclear.

61. It was not possible to assess if effects of vitamin D supplementation differed by race or ethnicity since populations in 3 RCTs were specific to the countries in which they were set (Japan, South Korea, Vietnam). One RCT (New Zealand) noted that 83% of participants were of European/other ethnicity, with the remaining 17% Maori, Polynesian, or South Asian but didn't consider further; 1 RCT (US) of African American women reported no effect of vitamin D on ARTI risk.

Overall summary

62. The systematic review and meta-analysis by Martineau et al (2017), reported that daily or weekly vitamin D supplementation reduces the risk of ARTIs, particularly among individuals with 25(OH)D concentrations <25 nmol/L. However, study settings, vitamin D supplemental doses, reporting and assessment of ARTIs and trial results were very heterogenous. Many of the included studies were in populations with pre-existing respiratory disease which may limit their applicability to the general population in the UK.

63. The systematic review by Vuichard Gysin et (2016) included only healthy populations and reported that vitamin D supplementation did not reduce the risk of ARTIs. However, the included studies differed with respect to settings, vitamin D dosing regimens, definition of outcomes and their assessment.

64. Evidence from the RCTs published after the Martineau et al (2017) review suggest, overall, no effect of vitamin D supplementation on reducing ARTI risk.

65. Differences in vitamin D supplementation doses and regimens, study settings, participants, study duration, definition and verification of outcomes (including type of respiratory infection) complicate interpretation of the evidence on vitamin D and ARTI risk.

66. It is not known if reported effects can be generalised to populations from Black, Asian and minority ethnic (BAME) groups in the UK since only one study (in the US)

included populations from an ethnic group and no studies specifically compared if race or ethnicity modified the effect of vitamin D supplementation on ARTI risk.

67. Due to the rapid nature of this review it was not possible, within the required timeframe, to grade the evidence.

68. This review did not include consideration of evidence on vitamin D and COVID-19 risk. Evidence on vitamin D and ARTI risk does not necessarily extrapolate to infection with SARS-COV-2. An evidence review of Vitamin D and COVID-19 risk has been conducted by the National Institute for Health and Care Excellence (NICE).

Conclusions

69. Overall, the evidence at this time does not support recommending vitamin D supplementation to prevent ARTIs in the general UK population. This conclusion does not impact on existing government advice on vitamin D (see below).

70. SACN will keep this topic under urgent review and consider updating this assessment if emerging evidence from ongoing RCTs on vitamin D and ARTI risk suggests a change to existing conclusions.

Recommendations

71. In order to protect musculoskeletal health, SACN recommends that the serum 25(OH)D concentration of all individuals in the UK should not fall below 25 nmol/L at any time of the year (SACN, 2016) (see paragraphs 9 to 13 for further details).

72. Government advice on the vitamin D intake required to support this recommendation is provided below.

UK government advice on vitamin D

73. UK government advice on vitamin D is based on SACN recommendations following its review of the evidence on vitamin D and health (SACN, 2016).

74. In spring and summer, most people get enough vitamin D through safe sunlight exposure and a healthy, balanced diet. During autumn and winter everyone needs to rely on dietary sources of vitamin D. Since it is difficult for most people to meet the 10 µg/day recommendation from consuming foods naturally containing or fortified with vitamin D, everyone is advised to consider taking a daily supplement (10 µg) of vitamin D in autumn and winter.

75. People from BAME population groups and people whose skin has little or no exposure to the sun (such as those in care homes or those who always cover their skin when outside) are advised to take a vitamin D supplement (10 µg/day) throughout the year.

76. Children aged 1 to 4 years should receive a daily vitamin D supplement of 10 µg and all babies aged under 1 year should receive a daily vitamin D supplement of 8.5 to 10 µg. Children who have more than 500ml of infant formula a day do not need any additional vitamin D as formula is already fortified.

77. UK Government advice on vitamin D was reissued in April 2020 during the national lockdown. Whilst advice to stay at home remains largely in place it is recommended that, in order to protect musculoskeletal health, everyone should consider taking a daily vitamin D supplement of 10µg since people may not be getting enough from sunlight exposure.

Annex 1 – Literature search

A rapid review approach was employed to address the following research question: Does vitamin D supplementation reduce the risk of acute respiratory tract infections in healthy children and adults?

Inclusion and exclusion criteria

Table 1 – Inclusion and exclusion criteria

	Included	Excluded
Population	Children and adults (including overweight and obese) in the UK and other countries	Children and adults with pre-existing disease
Intervention	Vitamin D supplementation	Co-intervention with other micronutrients or multivitamins
Comparison	Placebo (or no treatment)	
Outcomes	Incidence of acute respiratory tract infection	
Language	English	
Date of publication	1 January 2016 to present	
Study design	Systematic reviews, meta-analyses, pooled analyses of randomised trials, randomised controlled trials and controlled trials	Cohort studies, case control studies, cross-sectional studies, case reports, umbrella reviews
Publication type	Published	Grey literature, pre-prints
Setting	All	

Databases searched

Medline, Embase, ClinicalTrials.gov, Cochrane, New Group, Web of Science and the International Standard Randomized Controlled Trials Number (ISRCTN) Registry.

Search strategy

Searches were conducted for papers published between 1 January 2016 and 22 April 2020.

Search terms covered key aspects of the research question, including terms related to the intervention. The search strategy for Ovid Medline is presented in Table 2.

Table 2 – Search terms – Ovid Medline

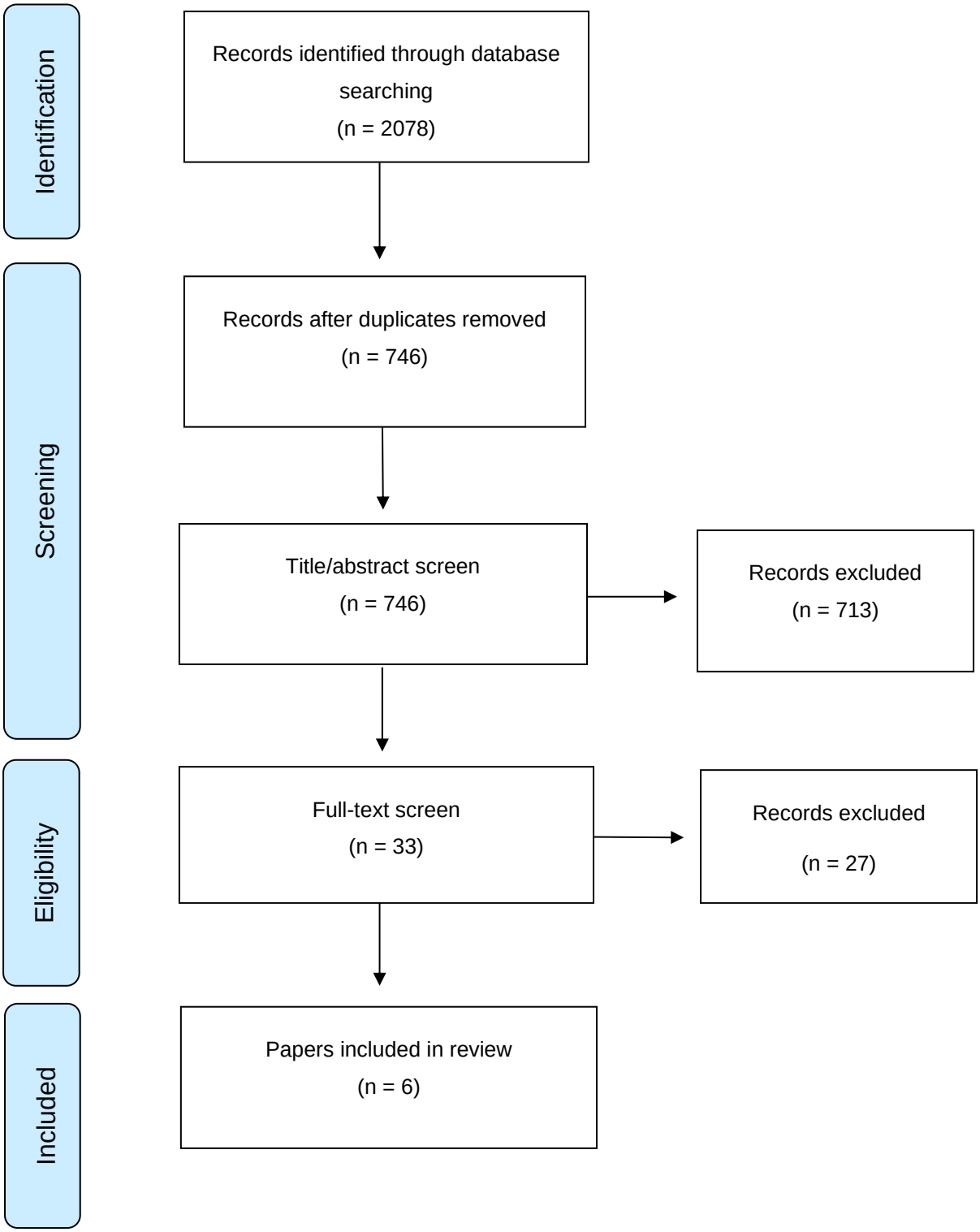
1	exp Vitamin D/
2	exp Ergocalciferols/
3	exp Cholecalciferol/
4	exp Calcitriol/
5	vitamin d.tw.
6	vitamin d2.tw.
7	ergocalciferol.tw.
8	vitamin d3.tw.
9	cholecalciferol.tw.
10	alphacalcidol.tw.
11	alfacalcidol.tw.
12	calcitriol.tw.
13	paricalcitol.tw.
14	doxercalciferol.tw.
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	exp Respiratory Tract Infections/
17	exp Common Cold/
18	exp Sinusitis/
19	exp Pharyngitis/
20	exp Laryngitis/
21	exp Tonsillitis/
22	exp Peritonsillar Abscess/
23	exp Croup/
24	exp Epiglottitis/
25	exp Supraglottitis/
26	exp Otitis Media/
27	exp Pneumonia/
28	exp Bronchopneumonia/
29	exp Bronchitis/
30	exp Pleurisy/
31	respiratory tract infection*.tw.
32	acute respiratory infection*.tw.
33	upper respiratory infection*.tw.
34	lower respiratory infection*.tw.
35	common cold*.tw.
36	sinusitis.tw.
37	pharyngitis.tw.
38	laryngitis.tw.
39	Laryngotracheobronchitis.tw.
40	tonsillitis.tw.
41	peritonsillar abscess.tw.
42	croup.tw.
43	epiglottitis.tw.
44	supraglottitis.tw.
45	Otitis Media.tw.
46	pneumonia.tw.
47	Bronchopneumonia.tw.
48	Bronchitis.tw.
49	Pleurisy.tw.
50	Pleuritis.tw.
51	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50
52	15 and 51 998
53	limit 52 to (english language and humans and yr="2016 - 2020")

Table 3 – Papers excluded on full text

Study	Reason for exclusion
Aglipay et al, 2017	Exclude: No placebo group, both groups taking vitamin D
Anonymous, 2017	Exclude: bulletin not a published paper
Arihiro et al, 2019	Exclude: participants with irritable bowel syndrome
Autier et al, 2017	Exclude: review of systematic reviews
Chandy et al, 2016	Exclude: placebo group advised to get sun exposure
Chi, 2016	Exclude: trial registry only
Ctri, 2017	Exclude: trial registry only
Galdo et al, 2018	Exclude: abstract only
Ginde et al, 2016	Exclude: included in Martineau et al (2017)
Hueniken et al, 2019	Exclude: compared 2 vitamin D doses – no placebo group
Jat, 2016	Exclude: systematic review and meta-analysis; published before Martineau et al (2017); all RCTs included in Martineau (2017)
Mandlik et al, 2020	Exclude: vitamin D group also given calcium
Martineau et al, 2019	Exclude: assessed COPD and asthma outcomes
Martineau et al, 2016a	Exclude: abstract of Martineau et al (2017) paper
Martineau et al, 2016b	Exclude: abstract of the Martineau et al (2017) paper
Morris et al, 2017	Exclude: conference summary
Nct, 2017	Exclude: trial registry only
Rejnmark et al, 2017	Exclude: review of systematic reviews
Rezaei et al, 2018	Exclude: not a systematic review
Rosendahl et al, 2018	Exclude: compared 2 vitamin D doses; no placebo or no treatment group
Scragg, 2020	Exclude: same RCT as Camargo et al (2019)
Singh et al, 2019	Exclude: participants were children with recurrent pneumonia
Tanner & Allen, 2018	Exclude: not a systematic review
Wimalawansa, 2018	Exclude: not a systematic review
Yakoob et al, 2016	Exclude: systematic review and meta-analysis published before Martineau et al (2017); included 2 RCTs; 1 of these included in Martineau (2017) and the other was unpublished.
Zhou et al, 2018	Exclude: compared 2 vitamin D doses; no placebo or no treatment group
Zisi et al, 2019	Exclude: not a systematic review

Flow diagram

Figure 1 – Flow diagram showing number of publications assessed for eligibility and included in the review



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Annex 2 – Summary of studies included in rapid review

Table 4 – Systematic review and meta-analysis

Study	Methods	Included	Results	Limitations and study conclusions (assessed by authors)
Vuichard Gysin et al (2016) **Aim**: to systematically summarise RCT evidence comparing vitamin D supplementation to placebo or no treatment on clinical and laboratory confirmed ARTIs in healthy adults and children **Study design**: systematic review and meta-analysis of RCTs **Countries**: High, middle & low income countries: Afghanistan, Australia (2), Canada, Finland, Israel, Japan (2), Mongolia, Netherlands, New Zealand (2), US (3) **Funding source**: Vuichard Gysin received scholarship from Lichtenstein Foundation (University of Basel, Switzerland). Funding agency had no role in study design, data collection and analysis, decision to publish, or preparation of manuscript.	**Search period**: to January 2016 **Databases searched**: Medline, EMBASE, CENTRAL, CINAHL, OpenGrey, clinical trials registry. **Language restrictions**: None **Inclusion criteria**: • RCTs of healthy individuals • Intervention: any form of vitamin D • Comparator: placebo or no treatment • Concomitant interventions allowed if type, dose, duration same in both groups. **Exclusion criteria**: • Inclusion of compound of micronutrients or multivitamin in either arm. • Studies with mycobacterial or fungal respiratory infections as sole outcome	**Number of studies**: 15 (14 in meta-analysis) **Study duration**: 7 weeks to 3 years (median 17 weeks). **Study population**: • 7053 healthy adolescents or adults (10 studies), infants (2 studies), children (2 studies) or older people (1 study). • Age: median, 19 years (IQR 10 to 49) **Intervention**: Vitamin D3. Average dose: 37.5 µg/day (range 7.5 to 92.5) (1500 IU; range: 300 to 3700). Frequency: ranged from daily to every 3 months. **Comparator:** All except 1 RCT used a placebo **Author's evaluation**: ROB (assessed using Cochrane RoB tool): • RoB in most studies, moderate to low. 4 at high risk (3 for selective	**Primary outcome:** Vitamin D vs comparator • Risk of ARTI: RR, 0.94 (95% CI 0.88 to 1.00) (I^2=57%). • First lab-confirmed ARTI: RR, 0.90 (95% CI 0.68 to 1.21) (I^2 =66%) **Secondary outcomes:** Symptom duration: MD, -0.06 (95% CI -0.29, 0.18) (p=0.64) (I^2=0%) Absenteeism: MD, 0.06 (95% CI -0.41, 0.54) (p=0.80) (I^2=35%) Severity of ARTI: OR, 0.95 (95% CI 0.76, 1.18) (p=0.6) (I^2=0%) **Subgroup analysis:** ARTI risk in those with 25(OH)D ≤50 vs >50 nmol/L: RR, 0.94 (95% CI 0.87, 1.01) (p=0.1) (I^2=0%) Daily or weekly vs monthly or quarterly bolus dose: RR, 0.94 (95% CI 0.88, 1.00) (p=0.1) (I^2=57%)	**Limitations**: • Major differences across studies with respect to population, settings, dosing regimens and outcome measurements. **Conclusions:** • No significant protective effect of vitamin D supplementation on clinical ARTI in otherwise healthy people of various ages. • Evidence insufficient to determine the comparative effectiveness of vitamin D versus placebo on laboratory confirmed ARTI. • Overall level of evidence low.

Study	Methods	Included	Results	Limitations and study conclusions (assessed by authors)
Declarations of interest: None.	**Outcome measures**: Primary outcomes: • first episode of clinical ARTI reported as cold or influenza-like illness with or without formal adjudication by medical personnel • first episode of lab confirmed ARTI assessed by standard microbiological methods. Secondary outcomes: • duration and severity of ARTI-symptoms • absenteeism due to ARTI **Statistical analysis**: Random-effects models. Heterogeneity explored by subgroup and meta-regression analyses.	reporting, 1 performance bias) • Large heterogeneity for 2 primary outcomes. • Both, funnel plot and Egger's test (p=0.03) suggested possible publication bias • Due to low number of studies in secondary outcomes, suspected risk of publication bias and downgraded overall quality of evidence for each individual outcome Study quality: assessed using GRADE • Overall study quality, low		

Abbreviations: ARTI, acute respiratory tract infection; IQR, inter-quartile range; IU, international units; MD, mean difference; randomized controlled trial; RR, risk ratio; ROB, risk of bias; 25(OH)D, 25-hydrovxy vitamin D

Table 5 – Randomised controlled trials

Author (Year) **Country**	**Population (**participants, number, age)	**Intervention/ Duration**	**Baseline 25(OH)D concentration** (nmol/L)	**Post intervention 25(OH)D concentration** (nmol/L)	**Outcome**	**Results**
Aloia et al (2019) USA	260 African-American women 68.2 years (average)	1. Mean dose 87 ± 37 µg/d (adjusted to maintain 25(OH)D >75nmol/L) 2. placebo 36 months	1. 53.8 ± 16.3 2. 55.5 ± 17.3	(12, 24, 36 months) 1. 107.5 ± 22.75, 115 ± 27.5, 117.5 ±28 2. 47.5 ± 20, 50 ± 19.75, 52.5 ± 25	Primary: bone density, physical performance Secondary: Incidence of ARTIs Self-reported occurrence of ARTIs assessed by questionnaire every 3 months – had /did not have ARTI since last visit)	Retention: 71% (n=184); ITT analysis No difference in occurrence of ARTIs in the vitamin D vs the placebo group. ARTI rate did not change significantly from baseline (slope, –0.008; p=0.232 for time effect); no difference between groups over time (p=0.775).
Camargo et al (2019) New Zealand	5110 adults Age 50 to 84 years. 66 years (mean)	1. Initial bolus, 5000 µg then 2500 µg/month 2. placebo 1.6 years (median)	Mean: 63 ± 24	(n=441 at 3 years) 1. 135 2. 63	Primary: cardiovascular disease Secondary: time to first reported ARTI (upper and lower) ARTI assessed monthly by mailed questionnaire about recent URTIs and LRTIs.	Retention: 87%; ITT analysis No difference in ARTIs between groups HR: 1.01 (0.94 to 1.07) (p=0.85) No evidence of benefit in those with 25(OH)D < 50 nmol/L or in separate analyses of URTI & LRTI
Jung et al (2018) South Korea	25 taekwondo athletes 19 to 22 years	1. 125 µg /day 2. placebo 4 weeks	1. 28.7 ± 1.51 2. 34.2 ± 2.16	1. 100.1 ± 4.70 2. 34.6 ± 1.66	Did not specify primary & secondary outcomes Symptoms of URTI (runny nose, sneezing, coughing) reported daily by questionnaire.	Retention: 68% (n=17); PP analysis URTI symptoms significantly lower in vitamin D group (7.7 ±1.06) compared to placebo group (13.0±1.60); p=0.011

Author (Year) **Country**	**Population (**participants, number, age)	**Intervention/ Duration**	**Baseline 25(OH)D concentration** (nmol/L)	**Post intervention 25(OH)D concentration** (nmol/L)	**Outcome**	**Results**
Loeb et al (2019) Vietnam	1300 children & adolescents 3 to 17 years	1. 350 µg/week 2. placebo 8 months	1. 65.7 2. 65.2	1. 91.8 2. 64.5	Primary: confirmed influenza infection and non-influenza respiratory viruses Symptoms of influenza and non-influenza respiratory viruses were assessed twice weekly by health workers and an oropharyngeal swab was obtained from participants with >1 symptom Confirmed by laboratory diagnosis.	Retention: 91.5% (n=1189); ITT analysis Influenza infection: No difference between groups; HR: 1.18 (95% CI, 0.79 to 1.78) (p=0.64) Non-influenza respiratory virus infection: Significantly greater reduction in vitamin D compared to placebo group HR: 0.76 (95% CI: 0.61 to 0.94) (p=0.01). All respiratory viruses: Significantly greater reduction in vitamin D compared to placebo group: HR: 0.81 (95% CI: 0.66 to 0.99) (p=NR).
Shimizu et al (2018) Japan	252 adults 45 to 74 years	1. 10 µg /day 25(OH)D 2. placebo 16 weeks.	1. 49.1±13.8 2. 48.6±13.1	1. 114.6±32.7 2. 59.7±20.6	Primary: incidence proportion of URTI Secondary: duration of URTI & incidence proportion of new URTI events every 4 weeks. Assessed by daily questionnaire.	Retention: 85% (n=215); PP analysis No difference between groups on incidence of URTI. (p=0.675) URTI duration shorter in 25OHD compared to placebo group (p=0.06).

Abbreviations: ARTI, acute respiratory tract infections; HR, Hazard ratio; ITT, intention to treat; LRTI, lower respiratory tract infection; NR, not reported; PP, per protocol; URTI, upper respiratory tract infection; 25(OH)D, 25-hydrovxy vitamin D

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