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The effects of vitamin D-fortified foods on circulating 25(OH)D concentrations in adults: a systematic review and meta-analysis

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Abstract

Improvement of vitamin D status of the general population has been a challenge for policymakers. We conducted a meta-analysis to evaluate whether vitamin D-fortified products can be a suitable solution for tackling vitamin D deficiency. Our secondary objective was to determine the effect of some variables including age, latitude and BMI on efficacy of this strategy. MEDLINE, PubMed, Embase, Cochrane Library and Google Scholar were searched and 231 studies were found in a preliminary search. After screening of titles and abstracts, 23 studies were selected. Pooled data comparing fortification with vitamin D +/- Ca with control showed statistically significant effect on total 25(OH)D concentrations (2002 participants, mean difference (MD): 25·4 nmol/l, (95 % CI 19·5, 31·3)). The subgroup analysis by duration of intervention (less than 12 weeks *v.* more than 12 weeks) and type of vehicle (dairy product, juice, grain product, oil and combination of dairy and grain products), isoform of the vitamin (D_3 *v.* D_2) and dose of the fortificant (≥ 1000 IU/d *v.* < 1000 IU/d) also indicated significant effect of fortification with vitamin D on serum 25(OH)D concentrations. In conclusion, the circulating 25(OH)D response to vitamin D-fortified food consumption is influenced by age, BMI and the baseline 25(OH)D concentrations. Notwithstanding, an average of 2 nmol/l increase in circulating 25(OH)D concentration for each 100 IU vitamin D intake per d is expected for general adult population. These findings can be informative for policymakers to tackle vitamin D deficiency through food fortification strategy.

Key words: **Vitamin D: Food fortification: Meta-analysis: Nutrition policy**

Hypovitaminosis D is a prevalent global public health problem causing a pressing need to address it promptly[1,2]. The occurrence of circulating 25-hydroxycalciferol (25(OH)D), the specific biomarker of vitamin D status, below 75 nmol/l is very common around the world[3]. However, concentrations below 30 nmol/l indicating severe deficiency are most common in regions such as South Asia and the Middle East[2,4,5].

Suboptimal vitamin D status is considered to impact the incidence of various health conditions such as poor bone health, muscle pain and weakness. There is a growing body of evidence indicating an association between low vitamin D status and increased risk of non-skeletal health outcomes, including CVD, hypertension, diabetes and certain malignancies[6,7]. While vitamin D is mainly obtained via the cutaneous biosynthesis following exposure to ultra-violet B light, body requirement for this vitamin may not be fully met just by sun exposure due to many reasons, including latitude, air pollution, age, sex, darker skin pigmentation or personal behaviour influenced by widespread public health advice on the association of sun exposure with skin cancers[4].

According to WHO/FAO, in the lack of sufficient skin synthesis, maintenance of vitamin D adequacy must be achieved through dietary sources[8]. However, the contribution of vitamin D intake from habitual diet is generally low and there is increasing evidence that the dietary supply is commonly insufficient to offset the deficit, especially during the winter months[9]. Consequently, additional attention is being paid to safe, applicable and efficient approaches to improve vitamin D intake in the general population such as supplementation[7] and food fortification[10]. Although supplementation has been repeatedly shown to be effective in improving vitamin D status[11,12], this strategy may not be sustainable at community level even among high-risk subgroups due to cost and low compliance[13]. There is, therefore, a need to establish and promote sustainable

Abbreviations: MD, mean difference.

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British Journal of Nutrition

food-based strategies to improve vitamin D status in population subgroups, without increasing the risk of excessive intakes[9,14,15]. This issue has been, and continues to be, a challenge for health policymakers[16].

Generally fortification and biofortification strategies are more sustainable and cost-effective, as compared with other community-oriented intervention approaches, and can be suitable for both developed and developing countries[17]. Though findings from different studies altogether indicate the efficacy of vitamin D fortification in raising circulatory 25(OH)D concentrations in both adults and children[18,19,20,21], technically there are still some issues to address for a mass fortification programme[15]. Among these, the possible effects of matrix of the food vehicle as well as consumers-associated factors including diet, initial vitamin D status and body weight are especially noticeable as they can affect vitamin D bioavailability[22,23,24]. Stability of vitamin D fortificant during processing is also challenging as some studies have reported up to 30 % and 50 % loss during heating in vitamin D-fortified cooking oils and flat breads, respectively[25,26]. Hence, new technologies of microencapsulation are being developed to overcome these problems[27]. These concerns are rising up the agenda for mandatory or voluntary food fortification programmes in a number of countries[8,28]. Notwithstanding, there are limited food vehicles suitable for vitamin D fortification which are consumed by the majority of the population. These include milk and milk products, margarines, bread, oils and fruit juices[29,30].

Several clinical trials on efficacy of vitamin D-fortified foodstuffs in adult subjects have been performed during the last two decades with different powers and qualities. The baseline vitamin D status of the participants, the latitude of the study place (that can affect endogenous vitamin D synthesis during the intervention period), the amount and the isoform of vitamin D fortificant used (D_2 *v.* D_3 and physiological *v.* pharmacological doses), the weight status of the participants and also the vehicle used for vitamin D fortification are among the factors causing conflicting results from those studies[31]. To provide an updated evidence for future attempts by policymakers to reduce the burden of vitamin D deficiency and to evaluate whether vitamin D-fortified products can be an efficient strategy for tackling low vitamin D status, we conducted a meta-analysis of studies, including recently published ones, performed worldwide on the effect of vitamin D-fortified products on circulating 25(OH)D concentration according to age, sex, BMI, latitude vitamin D isoform (D_2 *v.* D_3) and the vehicle.

Methods

This meta-analysis was planned, conducted and reported according to the widely accepted quality standards[32] and was registered at http://www.crd.york.ac./Prosperouk (registration no. CRD42020191749).

Description of the interventions

The interventions examined in this review were the foods fortified with vitamin D_2 or vitamin D_3 as a single ingredient or in combination with Ca. No limit was placed on the dose, type of vehicle or frequency at which fortified foods were taken.

Search strategy

A comprehensive search of electronic databases was conducted for eligible trials from January 2000 to July 2020. The following databases were covered: National Library of Medicine (PubMed), Scopus, Web of Science (WoS), Cochrane Database of Systematic Reviews (Cochrane Library, CDSR) and Google Scholar using the following search terms in titles and abstracts: (vitamin D OR cholecalciferol OR ergocalciferol) AND (fortification) AND/OR (fortified). All of the studies were limited to English language and those performed on humans.

Types of studies: inclusion and exclusion criteria

Two investigators separately searched and reviewed articles for eligibility via the following inclusion criteria: all studies had to have: (1) a randomised clinical trial design; (2) enrolled adults aged 18 years and older; and (3) data description as mean ± standard deviation and sufficient information on serum 25(OH)D concentrations at baseline and at the end of follow-up in each group or the net change values.

Studies were excluded based on the following criteria: (1) incomplete data; (2) duplicate publication of articles; (3) obscurely reported outcomes, or lack of control groups; and (4) non-interventional studies.

Types of interventions and outcome measures

We evaluated the effect of foods fortified with vitamin D_2 or vitamin D_3 alone or in combination with Ca *v.* unfortified foods or no intervention. Outcome measure was total serum/plasma 25(OH)D concentrations.

Data extraction and management

To review the articles, authors independently screened titles and/or abstracts to exclude studies which failed to meet the inclusion criteria and then obtained the full-text reports for further evaluations. Discrepancies were resolved through consensus. Detailed data of study design, context, participants' information, interventions and outcomes were extracted.

For multi-armed studies, pairs of arms relevant to the review were compared. Data for the control group were used for each intervention group comparison. The weight assigned to the control group was reduced by dividing the control group number (n) by the number of intervention groups.

The selection process in sufficient detail to complete a PRISMA flow diagram is demonstrated in the Fig. 1 and Tables 1 and 2.

Assessment of risk of bias in included studies

Criteria for the assessment of study quality were the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*[33], including random sequence generation, allocation concealment, blinding of participants, personnel and

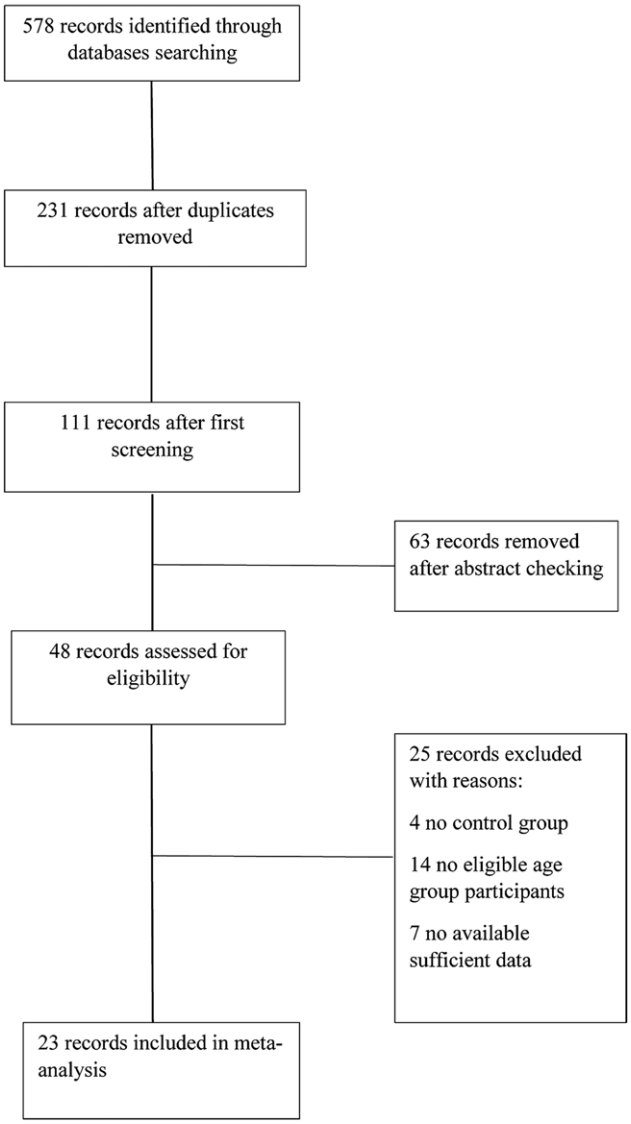

Fig. 1. Flow diagram of the study.

outcome assessment, incomplete outcome data, selective outcome reporting and other biases (bias due to problems not covered elsewhere, e.g. industry funding).

Assessment of reporting biases

Funnel plots were used to assess the potential existence of bias. We performed a regression asymmetry test for the detection of bias[34]; $P < 0{\cdot}10$ was considered significant.

Subgroup analysis and investigation of heterogeneity

If we identified substantial heterogeneity and there were sufficient data, we would investigate this heterogeneity using subgroup analyses and sensitivity analyses.

The following subgroup analyses were carried out:

- Duration of intervention
- Type and dose of the fortificant
- Population (gender and latitude of living place)
- Type of the fortified food

Sensitivity analysis

The aim of the sensitivity analysis was to examine the effect size when including studies meeting less stringent inclusion criteria. If there were sufficient data to allow for sensitivity analysis, this analysis would be performed for examining the effects on results by excluding:

- Trials at high risk of bias, as specified in the 'Assessment of risk of bias in included studies' section.
- Trials with small sample size (less than 15 participants in each group);

Meta-regression

Random effects model meta-regression analyses were performed to assess the sources of inter-trial heterogeneity.

Statistical analysis

Meta-analysis was performed using STATA version 16.0 (StataCorp.). We did not report any dichotomous data. For continuous outcomes, a mean difference (MD) and 95 % CI were calculated for each study (i.e. intervention group minus control group differences). In addition, heterogeneity was assessed using Q test and I^2 test. The fixed effect model was used when there was no statistically significant heterogeneity ($P > 0{\cdot}1$ and $I^2 < 50\,\%$), whereas a random effects model was employed on the contrary ($P < 0{\cdot}1$ or $I^2 > 50\,\%$).

Results

Characteristics of the included studies

Figure 1 shows the study selection procedure. Our search identified 231 unique studies of which 208 did not meet our inclusion criteria, resulting in 23 papers included for the systematic review. Mean follow-up varied between 3 weeks[35] to 2 years[36]. Of the twenty-three studies included, four were from North America[37,38,39] including Canada[40], six from Asia[41,42,43,44,45,46] and the rest from Europe and Australia[35,36,47,48,49,50,51,52,53,54,55,56,57] (Table 1).

Participants

Table 1 provides details of the eligible studies that evaluated the effect of fortified foods with vitamin D on circulating 25(OH)D concentrations. Twelve studies were conducted in women[35,44,45,47,48,49,50,51,52,54,56,57] and only two in men[36,53]. Subjects with type 2 diabetes were enrolled in three studies[41,45,46]. The number of participants included in trials

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Table 1. Characteristics of the studies selected for analysis
(Mean values and standard deviations)

Study	Location	Participants	Type and dose of vitamin D	Duration (week)	Sample size	Age (years)	Female (%)	BMI (kg/m^2)	Baseline 25(OH)D, nmol/l	Note
Biancuzzo, 2010[37]	USA, Boston	Aged 18–79 years, no history of intestinal malabsorption, severe medical illnesses, allergies, or intolerance or taking a supplement containing > 400 IU vitamin D/d.	Group 1: placebo capsule + orange juice without vitamin D (placebo orange juice), daily Group 2: placebo capsule + orange juice containing 1000 IU of vitamin D_3/236·6 ml, daily Group 3: Placebo capsule + orange juice containing 1000 IU vitamin D_2/236·6 ml, daily Group 4: 1000 IU of vitamin D_3 capsule + placebo orange juice, daily Group 5: 1000 IU of vitamin D_2 capsule + placebo orange juice, daily	11	Group 1: 15 Group 2: 18 Group 3: 17	Group 1: 40·8 (SD 10·8) Group 2: 41·4 (SD 12·6) Group 3: 40·1 (SD 15·6)	Group 1: 86·7 Group 2: 83·3 Group 3: 52·9	Group 1: 27·8 Group 2: 29·9 Group 3: 27	Group 1: 49·5 (SD 24) Group 2: 44·7 (SD 27·7) Group 3: 39·5 (SD 25)	Group 1, 2, 3 were included
Bonjour, 2012[49]	France, Paris	Post-menopausal women; BMI ranging from 18 to 27 kg/m^2; Ca intake < 650 mg/d, low vitamin D supply from sun exposure and food intake, no substitutive hormone-related therapy	Group 1: two servings (200 g) of food consisted of skimmed milk, soft, plain cheese fortified with vitamin D (+50 IU/100 g) and Ca (200 mg), daily Group 2: standard cheese (Ca: 90–120 mg/100 g), daily	6	Group 1: 36 Group 2: 35	Group 1: 57·1 (SD 3·9) Group 2: 56·1 (SD 3·9)	100	Group 1: 23·1 (SD 2·2) Group 2: 22·9 (SD 2·5)	Group 1: 58·8 (SD 20·8) Group 2: 57·3 (SD 16·8)	–
Bonjour, 2013[48]	France, Paris	Low vitamin D status, moderately elevated serum PTH level, Mini Nutritional Assessment score > 20; no consumption of food enriched with vitamin D and/or Ca; no treatment during the last 6 months for osteoporosis or other bone diseases, no osteoporotic fracture	Group 1: two servings of yogurt containing 400 IU of vitamin D_3 and 800 mg of Ca, daily Group 2: 0 IU of supplemental vitamin D_3 and 280 mg of Ca, daily	8	Group 1: 32 Group 2: 27	Group 1: 85·8 (SD 6·8) Group 2: 85·1 (SD 6·7)	100	Group 1: 26·2 (SD 3·9) Group 2: 26·6 (SD 5·2)	Group 1: 19·2 (SD 6·7) Group 2: 16·2 (SD 3·1)	

Table 1. (*Continued*)

Study	Location	Participants	Type and dose of vitamin D	Duration (week)	Sample size	Age (years)	Female (%)	BMI (kg/m^2)	Baseline 25(OH)D, nmol/l	Note
		during the year preceding the study								
Bonjour, 2015[47]	England, Hull	Women aged >60 years, 25(OH)D ≤ 50 nmol/l and PTH < 150 ng/ml.	Group 1: two servings of fortified yogurt (400 IU of vitamin D_3 and 800 mg of Ca, daily Group 2: 0 IU of vitamin D_3 and 280 mg of Ca, daily	12	Group 1: 24 Group 2: 24	Group 1: 74·3 (SD 6·8) Group 2: 72·8 (SD 7·8)	100	Group 1: 29·2 (SD 5·4) Group 2: 31·1 (SD 5·4)	Group 1: 34·1 (SD 11·7) Group 2: 35·1 (SD 11·8)	
Bonjour, 2018[50]	France, Auvergne–Rhône–Alpes	Post-menopausal women aged between 55 and 75 years	Group 1: control, daily Group 2: 125 g of yogurt containing 200 IU of vitamin D/d for 16 weeks followed by 8 weeks without product, daily Group 3: 250 g of yogurt containing 400 IU of vitamin D, daily	16	Group 1: 45 Group 2: 44 Group 3: 44	Group 1: 62·6 (SD 5·4) Group 2: 60·4 (SD 4·0) Group 3: 61·4 (SD 5·3)	100	Group 1: 24·5 (SD 2·7) Group 2: 24·5 (SD 3·3) Group 3: 24·7 (SD 2·7)	Group 1: 36·4 (SD 15·8) Group 2: 35·6 (SD 14·6) Group 3: 35·9 (SD 14·8)	
Daly, 2009[36]	Australia, Melbourne	Caucasian men aged >50 years not taking Ca–vitamin D supplements, no regular resistance training, BMI < 35 kg/m^2, no history of osteoporotic fracture or medical disease or medications that affect bone metabolism	Group 1: Ca–vitamin D_3-fortified milk, daily Group 2: control, daily	96	Group 1: 73 Group 2: 67	Group 1: 61·3 (SD 7·7) Group 2: 61·2 (SD 7·5)	0	Group 1: 26·2 (SD 3·3) Group 2: 26·7 (SD 3·2)	Group 1: 78 (SD 23) Group 2: 76 (SD 23)	
Grønborg, 2020[52]	Denmark, Copenhagen area	Low consumption of fish and fish products (less than weekly), a low frequency of taking vitamin D-containing supplements (less than weekly), no use of tanning facilities and no planned sun	Danish origin: Group 1: 800 IU of vitamin D_3/d through fortified yogurt, cheese, eggs and crisp bread, daily Group 2: control, daily Pakistani origin: Group 1: 800 IU vitamin D_3/d through fortified yogurt,	12	Danish origin Group 1: 31 Group 2: 35 Pakistani origin: Group 1: 33 Group 2: 37	Danish Group 1: 32 (SD 11) Group 2: 34 (SD 11) Pakistani Group 1: 36 (SD 10)	100	Danish Group 1: 24 (SD 4) Group 2: 25 (SD 5) Pakistani Group 1: 27 (SD 5)	Danish Group 1: 53·3 (SD 17) Group 2: 46·2 (SD 19) Pakistani Group 1: 44·5 (SD 21)	

Table 1. (*Continued*)

Study	Location	Participants	Type and dose of vitamin D	Duration (week)	Sample size	Age (years)	Female (%)	BMI (kg/m^2)	Baseline 25(OH)D, nmol/l	Note
		holiday (to a location more southerly than 47°N)	cheese, eggs and crisp bread daily Group 2: control, daily			Group 2: 36 (SD 9)		Group 2: 27 (SD 5)	Group 2: 49 (SD 23)	
Jafari, 2016[45]	Iran, Isfahan	Post-menopausal women with type 2 diabetes, not taking vitamin D, Ca, or *n*-3 supplements, not taking drugs which have obvious interaction with vitamin D or influence its metabolism, baseline serum 25(OH)D < 125 nmol/L, not having a history of malignancy, renal failure, liver, endocrinological or inflammatory disorders.	Group 1: 'FY' (received vitamin D-fortified low-fat yogurt, containing 2000 IU of vitamin D in 100 g), daily Group 2: 'PY' (received plain low-fat yogurt without additive), daily	12	Group 1: 30 Group 2: 29	Group 1: 57·8 (SD 5·5) Group 2: 56·8 (SD 5·7)	100	Group 1: 28·0 (SD 0·82) Group 2: 29·3 (SD 0·72)	Group 1: 62·2 (SD 4·52) Group 2: 62·7 (SD 4·3)	
Wanger, 2008[40]	Canada, Toronto	Healthy men and women between 18 and 60 years of age with no history of any medical disorders that might affect vitamin D or mineral metabolism; not using vitamin D supplements in excess of 400 IU/d; not using medications that could interfere with vitamin D metabolism; no significant sun exposure	Group 1: vitamin D-fortified regular-fat Cheddar cheese (DC) (33·6 g/serving) Group 2: vitamin D-fortified low-fat cheese (DLF) (41·4 g/serving) Group 3: vitamin D supplement (as an ethanolic solution) to be taken with food (i.e. during a meal) (DS1) Group 4: vitamin D supplement (as an ethanolic solution) to be taken without food (i.e. just before the bedtime) (DS2) Group 5: placebo cheese, a regular-fat Cheddar cheese (33·6 g/serving) containing no vitamin D (PC) Group 6: placebo supplement, (PS). Fortified cheeses and supplements contained 28 000 IU of cholecalciferol (vitamin D_3) per serving or dose. Each serving or dose was consumed orally once a week; this weekly dose is	8	Group1: 20 Group 2: 10 Group 5: 10	Group 1: 28·7 (SD 11·4) Group 2: 30·6 (SD 11·7) Group 3: 26·2 (SD 6·5)	50	Group 1: 25·2 (SD 5·0) Group 2: 24·2 (SD 3·3) Group 3: 29·2 (SD 3·9)	Group 1: 50·7 (SD 18·9) Group 2: 57·5 (SD 18·4) Group 3: 52·4 (SD 22·7)	Group 1, 2 and 5 were included

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Table 1. (*Continued*)

Study	Location	Participants	Type and dose of vitamin D	Duration (week)	Sample size	Age (years)	Female (%)	BMI (kg/m^2)	Baseline 25(OH)D, nmol/l	Note
			equivalent to a daily dose of 4000 IU of cholecalciferol (weekly)							
Tripkovic, 2017[57]	UK, Surrey	Healthy, free-living South Asian or White European women aged 20–64 years	Group 1: placebo juice with placebo biscuit, daily Group 2: juice fortified with 600 IU of vitamin D_2 with placebo biscuit (D2J), daily Group 3: placebo juice with biscuit fortified with 600 IU of vitamin D_2 (D2B), daily Group 4: juice fortified with 600 IU of vitamin D_3 with placebo biscuit (D3J), daily Group 5: placebo juice with biscuit fortified with 600 IU of vitamin D_3 (D3B), daily	12	Group 1: 65 Group 2: 67 Group 3: 66 Group 4: 70 Group 5: 67	Group 1: 44·1 (SD 11·5) Group 2: 44·3 (SD 11·2) Group 3: 43·2 (SD 13·2) Group 4: 43·0 (SD 12·7) Group 5: 43·7 (SD 12·8)	100	Group 1: 24·4 (SD 3·6) Group 2: 24·2 (SD 3·4) Group 3: 24·1 (SD 4·5) Group 4: 23·8 (SD 3·6) Group 5: 23·8 (SD 3·8)	Group1: 44·8 (SD 29·4) Group 2: 44·9 (SD 29·1) Group 3: 46·1 (SD 29·5) Group 4: 42·3 (SD 28·9) Group 5: 41·9 (SD 28·6)	
Nikooyeh, 2011[86]	Iran, Tehran	Subjects with type 2 diabetes, aged 30–60 years	Group 1: plain yogurt drink, daily Group 2: vitamin D-fortified yogurt drink (DY; containing 500 IU of vitamin D_3 and 150 mg of Ca/250 ml), daily Group 3: vitamin D + Ca-fortified yogurt drink (DCY; containing 500 IU of vitamin D_3 and 250 mg of Ca/250 ml), two servings/d, daily	12	Group 1: 30 Group 2: 30 Group 3: 30	Group1: 50·8 (SD 6·6) Group 2: 51·4 (SD 5·4) Group 3: 49·9 (SD 6·2)	61	Group 1: 29·9 (SD 4·7) Group 2: 29·2 (SD 4·4) Group 3: 29·1 (SD 5·5)	Group1: 41·6 (SD 44·5) Group 2: 44·4 (SD 28·7) Group 3: 44·5 (SD 43·7)	
Kukuljan, 2009[53]	Australia, Geelong	Healthy community-dwelling Caucasian men aged 50 to 79 years	Group 1: exercise + fortified milk, daily Group 2: exercise alone, daily Group 3: fortified milk alone (500 mg of Ca and 400 IU of vitamin D_3), daily Group 4: control group, two servings per d, daily	12	Group 1: 45 Group 2: 46 Group 3: 45 Group 4: 44	Group 1: 61·7 (SD 7·6) Group 2: 60·7 (SD 7·1) Group 3: 61·7 (SD 7·7) Group 4: 59·9 (SD 7·4)	0	NM	Group 1: 90·5 (SD 29·9) Group 2: 85·0 (SD 40·6) Group 3: 83·6 (SD 32·7) Group 4: 85·7 (SD 40·3)	Group 3 and 4 were included

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Table 1. (*Continued*)

Study	Location	Participants	Type and dose of vitamin D	Duration (week)	Sample size	Age (years)	Female (%)	BMI (kg/m^2)	Baseline 25(OH)D, nmol/l	Note
Kruger, 2018[44]	Malaysia, Selangor	Post-menopausal community-dwelling women	Group 1: two servings per d of regular milk powder (420 mg of Ca), daily Group 2: two servings per d of fortified milk powder (1200 mg of Ca, plus 96 mg of Mg, 2·4 mg of Zn and 600 IU of vitamin D), daily	12	Group 1: 60 Group 2: 61	Group 1: 60 (SD 4·3) Group 2: 59 (SD 3·9)	100	Group 1: 24·5 (SD 2·94) Group 2: 23·4 (SD 2·94)	Group 1: 64·8 (SD 18·9) Group 2: 62·3 (SD 18·9)	
Manios, 2017[54]	Greece, Athens	Post-menopausal women (55–75 years)	Group 1: 60 g (provided as two slices in a pack) of non-fortified reduced-fat Gouda-type cheese, daily Group 2: vitamin D_3-fortified, reduced fat Gouda-type cheese, daily	8	Group 1: 40 Group 2: 40	Group 1: 63·2 (SD 5·9) Group 2: 62·6 (SD 6·0)	100	Group 1: 29·0 (SD 2·9) Group 2: 28·0 (SD 3·8)	Group 1: 42·9 (SD 17·7) Group 2: 47·3 (SD 15·2)	
Johnson, 2005[38]	USA, South Dakota	Older (≥60 years) men and women	Group 1: process cheese fortified with vitamin D_3 (600 IU/d) Group 2: process cheese without vitamin D_3 Group 3: no process cheese	8	Group 1: 35 Group 2: 37 Group 3: 38	NM	57·2	NM	Group 1: 57·5 (SD 20·5) Group 2: 50·0 (SD 18·0) Group 3: 45 (SD 20)	Group 1 and 2 were included
Nikooyeh, 2016[42]	Iran, Tehran	Healthy subjects aged 20–60 years	Group 1: fortified bread (FP; 50 g of bread fortified with 1000 IU of vitamin D_3 plus placebo), daily Group 2: supplement (SP; 50 g of plain bread plus 1000 IU of vitamin D supplement, daily Group 3: control (CP; 50 g of plain bread plus placebo), daily	8	Group 1: 30 Group 2: 30 Group 3: 30	Group 1: 37·2 (SD 10·5) Group 2: 37·3 (SD 10·9) Group 3: 39·4 (SD 11·6)	45·5	Group 1: 26·5 (SD 4·7) Group 2: 25·7 (SD 3·7) Group 3: 27·2 (SD 4·0)	Group 1: 33·9 (SD 21·9) Group 2: 35·0 (SD 38·7) Group 3: 34·7 (SD 30·5)	Group 1 and 3 were included
Shab-Bidar, 2011[46]	Iran, Tehran	Subjects with T2D aged 29 to 67 years	Group 1: vitamin D_3-fortified doogh (FYD; containing 170 mg of Ca and 500 IU of vitamin D_3/250 ml), daily Group 2: plain doogh (PYD; containing 170 mg of Ca and no detectable vitamin D/250 ml), two servings/d, daily	12	Group 1: 50 Group 2: 50	Group 1:52·6 (SD 6·3) Group 2: 52·4 (SD 8·4)	57	Group1:28·6 (SD 4·0) Group 2: 30·0 (SD 4·2)	Group1:38·5 (SD 20·2) Group 2: 38·0 (SD 22·8)	
Toxaqui, 2013[56]	Spain, Madrid	Healthy Caucasian women aged18–35 years	Group 1:500 ml/d of a dairy product fortified with Fe but without vitamin D (D-placebo), daily Group 2: 500 ml/d of the product fortified with Fe	16	Group 1: 54 Group 2: 55	Group 1: 24·7 (SD 4·3) Group 2: 26·5 (SD 3·8)	100	NM	Group 1: 62·9 (SD 20·8) Group 2: 63·2 (SD 20·8)	

Table 1. (*Continued*)

Study	Location	Participants	Type and dose of vitamin D	Duration (week)	Sample size	Age (years)	Female (%)	BMI (kg/m^2)	Baseline 25(OH)D, nmol/l	Note
			and vitamin D (vitamin D-fortified), daily							
Tanta, 2011[55]	Greece, Athens	Post-menopausal women aged 55–65 years	Group 1: dietary group (DG), receiving 1200 mg of Ca daily for 30 months and 300 IU of vitamin D_3 for the first 12 months that increased to 900 IU for the remaining 18 months of intervention through fortified dairy products, daily Group 2: 1control group (CG), daily	12	Group 1: 20 Group 2: 20	Group 1: 32·5 (SD 5·1) Group 2: 32·5 (SD 3·5)	28	Group 1: 26·8 (SD 3·2) Group 2: 26·8 (SD 3·6)	Group 1: 35·1 (SD 9·0) Group 2: 38·2 (SD 7·8)	The data of first 12 months were included
Nikooyeh, 2019[43]	Iran, Tehran	Healthy men and women aged 18–65 years	Group 1: intervention (vitamin D-fortified sunflower oil with 500 IU/30 g) (DO), daily Group 2: control (unfortified sunflower oil) (SO), daily	12	Group 1: 39 Group 2: 34	NM	NM	NM	Group 1: 37·0 (SD 8·0) Group 2: 50·0 (SD 10·0)	
Tangpricha, 2003[39]	USA, Boston	Healthy adults aged 22–60 years	Group 1: 240 ml of orange juice fortified with 350 mg of Ca, daily Group 2: 240 ml of orange juice fortified with 350 mg of Ca and 1000 IU of vitamin D_3, daily	12	Group 1: 14 Group 2: 12	Group 1: 28·8 (SD 7·6) Group 2: 28·0 (SD 7·5)	100	Group 1: 23·7 (SD 3·8) Group 2: 23·3 (SD 4·2)	Group 1: 74 (SD 29·5) Group 2: 53 (SD 31·4)	
Green, 2010[51]	New Zealand, Dunedin	Women aged 18–45 years	Group 1: 75 g of milk powder, daily Group 2: 75 g of milk powder fortified with 200 IU of vitamin D_3, daily	12	Group 1: 36 Group 2: 37	Group 1: 27·3 (SD 1·9) Group 2: 28·8 (SD 5·6) Group 3: 29·0 (SD 5·1) Group 4: 31·1 (SD 5·9)	100	Group 1: 22·3 (SD 4·6) Group 2: 23·6 (SD 4·1) Group 3: 23·1 (SD 2·7) Group 4: 22·1 (SD 1·9)	Group 1: 29·0 (SD 9·9) Group 2: 28·9 (SD 11·0) Group 3: 27·1 (SD 11·1) Group 4: 29·6 (SD 8·6)	
Natri, 2006[35]	Finland, Helsinki	Women aged 25–45 years	Group 1: fortified wheat bread, daily Group 2: fortified rye bread, goal of 400 IU from fortified breads, daily Group 3: regular wheat bread (control), daily Group 4: regular wheat bread and 400 IU of cholecalciferol supplement a day (vitamin D control), daily	3	Group 1: 11 Group 2: 11 Group 3: 11 Group 4: 11					

NM: Not mentioned

Table 2. Demographic features and baseline variables of the studies selected for analysis (Mean values and standard deviations)

Study	Age (years)	Female (%)	BMI (kg/m^2)	Baseline 25(OH)D, nmol/l
Biancuzzo, 2010	Group 1: 40·8 (SD 10·8) Group 2: 41·4 (SD 12·6) Group 3: 40·1 (SD 15·6)	Group 1: 86·7 Group 2: 83·3 Group 3: 52·9	Group 1: 27·8 Group 2: 29·9 Group 3: 27	Group 1: 49·5 (SD 24) Group 2: 44·7 (SD 27·7) Group 3: 39·5 (SD 25)
Bonjour, 2012	Group 1: 57·1 (SD 3·9) Group 2: 56·1 (SD 3·9)	100	Group 1: 23·1 (SD 2·2) Group 2: 22·9 (SD 2·5)	Group 1: 58·8 (SD 20·8) Group 2: 57·3 (SD 16·8)
Bonjour, 2013	Group 1: 85·8 (SD 6·8) Group 2: 85·1 (SD 6·7)	100	Group 1: 26·2 (SD 3·9) Group 2: 26·6 (SD 5·2)	Group 1: 19·2 (SD 6·7) Group 2: 16·2 (SD 3·1)
Bonjour, 2015	Group 1: 74·3 (SD 6·8) Group 2: 72·8 (SD 7·8)	100	Group 1: 29·2 (SD 5·4) Group 2: 31·1 (SD 5·4)	Group 1: 34·1 (SD 11·7) Group 2: 35·1 (SD 11·8)
Bonjour, 2018	Group 1: 62·6 (SD 5·4) Group 2: 60·4 (SD 4·0) Group 3: 61·4 (SD 5·3)	100	Group 1: 24·5 (SD 2·7) Group 2: 24·5 (SD 3·3) Group 3: 24·7 (SD 2·7)	Group 1: 36·4 (SD 15·8) Group 2: 35·6 (SD 14·6) Group 3: 35·9 (SD 14·8)
Daly, 2009	Group 1: 61·3 (SD 7·7) Group 2: 61·2 (SD 7·5)	0	Group 1: 26·2 (SD 3·3) Group 2: 26·7 (SD 3·2)	Group 1: 78 (SD 23) Group 2: 76 (SD 23)
Grønborg, 2020	Danish Group 1: 32 (SD 11) Group 2: 34 (SD 11) Pakistani Group 1: 36 (SD 10) Group 2: 36 (SD 9)	100	Danish Group 1: 24 (SD 4) Group 2: 25 (SD 5) Pakistani Group 1: 27 (SD 5) Group 2: 27 (SD 5)	Danish Group 1: 53·3 (SD 17) Group 2: 46·2 (SD 19) Pakistani Group 1: 44·5 (SD 21) Group 2: 49 (SD 23)
Jafari, 2016	Group 1: 57·8 (SD 5·5) Group 2: 56·8 (SD 5·7)	100	Group 1: 28·0 (SD 0·82) Group 2: 29·3 (SD 0·72)	Group 1: 62·2 (SD 4·52) Group 2: 62·7 (SD 4·3)
Wanger, 2008	Group 1: 28·7 (SD 11·4) Group 2: 30·6 (SD 11·7) Group 3: 26·2 (SD 6·5)	50	Group 1: 25·2 (SD 5·0) Group 2: 24·2 (SD 3·3) Group 3: 29·2 (SD 3·9)	Group 1: 50·7 (SD 18·9) Group 2: 57·5 (SD 18·4) Group 3: 52·4 (SD 22·7)
Tripkovic, 2017	Group 1: 44·1 (SD 11·5) Group 2: 44·3 (SD 11·2) Group 3: 43·2 (SD 13·2) Group 4: 43·0 (SD 12·7) Group 5: 43·7 (SD 12·8)	100	Group 1: 24·4 (SD 3·6) Group 2: 24·2 (SD 3·40 Group 3: 24·1 (SD 4·5) Group 4: 23·8 (SD 3·6) Group 5: 23·8 (SD 3·8)	Group 1: 44·8 (SD 29·4) Group 2: 44·9 (SD 29·1) Group 3: 46·1 (SD 29·5) Group 4: 42·3 (SD 28·9) Group 5: 41·9 (SD 28·6)
Nikooyeh, 2011	Group 1: 50·8 (SD 6·6) Group 2: 51·4 (SD 5·4) Group 3: 49·9 (SD 6·2)	61	Group 1: 29·9 (SD 4·7) Group 2: 29·2 (SD 4·4) Group 3: 29·1 (SD 5·5)	Group 1: 41·6 (SD 44·5) Group 2: 44·4 (SD 28·7) Group 3: 44·5 (SD 43·7)
Kukuljan, 2009	Group 1: 61·7 (SD 7·6) Group 2: 60·7 (SD 7·1) Group 3: 61·7 (SD 7·7) Group 4: 59·9 (SD 7·4)	0	NM	Group 1: 90·5 (SD 29·9) Group 2: 85·0 (SD 40·6) Group 3: 83·6 (SD 32·7) Group 4: 85·7 (SD 40·3)
Kruger, 2018	Group 1: 60 (SD 4·3) Group 2: 59 (SD 3·9)	100	Group 1: 24·5 (SD 2·94) Group 2:23·4 (SD 2·94)	Group 1: 64·8 (SD 18·9) Group 2: 62·3 (SD 18·9)
Manios, 2017	Group 1: 63·2 (SD 5·9) Group 2: 62·6 (SD 6·0)	100	Group 1: 29·0 (SD 2·9) Group 2: 28·0 (SD 3·8)	Group 1: 42·9 (SD 17·7) Group 2: 47·3 (SD 15·2)
Johnson, 2005	NM	57·2	NM	Group1:57·5 (SD 20·5) Group 2:50·0 (SD 18·0) Group 3:45 (SD 20)
Nikooyeh, 2016	Group 1: 37·2 (SD 10·5) Group 2: 37·3 (SD 10·9) Group 3: 39·4 (SD 11·6)	45·5	Group 1: 26·5 (SD 4·7) Group 2: 25·7 (SD 3·7) Group 3: 27·2 (SD 4·0)	Group 1: 33·9 (SD 21·9) Group 2: 35·0 (SD 38·7) Group 3: 34·7 (SD 30·5)
Shab-Bidar, 2011	Group 1: 52·6 (SD 6·3) Group 2: 52·4 (SD 8·4)	57	Group 1: 28·6 (SD 4·0) Group 2: 30·0 (SD 4·2)	Group 1: 38·5 (SD 20·2) Group 2: 38·0 (SD 22·8)
Toxaqui, 2013	Group 1: 24·7 (SD 4·3) Group 2: 26·5 (SD 3·8)	100	NM	Group 1: 62·9 (SD 20·8) Group 2: 63·2 (SD 20·8)
Nikooyeh, 2019	Group 1: 32·5 (SD 5·1) Group 2: 32·5 (SD 3·5)	28	Group 1: 26·8 (SD 3·2) Group 2: 26·8 (SD 3·6)	Group 1: 35·1 (SD 9·0) Group 2: 38·2 (SD 7·8)
Tangpricha, 2003	NM	NM	NM	Group 1: 37·0 (SD 8·0) Group 2: 50·0 (SD 10·0)
Green, 2010	Group 1: 28·8 (SD 7·6) Group 2: 28·0 (SD 7·5)	100	Group 1: 23·7 (SD 3·8) Group 2: 23·3 (SD 4·2)	Group 1: 74 (SD 29·5) Group 2: 53 (SD 31·4)
Natri, 2006	Group 1: 27·3 (SD 1·9) Group 2: 28·8 (SD 5·6) Group 3: 29·0 (SD 5·1) Group 4: 31·1 (SD 5·9)	100	Group 1: 22·3 (SD 4·6) Group 2: 23·6 (SD 4·1) Group 3: 23·1 (SD 2·7) Group 4: 22·1 (SD 1·9)	Group 1: 29·0 (SD 9·9) Group 2: 28·9 (SD 11·0) Group 3: 27·1 (SD 11·1) Group 4: 29·6 (SD 8·6)

was 2002 (1173 in the intervention group and 829 in the control group). All trials but four studies[38,39,53,56] reported BMI of participants at baseline. Only three studies were conducted in participants who were initially vitamin D insufficient[35,47,48], and vitamin D status was not among the inclusion criteria in other studies.

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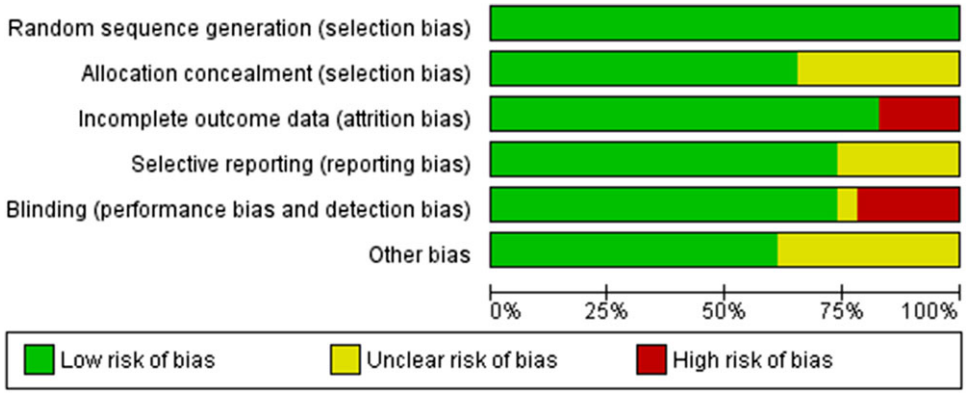

Fig. 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Mean baseline serum 25(OH)D concentrations across the trials ranged from 19·2 (SD 6·7) nmol/l[48] to 83·6 (SD 32·7) nmol/l[53] in the subjects of the intervention groups and from 16·2 (SD 3·1) nmol/l[48] to 85·7 (SD 40·3) nmol/l[53] in those of the control groups.

Intervention and control groups

The range of dose of vitamin D used as fortificant was 100 /d[49] to 4000 IU/d[40]. Ten trials applied vitamin D plus Ca (100 mg/d to 1200 mg/d)[36,41,44,47,48,49,50,53,55]. Most trials (twenty-one out of twenty-three) used dairy products as the vehicles for vitamin D fortification. With the exception of two studies in which control group received no intervention[50,53], all other included studies used unfortified foods as a placebo for control group.

Risk of bias in the included studies

All trials provided data on losses to follow-up; only four reported losses of >10 %[36,37,44,47]. In eight trials, the information on the methods used for allocation concealment was unclear[35,36,38,40,44,49,51,54]. Two trials reported small sample size (< 15 subjects in each arm)[35,40] (Figs. 2 and 3).

Effects of interventions

Serum 25(OH)D concentrations. Twenty-three trials compared vitamin D alone or combined with Ca with control. From five trials two pairs of arms and from one study four arms relevant to the review were compared. Pooled data comparing vitamin D with or without Ca with control showed statistically significant effect on circulating 25(OH)D concentrations (2002 participants, MD: 25·4 nmol/l, (95 % CI 19·5, 31·3) (Fig. 4).

Subgroup analyses. We conducted stratified analyses according to duration of intervention (less than 12 weeks *v.* 12 weeks and more), vehicle (dairy product, juice, grain product, oil and dairy together with grain products), isoform of the vitamin (D_3 *v.* D_2) and dose of the fortificant (≥ 1000 IU/d *v.* < 1000 IU/d). We found a statistically significant effect in the subgroups of all studies with all doses used for fortification (both more than and less than 1000 IU/d). However, the effect was significantly stronger in those trials that used more than 1000 IU vitamin D a day (>1000 IU, MD: 41·5 nmol/l, (95 % CI 33·0, 50·0) *v.* < 1000 IU, MD: 18·2, (95 % CI 12·7, 23·7), $P < 0·001$) (Fig. 5).

There was no difference between trials that used vitamin D_2 or D_3 as fortificant (MD: 27·9 nmol/l, (95 % CI 19·3, 36·4) *v.* MD: 25·2 nmol/l, (95 % CI 18·7, 31·7), $P = 0·62$). However, it is noteworthy that only two trials (three arms) assessed the effect of vitamin D_2[37,57] (Fig. 5).

The subgroup analysis by duration of intervention (less than 12 weeks *v.* more than 12 weeks) and type of vehicle (dairy product, juice, grain product, oil and combination of dairy and grain products) also indicated significant effect of fortification with vitamin D on circulating 25(OH)D concentrations (Fig. 5).

Thirteen trials included both men and women and showed better effect compared with those trials that included just women (MD: 35·3 nmol/l, (95 % CI 23·7, 47·0) *v.* MD: 19·3 nmol/l, (95 % CI 14·4, 24·1), $P = 0·01$) (Fig. 6).

We also conducted stratified analyses according to the latitude of place wherein trials had been performed. Most of the trials were conducted in countries located in latitude higher than 35°. The treatment effect was better in trials from countries located in lower than 35°. However, no differing patterns were clearly evident between these subgroups (χ^2 3·65, P 0·06) (Fig. 6).

Sensitivity analysis. We excluded trials at high risk of attrition bias (> 10 % loss to follow-up) in order to assess whether this exclusion could affect the overall results. However, the analyses demonstrated very similar findings (MD: 26·1 nmol/l, (95 % CI 19·2, 32·9)). Excluding the trials with small sample size (less than 15) from each arm made no remarkable change in the overall results (MD: 24·5 nmol/l, (95 % CI 18·7, 30·2)).

Meta-regression. The meta-regression revealed a significant association between age of participants (β -0·48, (95 % CI -0·67, -0·29), $P < 0·001$), baseline circulating 25(OH)D

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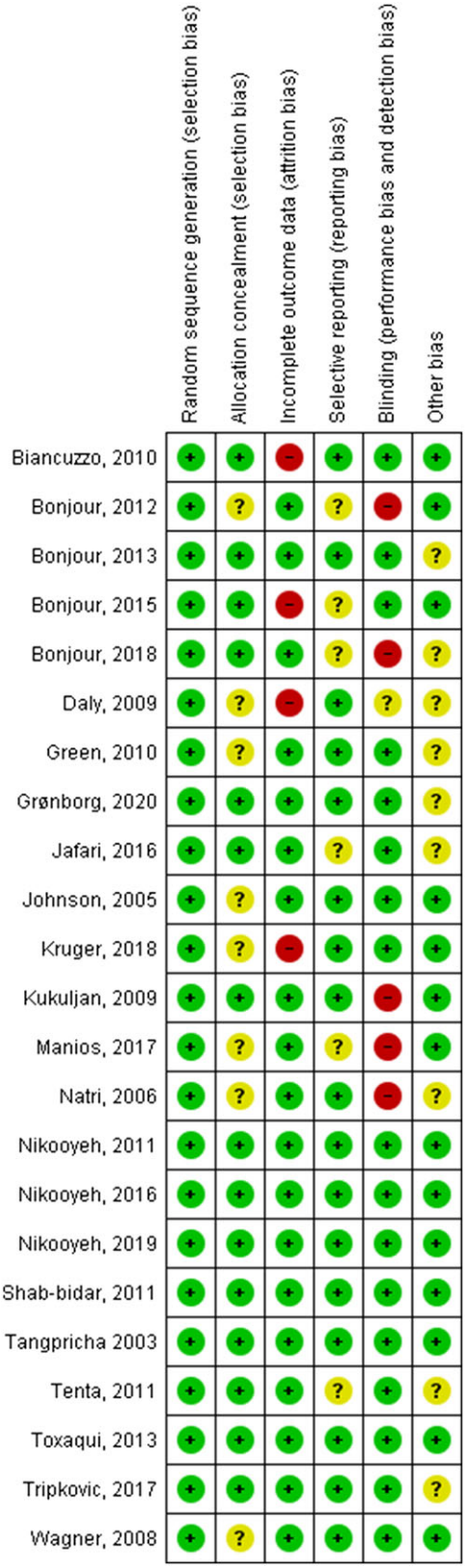

Fig. 3. Summary of the risk of bias for each study.

concentration (β -0·47, (95 % CI -0·72, -0·22), $P < 0·001$) and dose of the fortificant (β 0·02, (95 % CI 0·01, 0·02), $P < 0·001$) with the difference in circulating 25(OH)D concentrations between intervention and control groups. The BMI of participants at the beginning of the study ($P = 0·321$) and latitude of location ($P = 0·096$) did not significantly influence the between-group difference of 25(OH)D concentrations. The analysis showed that circulating 25(OH)D concentrations increase by 2 nmol/l for every 100 IU of vitamin D after adjustment for age, BMI, baseline circulating 25(OH)D concentration and latitude (Table 3).

The results of the meta-analysis demonstrated a quadratic, dose–response relationship between treatment effect and circulating 25(OH)D concentrations at baseline with higher effects in participants with lower initial 25(OH)D concentrations (Fig. 7).

The meta-regression in subgroups of studies that had baseline 25(OH)D lower than 50 nmol/l showed an increment in circulating 25(OH)D concentrations by 3 nmol/l for every 100 IU of vitamin D after adjustment for age, BMI and latitude.

Analyses of bias risk. A regression asymmetry test to the analysis of the bias risk of publications showed no significant evidence of bias ($P = 0.670$).

Discussion

The findings of this meta-analysis showed that foods fortified with vitamin D, either alone or in combination with Ca, are effective means to improve vitamin D status of the consumers in a dose-dependent manner, that is, fortificant dose of 1000 IU or more a day is more effective. However, it should be noted that all the studies included in this meta-analysis were conducted under controlled conditions, that is, certain amount of the fortified food for a limited period of intervention. For a mass fortification programme, therefore, determination of the fortificant dose is crucial for which several questions must be answered including the vitamin D status of the target population and the goal concentration of 25(OH)D that must be attained by fortification[58].

Our analyses failed to show a superiority of vitamin D_3 over D_2 as a fortificant. The efficacy of these two isoforms has been the subject of several supplementation studies, most of which reported the higher efficacy of D_3[59,60,61,11]. However, these studies commonly used high-dose, low-frequency supplement intake. The shorter half-life of 25(OH)D_2, compared with 25(OH)D_3, may partly explain the higher efficacy of D_3 supplementation[62]. Furthermore, at least one study found the daily vitamin D supplementation, as compared with weekly and monthly, was more effective in improving vitamin D status of the elderly subjects[63]. Along the same line, a fortification study using daily intake of low dose of both D_2 and D_3 as fortificants did not find any significant difference between these two isoforms in raising circulating 25(OH)D concentrations[64]. Nevertheless, this finding should be interpreted cautiously due

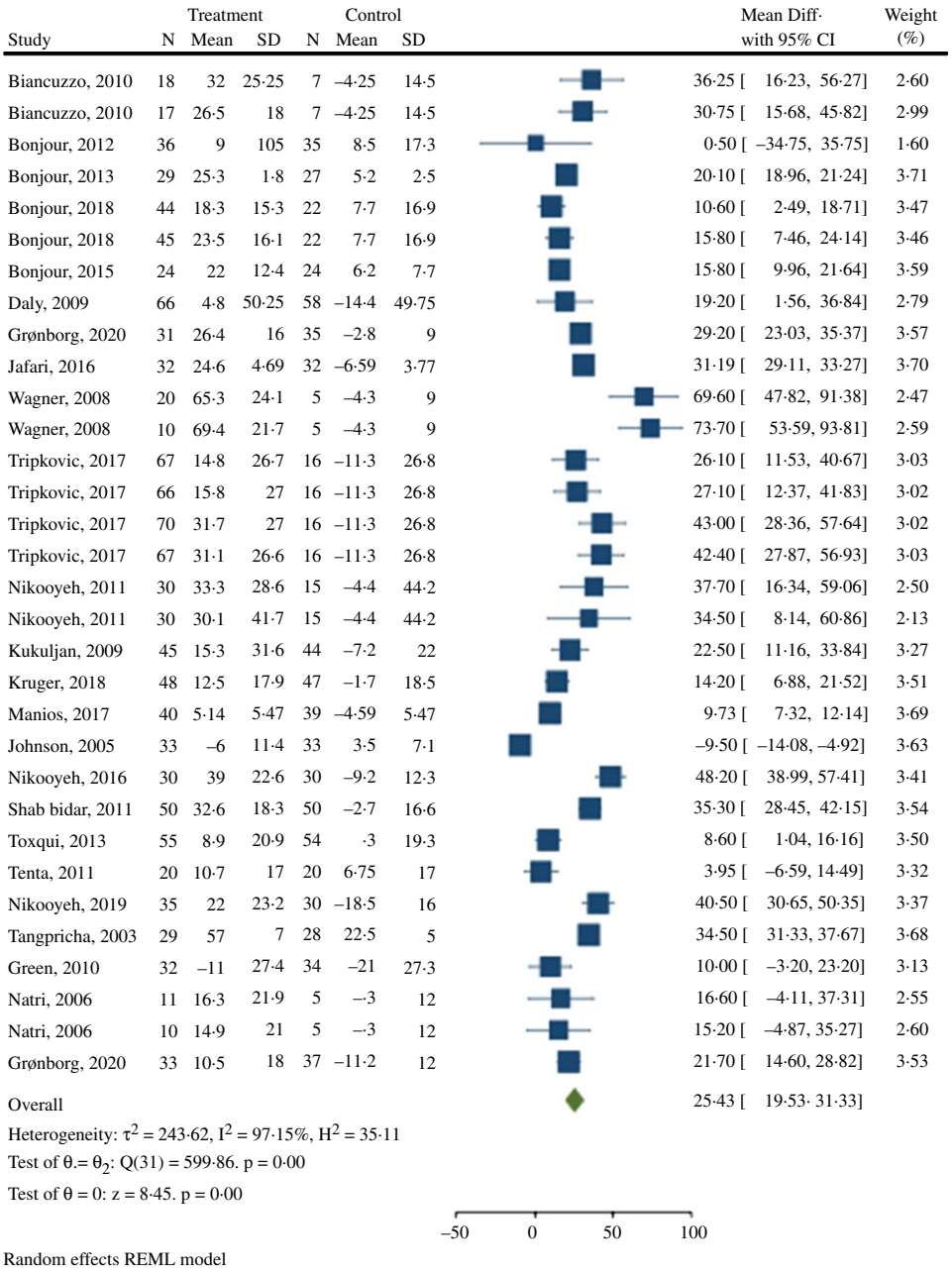

Fig. 4. Forest plot of the effect of vitamin D_2/D_3-fortified foods (with or without calcium) compared with control on absolute mean change.

to paucity of the fortification studies that have compared the efficacy of D_2 *v.* D_3.

Our findings indicate that duration of vitamin D-fortified product consumption longer than 12 weeks does not result in more increment in 25(OH)D concentration. The active metabolite of vitamin D, 1, 25$(OH)_2$D, is under homeostatic control. While increasing 25(OH)D following consumption of a fortified product will cause a shift to 1, 25(OH)2D production, an increase in 1, 25(OH)2D will induce metabolic clearance of 25(OH)D[65]. Consequently, once 25(OH)D reaches to its maximum concentration, continuation of vitamin D-fortified food consumption will just maintain the serum levels. This issue is especially important for a successful fortification programme as the half-life of 25(OH)D is just about 2–3 weeks[66].

Choosing a proper vehicle for fortification is a very critical issue for which several aspects must be taken into consideration including coverage and consumption of the fortified products as well as bioavailability issues[67,8]. While dairy products may be one of the best choices for fortification[68], especially in the countries with high milk consumption per capita[69], our analyses showed less efficacy of dairy products in terms of raising circulating 25(OH)D concentrations than oil, fruit juice and grain products. We have no explanation for this finding at present. Notwithstanding, we found out that the mean baseline

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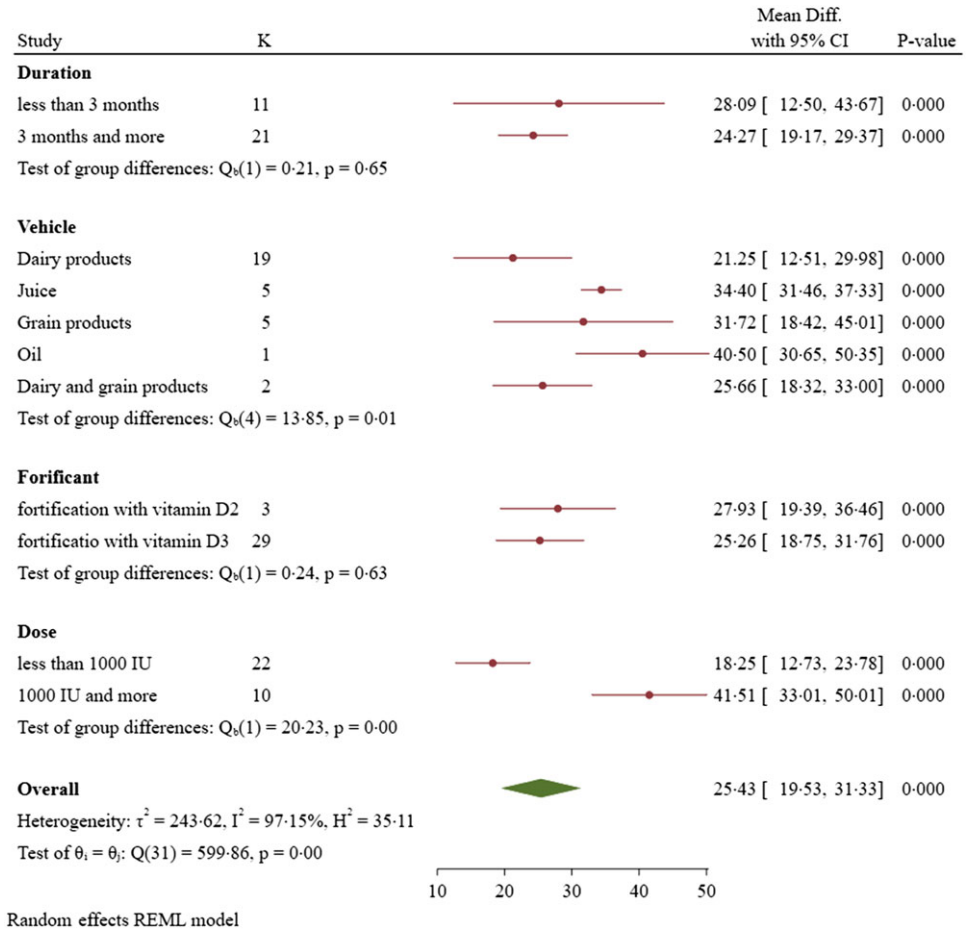

Fig. 5. Forest plot of subgroup analysis of the effect of vitamin D-fortified foods (with or without calcium) compared with control on absolute mean change.

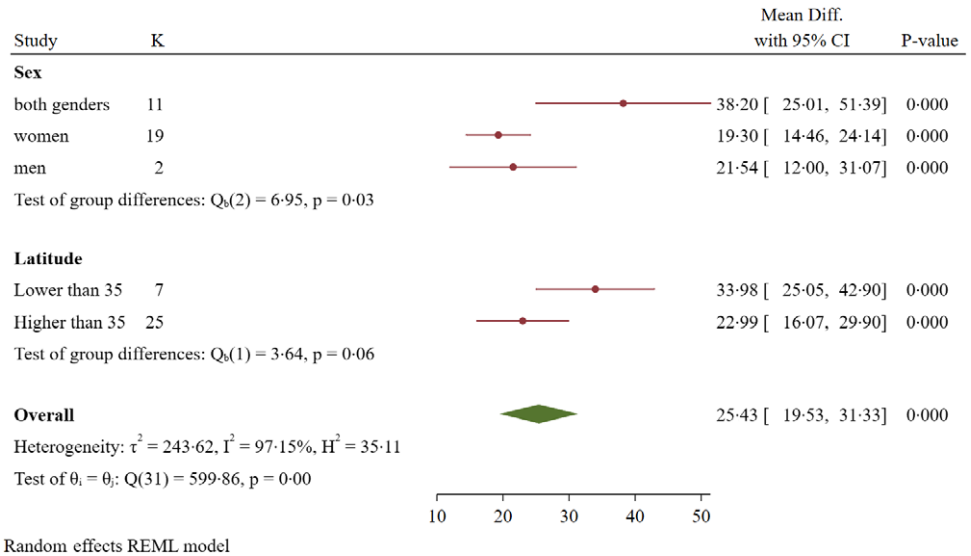

Fig. 6. Forest plot of subgroup analysis (based on sex of participants and latitude of study location) of the effect of vitamin D-fortified foods (with or without calcium) compared with control on absolute mean change.

Table 3. Multivariate meta-regression models (Coefficients and 95 % confidence intervals)

	Coefficients	95 % CI	*P*	R^2
Dose of fortificant (IU)	0·02	0·01, 0·022	<0·001	90·2
Age (years)	−0·48	−0·67, −0·29	<0·001	
Baseline 25(OH)D (nmol/l)	−0·47	−0·72, −0·22	<0·001	
Latitude (degree)	−0·22	−0·48, 0·03	0·096	
BMI (kg/m^2)	0·63	−0·62, 1·89	0·321	

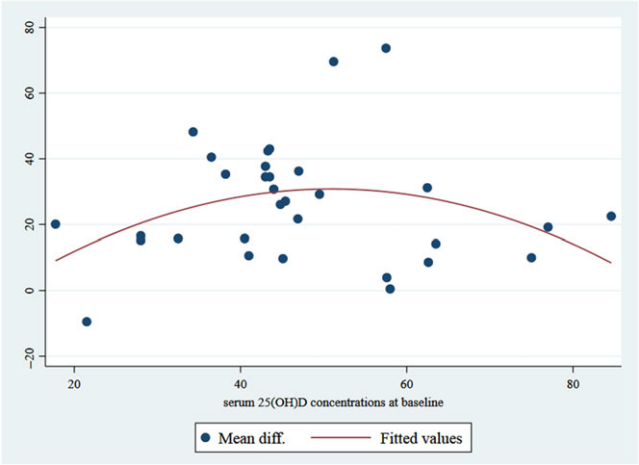

Fig. 7. Association between treatment effect and 25(OH)D concentrations (nmol/l) at baseline.

25(OH)D concentration in the studies of fortified dairy products was significantly higher than other studies (51 (SD 17·4) *v.* 40·4 (SD 6·9) nmol/l, $P = 0·049$). This may, at least in part, explain the reason of this observation. Though juices may be considered as a good vehicle for market-driven fortification, it can hardly be considered as a suitable vehicle for mass fortification due to its sugar content and also various consumption patterns among different population subgroups[70,71]. Edible oils, on the other hand, could be a suitable choice for fortification with certain micronutrients including vitamin D with the advantage of broad population coverage in many countries[30,72,73]. However, high diversity of both amount and type of household edible oils in most countries may potentially cause several technical problems for using them as a vehicle in a mass fortification programme[74,75,76]. Moreover, due to scarcity of evidence on efficacy of vitamin D-fortified cooking oils, more studies are warranted. Nevertheless, edible oils can be considered as appropriate vehicles for market-driven fortification thus contributing in overall amount of vitamin D intake[77]. Grain products including bakery wheat flour, on the other hand, can be regarded as an appropriate vehicle for vitamin D fortification, especially in the countries wherein bread is a staple food and there is an ongoing flour fortification programme for other micronutrients like Fe and folate[42,78].

The results of this meta-analysis revealed more efficacy of those fortification studies whose subjects were of both sexes than the studies conducted just on women. This may, at least in part, be explained by the higher percentage of body fat mass in women than in men[79] and the inverse association between percentage of fat mass and circulating 25(OH)D[80,81].

We found an inverse association between age and the initial circulating 25(OH)D concentrations of the participants and the rise in serum 25(OH)D concentrations following the consumption of vitamin D-fortified foods. The effect of age on vitamin D metabolism is especially noticeable as decreased dermal synthesis and intestinal absorption of vitamin D due to ageing have already been documented[82,83]. As dietary intake may decrease with ageing[84,85], D fortification of foodstuffs may be less efficient in the elderly people. Effectiveness of vitamin D-fortified foodstuffs in this age group needs more investigations. The effect of initial (pre-intervention) concentration of serum 25(OH)D on the amount of rise of circulating 25(OH)D following vitamin D intake has been already reported and reconfirmed recently[86,87]. Actually, this is a homeostatic mechanism through which the enzyme 24-hydroxylase is activated whenever the conversion of 25(OH)D to its active form 1, 25(OH)2D reaches to its threshold, whereby catabolism of both metabolites is enhanced[88].

Several dose–response studies have reported various amounts of 25(OH)D rise following vitamin D intake (mostly in the form of supplement). One study reported an average of 1·2 nmol/l increase in serum 25(OH)D for every 100 IU vitamin D in supplementation interval of 0–1000 IU/d[89], whereas another study suggested 5 nmol/l increase per 100 IU/d[90]. However, as mentioned earlier, the response to vitamin D intake is influenced by initial concentrations of 25(OH)D, age and BMI[83,87,89]. Therefore, our estimation of 2 nmol/l increase in 25(OH)D concentration for every 100 IU vitamin D intake per d, which is adjusted for all these variables, seems reasonable for designing mass fortification programmes.

Conclusion

With the high occurrence of vitamin D deficiency and commonly inefficient direct sun exposure around the world, we should inevitably rely on dietary approaches, including supplementation and food fortification, to improve vitamin D status of the general population. While supplement use has the disadvantages of potential risk of overdosing and poor adherence for several reasons including high costs which makes it less sustainable strategy[58], food fortification is indicated as the most sustainable and cost-effective approach to improve nutritional status of the whole community[15]. A study from the USA reported that 3·2 % of the general population use vitamin D supplements at high doses, that is, ≥100 μg (4000 IU)/d[91]. Nevertheless, food fortification has some disadvantages including lower effectiveness than supplements due to low consumption of the fortified foods in some subpopulations and/or suboptimal amount of the fortificant in the vehicle. The establishment of the effective dose of vitamin D fortificant considering its upper tolerable intake level and also selecting a suitable staple food(s) as a vehicle(s) is, therefore, necessary for a successful mass fortification

programme[92]. Our findings showed that vitamin D fortification of foodstuffs is an effective strategy to combat vitamin D deficiency, though the circulating 25(OH)D response to vitamin D-fortified food consumption can be under the influence of age, BMI and the baseline 25(OH)D concentrations. Notwithstanding, an average increase of 2 nmol/l increase in circulating 25(OH)D concentration for each 100 IU vitamin D intake per d is expected for general adult population. These findings can be beneficial for policymakers to tackle vitamin D deficiency through food fortification strategy.

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B. N., with the aid of T. N., designed the study and performed the searches and data extraction. T. N. and B. N. analysed and interpreted the data and were major contributors in writing the manuscript. Both authors read and approved the final manuscript.

The authors declare that there are no conflicts of interest.

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