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Using food fortification to improve vitamin D bioaccessibility and intakes

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Vitamin D intakes and status are low in many countries due to seasonal UVB exposure variation and the fact that few foods are naturally vitamin D rich. Data modelling studies show that vitamin D intakes increase with food fortification, and countries with mandatory fortification policies have higher vitamin D intakes and status compared to countries without. While many foods can be vitamin D fortified, vitamin D bioavailability differs depending on fortification methods, food structure and composition. Randomised controlled trials (RCT) report that vitamin D_2 bioavailability varies between foods, whereas vitamin D_3 is bioavailable from many foods. *In vitro* studies suggest that altering the lipid composition of fortified foods increases vitamin D_3 absorption. Olive oil increased vitamin D_3 absorption during *in vitro* digestion compared to other dietary oils. Additionally, when vitamin D_3 was incorporated into micelles formed from *in vitro* digestion of olive oil, more vitamin D_3 was absorbed compared to other dietary oils. However, in a human postprandial study, a preformed vitamin D_3 micelle dairy drink did not increase vitamin D_3 absorption, and a vitamin D_3 olive dairy drink increased vitamin D_3 absorption in vitamin D insufficient participants only. Action is urgently needed to improve vitamin D intakes and status worldwide. Food fortification improves vitamin D intakes; however, fortification strategies unique to each country are needed. This review will synthesise the literature describing data modelling and intervention trials that assess the safety and efficacy of vitamin D fortification strategies, and those manipulating food composition to alter vitamin D bioavailability from fortified foods. Additionally, RCT examining the impact of vitamin D fortification strategies on vitamin D intakes and status over time are reviewed.

Key words: Vitamin D: Food fortification: Lipids

Vitamin D is a fat-soluble nutrient with steroid-like actions in the body, and is essential for calcium homeostasis and bone metabolism. Vitamin D is also involved in immune function and glucose metabolism, and low vitamin D status is associated with an increased risk of several diseases including diabetes, cancer, CVD and multiple sclerosis[1–3]. Vitamin D has two vitamers, ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). Vitamin D_2 and D_3 are metabolised in the same way, undergoing a two-step hydroxylation in the liver and kidneys to produce 25-hydroxyvitamin D (25(OH)D) and then 1,25-dihydroxyvitamin D[4]. Vitamin D_3 is synthesised in the skin following UVB ray exposure. Endogenous vitamin D_3 synthesis does not always meet physiological needs due to location, age, skin-protective practices or skin pigmentation[5]. Therefore, dietary vitamin D is important to meet minimum requirements. Vitamin D status is measured via circulating 25(OH)D

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; FA, fatty acids; RCT, randomised controlled trial.
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concentrations and the Institute of Medicine define 25(OH)D >50, <50 and <30 nmol/l as vitamin D sufficient, insufficient and deficient, respectively[6]. Countries at northern latitudes tend to have higher rates of vitamin D insufficiency. In Ireland, 27 % of older adults are vitamin D insufficient during the summer months, increasing to 59 % during the winter months when UVB exposure is low[7]. In addition, the mean daily intake of vitamin D for older adults in Ireland is 6·9 ± 10·5 μg, with 87 % of men and 77 % of women having intakes below the RDA of 15–20 μg[8,9].

Dairy products, bread and breakfast cereals are the most commonly vitamin D fortified foods. In countries with no mandatory fortification policy, data modelling shows that vitamin D food fortification can improve vitamin D intakes[10]. In Finland, for example, data modelling studies led to a mandatory vitamin D food fortification policy which increased population 25(OH)D concentrations by 18 nmol/l[10,11]. However, food matrix and composition may alter vitamin D absorption and bioavailability[12,13], thus proposed fortification strategies may not be as successful as documented in data modelling studies. Therefore, before mandatory vitamin D food fortification policies are implemented, we need a more complete understanding of vitamin D absorption and how we can manipulate fortified foods to maximise vitamin D absorption. Increasing mandatory vitamin D food fortification policy effectiveness will increase population 25(OH)D concentrations and potentially lead to other health benefits for older adults. This review will synthesise the literature describing data modelling exercises to determine the impact of vitamin D fortification scenarios, the potential to manipulate fortified foods to improve vitamin D absorption and randomised controlled trials (RCT) that compare the effect of different types of fortified foods on the vitamin D status in an attempt to evaluate the potential of using vitamin D fortification to improve vitamin D bioaccessibility, intakes and status.

Increasing vitamin D intakes using food fortification

Increasing dietary vitamin D intakes is most effective at improving vitamin D status as UVB exposure varies across countries and seasons and carries skin cancer risk. However, supplement compliance and dietary vitamin D intake from natural food sources are low[7,14]. Therefore, policy makers, researchers and manufacturers must look to commonly consumed foods when considering vitamin D fortification. Vitamin D_2 or D_3 can be added to foods using traditional fortification or biofortification. Traditional fortification usually involves the addition of a vitamin D premix to foods during processing in controlled amounts[15]. Premixes are a blend of vitamins and minerals in a carrier, which may be an oil blend, dried dairy powder or dried grains, depending on the food product. Biofortification typically involves increasing the vitamin D content of animal products, such as eggs, meat or fish, by supplementing animal diets with vitamin D, or by animal or mushroom UV exposure[15,16]. This review will focus on traditional vitamin D food fortification and will indicate vitamin D_2 or D_3. Vitamin D fortification policies vary worldwide and can be classified into three groups: mandatory fortification (implemented in Canada and Finland), voluntary fortification (implemented in Ireland and the UK) and limited fortification (remainder of Europe and Asia)[17]. Mandatory vitamin D fortification policies are implemented as few foods are naturally vitamin D rich, supplement compliance is low and mandatory food fortification does not require behaviour change[18,19]. Vitamin D fortification policies successfully increase vitamin D intakes, and countries with mandatory fortification policies have intakes that are about 2–3 μg greater than those with voluntary food fortification[11,14,20,21].

Vitamin D food fortification data modelling studies have resulted in successful national fortification policies[10,11]. Finland introduced mandatory vitamin D fortification of liquid dairy products (1 μg/418·4 kJ (100 kcal)) and fat spreads (20 μg/100 g) following a modelling study reporting a potential increase in vitamin D intakes of about 21 μg/d when several foods were fortified simultaneously[10]. A subsequent study using nationally representative data reported that vitamin D intakes doubled as a result of mandatory fortification[11]. Several other countries without a mandatory vitamin D fortification policy are now examining the potential impact of fortification across different population subgroups (Table 1)[22,23]. For example, a Danish study modelled seven strategies with a combination of fish, vitamin D_3 fortified foods and dietary supplements[22]. With fortified foods alone, the 5th and 99th percentiles for vitamin D intake were 21·0 and 23·6 μg, respectively[22]. Similarly, a Belgian data modelling study using national survey data examined the effect of sixty-three fortification combinations including breakfast cereals, bread, fruit juice, fats and oils, milk and milk beverages, yogurt and cream cheese[23]. All six food groups fortified at 0·47 μg/4·184 kJ (1 kcal) were safest and most effective for all population groups[23]. Fortification above 0·47 μg/4·184 kJ (1 kcal) resulted in intakes above the tolerable upper limit in children, highlighting the importance of fortification modelling across all cohorts before implementation[23].

Although mandatory folic acid fortification was recently announced in the UK, a vitamin D policy does not yet exist. Therefore, Allen *et al.* modelled milk and starch vitamin D_2 and vitamin D_3 fortification using UK National Diet and Nutrition Survey data[24]. Vitamin D fortification of starch was modelled at a concentration of 5–30 μg/100 g and milk in a range of 0·5–7 μg/100 g[24]. Fortifying wheat starch with 10 μg/100 g was most effective at increasing population vitamin D intakes whilst keeping the entire sample below the tolerable upper limit; increasing the mean daily intake from 3·7 to 10·8 μg and reducing the proportion of the population not meeting intake recommendations from 93 to 50 %[24]. Contrary to other studies that fortified multiple foods[10,22], fortifying milk and starch together at a lower concentration was not as effective as fortifying starch only at a higher concentration[24]. Another very recent study also using National Diet and Nutrition Survey data reports that cow's milk vitamin D_3 fortification

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Table 1. Characteristics of vitamin D food fortification data modelling studies

Ref	Year	Region	Population group	Food	Vitamin D dose
[10]	2007	Finland	Adults	Dairy products, bread juice, cereals, jam, sweets, soft drinks, biscuits, mineral water, salad dressings and snacks	0·72–5·50 μg/418·4 kJ (100 kcal)
[66]	2013	Germany	Infants, children, adults and older adults	Milk and milk products, bread and juice	3·1–249·9 μg/100 g
[24]	2015	UK	Infants, children, adults and older adults	Wheat starch and milk containing foods	2·5–10·0 μg/100 g
[26]	2017	Ireland	Children	Cow's milk	1·0–2·0 μg/100 ml
[22]	2018	Denmark	Women	Yogurt, cheese, eggs and crispbread	20 μg/d total
[23]	2019	Belgium	Children and adults	Breakfast cereals, fats, juices and dairy	0·0–1·0 μg/100 g
[67]	2019	England and Wales	Infants, children, adults and older adults	Starch	10·0 μg/100 g
[27]	2020	Ireland	Older adults	Cow's milk and bread	1·5–5·0 μg/100 g
[25]	2021	UK	Children, adults and older adults	Cow's milk	1·0–2·0 μg/100 ml
[68]	2021	The Netherlands	Adults	Bread, milk*, oils, juices, spreads, breakfast cereals	Not stated

* Milk type not stated.

in the UK would increase the proportion meeting intake recommendations by about 12 %[25]. Lastly two studies have modelled the effect of fortification on vitamin D intakes in preschool children and older adults in Ireland[26,27]. In preschool children, low-dose cow's milk fortification increased intakes by 1·9–4·3 μg[26]. Similarly in older adults, mandatory cow's milk vitamin D_3 fortification would increase intakes by 2–4 μg and bread vitamin D_3 fortification would increase intakes by 3–9 μg[27]. While the results from these studies are promising, modelling has not been completed in school-aged children, teenagers or adults in Ireland, thus the results are not applicable to the entire population. Regardless, these studies provide evidence that vitamin D food fortification could effectively increase vitamin D intakes in Ireland. Although modelling studies are promising, an ineffective 'blanket' approach is often used and targeting foods such as dairy products does not account for non-consumers or lower consumption rates in certain population groups[28]. Before fortification is implemented, modelling studies should assess the potential of fortifying multiple foods groups, and RCT should demonstrate their effectiveness on vitamin D status over time.

Increasing vitamin D bioaccessibility and bioavailability

Older *in vitro* and radiolabelled studies suggest that vitamin D absorption from a usual diet is about 80 %, but beyond that very little is known about vitamin D absorption from fortified foods[29–32]. Most of the published literature dates to the 1970s and 1980s and most studies compare vitamin D absorption in disease cases where absorption might be compromised (Table 2)[33–39]. One of the first studies describing vitamin D_3 absorption in healthy participants reported the importance of the lipid component of the food/meal for vitamin D absorption[35]. However, there is a significant gap in the literature until very recently when results from two postprandial studies were published[40,41]. Dawson-Hughes *et al.* showed that consuming a vitamin D_3 supplement with a lipid-containing meal increases absorption by about 32 %[40]. The second study compared the effects of 25(OH)D or vitamin D_3 fortification in a high-lipid dairy drink[41]. Postprandial 25(OH)D concentrations were significantly higher after the 25(OH)D drink compared to the vitamin D_3 drink. The results from this study suggest that vitamin D_3 absorption and/or hydroxylation is incomplete when added in a traditional form and provides evidence that 25(OH)D fortification could be considered as an alternative[41]. Although limited, this research suggests that lipids are important for vitamin D absorption and that dairy drinks are an effective delivery system.

Table 2. Characteristics of postprandial radiolabelled vitamin D studies

Ref	Year	*n*	Food	Population group
[36]	1972	13	Milk*	Patients with epilepsy
[35]	1978	20	Lipid altered meals	Healthy
[33]	1980	18	Milk*	Patients with GI disease
[34]	1981	12	Milk*	Healthy
[37]	1982	16	Milk*	Patients with liver disease
[38]	1987	13	Enteral feed	Patients with liver disease
[39]	1991	16	Enteral feed	Patients with Crohn's disease

* Milk type not stated.

Building on the human evidence, recent *in vitro* studies examined the impact of different fatty acids (FA) and combinations of FA on vitamin D_3 absorption[12,42,43]. For example, based on previous cholesterol work and the fact that vitamin D is derived from cholesterol, Goncalves *et al.* hypothesised that vitamin D_3 micelle formation could be altered by different dietary lipids[12]. Using Caco-2 cells, the authors examined the effect of single FA, mixed FA mimicking dietary oils, and

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micelles produced *in vitro* on vitamin D_3 uptake and efflux from cells[12]. Results showed that long-chain FA and PUFA decreased vitamin D_3 absorption in this model, whilst MUFA, particularly oleic acid, increased absorption[12]. There were no negative effects on uptake when long-chain FA were given in combination with other FA[12]. Oleic acid also improved vitamin D_3 secretion from the enterocyte which was in line with previous findings, and the authors hypothesised that this is due to increased chylomicron synthesis[12,44]. MUFA decreased mRNA expression of NPC1L1, which is essential for cholesterol (and potentially vitamin D_3) transport across the brush border membrane of the intestine, but oleic acid had no effect[12]. As a result, the authors suggest that pre-formed micelles comprised of oleic acid would improve vitamin D_3 absorption[12].

Another study examined vitamin D_3 bioaccessibility from lipid emulsions[42]. The authors used long-chain TAG and medium-chain TAG oils rather than free FA, and an *in vitro* digestion model rather than a cell model[42]. Despite these differences, results were similar to that of Goncalves *et al.*[12], suggesting that a chain length of 16–18 carbons is optimal for vitamin D_3 absorption[42]. The authors hypothesised that this is due to long-chain TAG forming mixed micelles that can accommodate large molecules, such as vitamin D_3, and have a higher solubility[42,45]. A more recent *in vitro* study examined the effects of pre-formed oleic acid vitamin D_3 micelles or vitamin D_3 in oil mixtures on vitamin D_3 bioaccessibility in a Caco-2 model[43]. The results support those of Goncalves *et al.*[12], reporting higher vitamin D_3 bioaccessibility and cellular uptake from the pre-formed micelle compared to the oil mixture[43]. To date, only one human study has examined how different lipids effect vitamin D_3 absorption[46]. This cross-over postprandial study examined changes in 25(OH)D following a vitamin D_3 fortified olive oil, fish oil or non-lipid dairy drink compared to a preformed vitamin D_3 micelle dairy[46]. The vitamin D_3 olive oil dairy drink increased 25(OH)D in vitamin D-insufficient participants, but there was no change in 25(OH)D following other fortified drinks[46]. This research suggests that the lipid/FA composition of fortified foods will impact vitamin D_3 absorption, and that the effect is different depending on vitamin D status[46]. Although these results show potential for improving vitamin D absorption by manipulating the lipid delivery system within a food, they also highlight the gap in the literature; as currently no studies have examined these effects using an RCT design. Therefore, before these *in vitro* results can inform food fortification, we must perform more well-designed human postprandial studies and RCT.

Vitamin D food fortification randomised controlled trials

A large body of high-quality work reports the effects of vitamin D supplementation on 25(OH)D[47,48]; however, this review focuses on vitamin D food fortification specifically. Most vitamin D food fortification trials focus on a single food group like some modelling studies[25,26]. In 2012, Black *et al.*[49] updated a systematic review and meta-analysis on the efficacy of vitamin D fortified foods published by O'Donnell *et al.* in 2008[50]. The updated meta-analysis reports a treatment effect of 19·4 nmol/l and an increase of 1·2 nmol/l per 1 μg vitamin D in fortified foods[49]. However, there was significant study heterogeneity due to different population groups, vitamin D fortification concentrations and study durations. Since 2012, several vitamin D fortification studies have been published. The next section of this review examines the more recent studies and summarises the available evidence to support vitamin D food fortification strategies in non-pregnant adults (Tables 3 and 4).

Vitamin D_2 v. *vitamin D_3 fortification*

There is a debate as to whether or not vitamin D_2 and vitamin D_3 supplementation are bioequivalent. A recent meta-analysis concluded vitamin D_3 is superior to D_2 when delivered as supplements or inter-muscular injections[47], but newer food fortification studies yield mixed results[13,51–54]. One food fortification RCT found no difference in vitamin D_2 bioavailability between mushroom soup and supplements[52]. Another study compared 25(OH)D concentrations following a 4-week intervention with 5 or 10 μg vitamin D_2 or D_3 fortified malted drinks[53]. Data analysis indicated that 1 μg of vitamin D in a fortified malted drink resulted in an about 2 nmol/l increase of 25(OH)D, with equal increments in the D_2 and D_3 groups[53]. However, as there were only eight participants in each group, these results should be confirmed in a larger cohort[53]. In contrast, another study showed that vitamin D_2 from irradiated yeast is not bioavailable[13]. Participants consumed a regular bread and placebo supplement, regular bread and vitamin D_2 supplement, regular bread and vitamin D_3 supplement or vitamin D_2 bread and placebo supplement daily for 8 weeks. Total 25(OH)D did not increase from baseline in the vitamin D_2 bread and placebo group but increased by 9·6 and 17·0 nmol/l in the vitamin D_2 and D_3 supplement groups, respectively[13]. The reason for the poor bioavailability of vitamin D_2 irradiated yeast is unclear but may be due to the baking process or vitamin D_2 being indigestible in this form[13]. In contrast, another study reports vitamin D_3 bioavailability from bread when a vitamin D_3 premix was added to starch, rather than using irradiated yeast[54]. Participants consumed either 25 μg fortified bread with placebo supplement, placebo bread with a 25 μg vitamin D supplement or placebo supplement and bread for 8 weeks[54]. There was no difference in 25(OH)D increase between the vitamin D supplement or vitamin D bread groups[54].

Tripkovic *et al.* also compared vitamin D_2 and D_3 when consumed from a fortified orange juice or biscuit[51]. Participants consumed either a placebo juice and biscuit, 15 μg vitamin D_2 juice and placebo biscuit, placebo juice and a 15 μg vitamin D_2 biscuit, placebo biscuit and 15 μg vitamin D_3 juice or finally a 15 μg vitamin D_3 biscuit and placebo juice for 12 weeks. Serum 25(OH)D changed by 14·8, 15·8, 31·8 and 31·1 nmol/l for the vitamin D_2 juice, vitamin D_2 bread, vitamin D_3 juice

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Table 3. Characteristics of vitamin D fortification randomised controlled trials

Ref	Year	*N*	Food	Vitamin D dose	Location	Population	Age (years)	Duration (weeks)	Season	25(OH)D analysis
[52]	2011	24	Mushroom soup	700 μg/portion	Germany	Adults	<45	5	Jan–Mar	RIA
[53]	2012	40	Malted drinks	5 μg/portion 10 μg/portion	UK	Adults	18–65	4	Feb–Mar	UPLC-MS/MS
[55]	2013	165	Cow's milk	5 μg/portion	Spain	Women	18–35	16	Jan–May	ELISA
[58]	2014	49	Cow's milk	2 μg/portion	Japan	Women	18·5*	8	May–Jul	RIA
[63]	2014	152	Snack bar	25 μg/portion	USA	Adults	18–72	9	Feb–Apr	RIA
[69]	2015	335	Biscuit and juice	15 μg/portion	UK	Women	20–64	12	Oct–Mar	HPLC-MS/MS
[59]	2015	102	Mozzarella	0·75 μg/portion 100 μg/portion	Canada	Adults	18–70	10	Feb–Apr	CLIA
[13]	2016	33	Bread	25 μg/portion	Finland	Adults	20–40	8	Feb–Apr	IEMA
[54]	2016	90	Bread	25 μg/portion	Iran	Adults	20–60	8	Feb–Mar	HPLC
[61]	2017	133	Yogurt	5 μg/portion 10 μg/portion	France	Women	55–75	14	Jan–Aug	ELISA
[60]	2017	79	Gouda	5·7 μg/portion	Greece	Women	55–75	8	Jan–Mar	LC–MS/MS
[28]	2019	143	Yogurt, cheese, eggs and crisp bread	20 μg/portion	Denmark	Women	18–50	12	Jan–Mar	LC–MS/MS
[56]	2019	133	Cow's milk	15 μg/portion	Malaysia	Women	30–50	52	Not reported	IDLC-MS/MS
[62]	2019	40	Yogurt	5 μg/portion	France	Women	65+	13	Sep–Jan	RIA
[57]	2020	144	Cow's milk	7·5 μg/portion	Australia	Women	45–65	17	All	LC-MS/MS

Ref, reference; LC-MS/MS, liquid chromatography tandem MS; IDLC-MS/MS, isotope dilution liquid chromatography tandem MS.
* Mean age.

and vitamin D_3 bread groups, respectively[51]. Vitamin D in both forms was efficacious from orange juice and biscuits, however vitamin D_3 bioavailability was superior[51]. Results from these studies suggest that food structure, fortification type and the vitamer impact vitamin D bioavailability. This level of knowledge is important for targeting improved status for subgroups of the population, particularly those who avoid certain food groups, e.g. vegetarians.

Dairy vitamin D fortification studies

Other studies focus on vitamin D fortification of dairy products due to cost-effectiveness, high consumption rates and bioavailability (Table 4). Some countries, such as Canada and Finland, already mandate vitamin D fortification of all fluid milks[11,17]. However, other countries have published data supporting fortification where it is not yet mandated. In Spain, a 5 μg vitamin D fortified skimmed cow's milk daily for 16 weeks increased by 25(OH)D concentrations by 8·9 nmol/l with high compliance and no adverse side effects[55]. In a Chinese cohort, a 15 μg fortified cow's milk increased 25(OH)D concentrations by 7·6 nmol/l over a 1-year period[56]. In Australia, a 7·5 μg vitamin D fortified cow's milk increased 25(OH)D concentrations by 9·1 nmol/l after 4 months[57]. Lastly, in Japan, a 2 μg vitamin D fortified cow's milk consumed daily for 8 weeks increased serum 25(OH)D by 56 %, although this figure likely overestimates the impact of the fortified food as the data were collected during summer months[58]. All of these studies report a significant increase in 25(OH)D concentrations in response to vitamin D fortified milks; however, it is worth noting that all studies recruited female participants only. The bias towards female recruitment is likely due to the role vitamin D plays in bone health and the higher risk of osteoporosis in females. Regardless, it will be important to determine the efficacy of vitamin D fortified foods for males also, particularly if a mandatory vitamin D fortification policy is expected.

Other studies have used other dairy foods to deliver vitamin D. A Canadian study reported increases in serum 25(OH)D when participants consumed a cheese pizza once weekly for 8 weeks, fortified with 5 or 700 μg of vitamin D[59]. Pizza containing the higher dose of vitamin D increased serum 25(OH)D concentrations by 72·9 nmol/l; however, very high-dose fortification is unlikely from a policy perspective. In contrast, an 8-week study with fortified Gouda[60] and a 6-month study with fortified yogurt[61] in the range of 5–10 μg improved 25(OH)D concentrations to sufficiency with no adverse effects reported. Similarly, in a fortification trial in France, a daily 5 μg vitamin D_3 yogurt was effective at maintaining baseline 25(OH)D concentrations of older women during the winter months[62]. These results show that a vitamin D fortified yogurt is effective at preventing the expected seasonal decline in 25(OH)D in vitamin D-sufficient participants and could be used to maintain year-round vitamin D status. This recent research supports the safety and efficacy of dairy product vitamin D fortification and its effectiveness at increasing 25(OH)D concentrations and preventing seasonal declines in vitamin D status in vitamin D-sufficient groups.

Other food vitamin D fortification studies

Finally, other studies have examined snack bar[63], bread and juice[28] vitamin D fortification, accounting for non-consumers of dairy at a population level. In one study, vitamin D-sufficient participants undergoing army

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Table 4. Circulating 25(OH)D in vitamin D fortification randomised controlled trials

		Intervention group				Placebo control group			
Ref	Year	Food	Baseline 25(OH)D (nmol/l)	Post 25(OH)D (nmol/l)	Δ 25(OH)D (nmol/l)	Food	Baseline 25(OH)D (nmol/l)	Post 25(OH)D (nmol/l)	Δ 25(OH)D (nmol/l)
(52)	2011	D_2 mushroom soup	34·0 ± 11·0	56·7 ± 7·2	22·7±[b]	Placebo soup	38·7 ± 14·2	28·7 ± 8·7	−10·0 ± [b]
		D_2 supplement	28·7 ± 10·0	58·0 ± 11·2	29·3±[b]				
(53)	2012	5 μg D_2 malted drink	48·0 ± 26·6	52·9±[b]	4·9 (−2·3, 12·7)	Placebo malted drink	62·9 ± 20·8	63·2 ± 18·3	0·3 ± [b]
		5 μg D_3 malted drink	41·9 ± 14·1	55·5±[b]	13·6 (4·1, 23·0)				
		10 μg D_2 malted drink	31·3 ± 22·1	43·2±[b]	11·9 (2·7, 21·2)				
		10 μg D_3 malted drink	30·9 ± 29·1	50·6±[b]	19·7 (9·4, 30·1)				
(55)	2013	D_3 skimmed cow's milk	62·3 ± 20·8	71·2 ± 21·1	8·9±[b]	Placebo cow's milk	62·9 ± 20·8	59·4 ± 19·6	−3·5 ± [b]
(58)	2014	Vitamin D cow's milk	23·1 ± 4·7	36·0 ± 8·4	12·9±[b]	No placebo control group			
(63)	2014	D_3 snack bar	57·9 ± 25·7	69·9 ± 15·0	12·0±[b]	Placebo bar	51·5 ± 20·3	61·4 ± 13·8	9·9 ± [b]
(69)	2015	D_2 juice, placebo biscuit	[a]44·9 (37·8, 52·0)	[a]59·7 (53·9, 65·4)	[a]14·8 ([b])	Placebo juice, placebo biscuit	[a]44·8 (37·5, 52·1)	[a]33·5 (27·8, 39·3)	[a]−11·2 (16·7, −5·8)
		Placebo juice, D_2 biscuit	[a]46·1 (38·9, 53·4)	[a]61·9 (56·0, 67·7)	[a]15·8 ([b])				
		D_3 juice, placebo biscuit	[a]42·3 (35·4, 49·2)	[a]74·0 (68·1, 79·9)	[a]31·7 ([b])				
		Placebo juice, D_3 biscuit	[a]41·9 (34·9, 48·9)	[a]73·0 (67·1, 78·9)	[a]31·1 ([b])				
(59)	2015	5 μg D_3 mozzarella	48·9 ± 24·4	53·8 ± 22·9	5·1 ± 11·1	No placebo control group			
		700 μg D_3 mozzarella	44·2 ± 21·1	117·4 ± 23·5	72·9 ± 21·9				
(13)	2016	D_2 bread, placebo	64·6 ± 15·1	Not stated	Remained at baseline	Placebo bread + supplement	66·2 ± 18·6	Not stated	Remained at baseline
		Bread, D_2 supplement	63·5 ± 11·3	Not stated					
		Bread, D_3 supplement	66·6 ± 14·8	Not stated	9·6±[b]				
					17·0±[b]				
(54)	2016	D_3 bread, placebo supplement	33·9 ± 21·9	72·9 ± 23·1	39·0 ± 22·6	Placebo bread + supplement	34·7 ± 30·5	25·4 ± 21·8	−9·2 ± 12·3
			35·0 ± 38·7	63·9 ± 31·0	28·9 ± 31·2				
		Bread, D_3 supplement							
(61)	2017	5 μg D_3 yogurt	36·5 ± 14·6	52·6 ± 17·0	16·1±[b]	Placebo yogurt	36·4 ± 15·8	49·5 ± 18·8	13·1 ± [b]
		10 μg D_3 yogurt	35·9 ± 14·8	58·9 ± 19·9	23·0±[b]				
(60)	2017	D_3 cheese	47·3 ± 15·2	52·5 ± 12·0	5·14±[b]	Placebo cheese	42·9 ± 17·7	38·3 ± 18·9	−4·59 ± [b]
(28)	2019	D_3 yogurt, cheese, eggs and crispbread	53·3 ± 17·0*	77·8 ± 14·0*	26·4 ± 16·0*	Placebo yogurt, cheese, eggs & crispbread	46·2 ± 19·0*	44·0 ± 17·0*	−2·8 ± 9·0*
			44·5 ± 21·0†	54·7 ± 18·0†	10·5 ± 18·0†		49·0 ± 23·0†	54·7 ± 18·0†	−11·2 ± 12·0†
(56)	2019	D_3 cow's milk drink	53·2±[b]	60·8±[b]	7·6±[b]	Placebo cow's milk	48·6±[b]	55·0 ± [b]	6·4 ± [b]
(62)	2019	D_3 yogurt	52·6 ± 14·3	Not stated	Remained at baseline	Placebo yogurt	47·0 ± 16·2	Not stated	Not stated
(57)	2020	D_3 cow's milk	61·6 ± 21·4	Not stated	9·1 (5·7, 12·4)	Placebo cow's milk	64·2 ± 24·7	Not stated	−11·8 (−15·3,−8·2)

Ref, reference; 25(OH)D, 25-hydroxyvitamin D.
Data reported as mean ± standard deviation unless otherwise state.
[a] 95% CI; [b]data not reported.
* Danish cohort.
† Pakistani cohort.

combat training consumed either a placebo snack bar or a bar fortified with 1032 mg calcium and 15 μg vitamin D for 9 weeks[63]. Vitamin D was bioavailable from the bar and effectively maintained vitamin D sufficiency, as serum 25(OH)D increased by 4·8 nmol/l in the treatment group, and participants did not experience any adverse effects[63]. Lastly, a large RCT examined the effectiveness of multiple food fortification in a Danish and Pakistani cohort[28]. A combination of yogurt, cheese, eggs and crisp bread provided participants with 20 μg/d, increasing 25(OH)D by 26·4 and 10·5 nmol/l in Danish and Pakistani participants, respectively[28]. The lower 25(OH)D increment in the Pakistani cohort was due to poor compliance, highlighting that low-dose fortification is effective but also the importance of targeting appropriate foods for different population cohorts[28]. RCT examining compliance and efficacy of foods such as snack bars and eggs are essential to account for non-consumers of milk and bread, and consumers of ethnic diets. Dietary patterns should also be examined in minority groups and highly consumed foods should be targeted for food fortification to ensure maximal effectiveness in these minority ethnic groups.

Future directions of vitamin D food fortification

Vitamin D fortification policies are urgently needed worldwide, as vitamin D intakes and status remain low in many countries, particularly in those at northern latitudes[7,21]. Countries without a vitamin D fortification policy can model national survey data to determine the most effective and safe fortification policy, when implemented alongside supplementation and natural vitamin D sources. Once target foods have been identified using data modelling, maximal vitamin D absorption from these foods should be ensured before a fortification policy is implemented. Maximal vitamin D absorption from fortified foods may be achieved by altering food structure or composition, but more human absorption studies are needed to confirm hypotheses derived from *in vitro* data before implementation as part of a fortification policy. These modelling and absorption studies should then be translated into RCT which can determine food fortification safety and efficacy, and account for variations in vitamin D food content and eating patterns across countries, as well as inter-individual response to vitamin D treatments[64]. The resulting vitamin D fortification policy should result in a high proportion of the population meeting intake recommendations, with little or no individuals exceeding the 100 μg tolerable upper limit. These policies are most effective if they account for variations in staple foods, ethnic diets and non-consumers of certain food groups, such as vegetarians and vegans. Lastly, multiple foods should be fortified at a low dose, as this increases population vitamin D intakes and status most effectively[11].

Food fortification policies are most effective if monitored and re-evaluated after implementation. Therefore, national survey data should be analysed after policy implementation to determine how fortification is affecting intakes. Fortification strategies can be remodelled if intakes or status remain low, and policy can be revised accordingly. However, this is only possible with a rolling national survey programme, such as the National Diet and Nutrition Survey within the UK[21]. Vitamin D fortification policies should also be supported financially by the government, so the financial burden does not fall on consumers, as social class and wealth are predictors of vitamin D status[65]. Vitamin D food fortification reduces skeletal and non-skeletal diseases incidence, and the healthcare savings outweigh government costs associated with vitamin D food fortification[2]. Lastly, vitamin D policies should be supported by nationwide education campaigns to increase public awareness of the effects of low vitamin D status, vitamin D supplementation and vitamin D sources. These education programmes should focus on vitamin D functions and sources, recommended daily intakes and tolerable upper limit, and emphasise the importance of routine 25(OH)D testing by primary care teams.

To conclude, mandatory vitamin D fortification policies are urgently needed worldwide. Data modelling of nationally representative data can be used to inform and design country-specific effective vitamin D fortification policies. These data modelling studies should be supported by RCT that ensure safety and efficacy of these policies at a national level. Additionally, manipulating the composition of fortified foods may increase fortification policy effectiveness by increased vitamin D bioavailability from these foods. However, this area of research is still in the early stages, and more human studies are needed before novel food composition manipulation is incorporated into national policy. Lastly, fortification policies are most beneficial if supported by nationwide vitamin D education campaigns and if they are routinely monitored to ensure ongoing effectiveness.

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Conflict of Interest

None.

Authorship

A. F. M completed the review, advised and critically evaluated by A. M. O. Both authors read and approved the final manuscript.

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