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Vitamin D Food Fortification is an Effective Approach for Improving Vitamin D Status; A Systematic Review

Roya Sakhaei; MSc[1,2], Nasir Talenezhad; BSc[1,2], Mohammad Mohammadi; MSc[1,2] & Nahid Ramezani-Jolfaie; MSc[*1,2]

[1] *Nutrition and Food Security Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.*
[2] *Department of Nutrition, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.*

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Corresponding author
Ramezani.n.j@gmail.com
Department of Nutrition, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

Postal code: 8915173160
Tel: +(98) 3531492136

ABSTRACT

Background: Low vitamin D (vit D) serum levels have been linked to various diseases such as multiple sclerosis, cardiovascular diseases, and diabetes. Maintenance of optimal vit D level should be supported by foods and supplements. Limited food sources of vit D made researchers focus on food fortification in recent years. **Methods:** A systematic review of randomized controlled trials reporting the impact of vit D food fortification on 25-hydroxy vitamin D [25(OH)D] level was conducted on PubMed, Scopus, ISI Web of Science and Google Scholar from inception up to August 2017. **Results:** Sixteen studies met the inclusion criteria and most of them (n =14) have represented the significant effect of food fortification on the improvement of vit D status of the participants. However, two studies failed to find any reasonable associations. Furthermore, it was observed that vit D food fortification has a greater impact on the people with lower 25(OH)D serum levels. **Conclusions:** Fortification of foods with vit D has a significant impact on serum 25(OH)D concentrations. Therefore, food enrichment is an economical and effective approach for different populations to prevent vit D deficiency.

Keywords: *Vitamin D; 25-hydroxy vitamin D; 1, 25 dihydroxy vitamin D; Food fortification.*

Introduction

Vitamin D (vit D) belongs to the class of fat-soluble steroids that is categorized as two forms; cholecalciferol (vit D_3) and ergocalciferol (vit D_2) which are derived from animal and plant sources, respectively (Holick, 2007, Jolfaie *et al.*, 2016). Although sunlight exposure is the main source of vit D (Baeke *et al.*, 2007, Singh *et al.*, 2011), access to other sources of vit D through diet is also possible (Holick, 2007, Spiro and Buttriss, 2014).

Natural Sunlight exposure (UV light of wavelength 290-315 nm) can penetrate the epidermis and photolysis 7-dehydrocholesterol to previtamin D_3, which is metabolized in the liver after its entrance. Vit D_3 is then converted to 25-hydroxy vitamin D [25(OH)D] by 25-hydroxylases in the liver. Subsequently, 1, 25-dihydroxy vitamin D [1,25(OH)2D] is made in the kidneys by 1-hydroxylation of 25(OH)D (Bauer *et al.*, 2013, Spiro and Buttriss, 2014). Although 1,25(OH)2D is the

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active metabolite of vit D, the plasma concentration of 25(OH)D is the best clinical indicator of vit D status (Runia *et al.*, 2012).

Vit D deficiency is a worldwide concern and presents when serum 25(OH)D levels are below 50 nmol/L (20 ng/ml) (Christodoulou *et al.*). Dark pigmentation, lack of sufficient sun exposure, wearing clothes covering most of the body, sunscreen use, air pollution, and aging are known as common causes of vit D deficiency (Holick, 2002, Nicolaidou *et al.*, 2006, O'Riordan *et al.*, 2008, Sloka *et al.*, 2009, van der Meer *et al.*, 2006). Additionally, vegetarians and lactose intolerant people are highly at the risk of vit D deficiency (Alharbi and El-Sohemy, 2017, Outila, 2001).

Vit D deficiency adversely affects the health, leading to increased risk for several diseases including rickets in children or osteoporosis in adults, cardiovascular diseases, diabetes, cancer, and autoimmune diseases such as multiple sclerosis (Garland *et al.*, 2006, Garland *et al.*, 2009, Kriegel *et al.*, 2011, Norman *et al.*, 1974, Papandreou and Hamid, 2015, Pierrot-Deseilligny and Souberbielle, 2013, Wagner and Greer, 2008). Therefore, sufficient vit D status plays a major role in the prevention and treatment of various diseases (Holick, 2004, Holick *et al.*, 2011, Jolfaie *et al.*, 2016).

Several studies have suggested that vit D supplementation can increase circulating serum 25(OH)D levels (Björkman *et al.*, 2009, Havens *et al.*, 2012, Todd *et al.*, 2015). In addition to vit D supplementation, food fortification would be advisable to compensate vit D deficiency. Today, food fortification is considered to be a common strategy to improve and combat vit D deficiency. Vit D food fortification is an important and inexpensive strategy to certify the adequacy of vit D intake among populations (Biancuzzo *et al.*, 2010a, Calvo *et al.*, 2004, Upreti *et al.*, 2002).

Vit D3 is typically added to foods such as cheese and yogurt (Al-Khalidi *et al.*, 2015, Green *et al.*, 2010, Johnson *et al.*, 2005, Levinson *et al.*, 2016, Madsen *et al.*, 2013, Neyestani *et al.*, 2012, Rich-Edwards *et al.*, 2011, Wagner *et al.*, 2008), orange juice (Biancuzzo *et al.*, 2010b, Tangpricha *et al.*, 2003, Tripkovic *et al.*, 2017), bread (Itkonen *et al.*, 2016, Natri *et al.*, 2006, Nikooyeh *et al.*, 2016) and mushrooms (Mehrotra *et al.*, 2014, Urbain *et al.*, 2011). The efficiency of vit D2 as a fortificant in raising and maintaining blood concentrations of 25(OH)D is not yet definitively proven (Itkonen *et al.*, 2016, Mehrotra *et al.*, 2014, Urbain *et al.*, 2011). Due to the concern about the changes in cooking and preparation of foods, studies have used several fortification methods including the use of ultraviolet radiation and water-soluble vit D (Biancuzzo *et al.*, 2010b, Mehrotra *et al.*, 2014, Natri *et al.*, 2006, Urbain *et al.*, 2011).

The main purpose of the present systematic review was to evaluate the findings from available studies regarding the effect of food fortification with vit D on serum 25(OH)D levels.

Materials and Methods

Search strategy: A systematic search was performed among the published studies in the following electronic databases: PubMed (www.pubmed.com), Scopus (www.scopus.com), ISI Web of Science (www.isiknowledge.com) and Google Scholar (www.scholar.google.com) from inception up to August 2017. The search was done without restriction on language or publication year, using the combined MeSH and non-MesSH terms as follows: (vitamin D, vitamin D2, vitamin D3, vitamin-D2, vitamin-D3, 25-hydroxy vitamin D, 25-hydroxyvitamin D2, 25-hydroxyvitamin D3, 1,25-dihydroxy vitamin D, 1,25-dihydroxy vitamin D2, 1,25-dihydroxy vitamin D3, 25(OH)D, 25(OH)D2, 25(OH)D3, 1,25(OH)2D, 1,25(OH) 2D2, 1,25(OH) 2D3, hydroxycalcidol, 7-dehydrocholesterol, ergosterol, calcitriol, 25-hydroxy cholecalciferol, calcidiol, cholecalciferol, ergocalciferol) AND ("fortified food", "fortified foods", "Enriched Food", "Enriched Foods", "enriched food", "enriching food", "enhanced foods", "complementary food").

Broad screening of titles and abstracts were carried out by Talenezhad N and Mohammadi M to exclude irrelevant studies. Discrepancies between reviewers were resolved by the third author (Ramezani-Jolfaie N). In order to look for potential eligible articles and

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to increase the sensitivity of the search; the references of the retrieved studies were also checked.

Eligibility criteria: The literature that met the following criteria were considered for inclusion in the present systematic review: 1) original articles; 2) randomized controlled clinical trials (RCTs); 3) studies evaluating the effect of fortified foods with vit D on serum 25(OH)D. The studies that did not measure vit D levels, were non-human (in vitro and animal), used fortified food with vit D and another nutrient were excluded from the research. Moreover, the studies that besides vit D food enrichment, had used vit D supplementation were also excluded from the present research since the effect of enrichment could not be controlled separately.

Data extraction: Two reviewers (Talenezhad N, Ramezani-Jolfaie N) independently extracted the data in each study and participant characteristics including the author's last name, publication date, the country in which study was conducted, study design, study duration, number of participants, gender (female/male/both), age (mean or range), type of fortified food, dose, type of vit D, baseline, endpoint and changes in 25(OH)D levels. Data were then tabulated for further evaluations.

Quality assessment: The Cochrane Collaboration's tool for assessing the risk of bias was employed to describe the methodological quality of eligible trials. This tool consists of six domains including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. The included studies were classified into three categories: “yes” (low risk of bias), “no” (high risk of bias) or “unclear” (uncertain risk of bias) (Higgins and Green, 2011). The quality of each study was evaluated as good (low risk for more than two domains), fair (low risk for two domains), and weak (low risk for less than two domains).

Results

Study selection and characteristics: A total of 791 articles were retrieved based on electronic data search. After further reading of title and abstract, deduplication and exclusion of irrelevant articles, 44 studies were totally remained for the full-text screening, and 30 articles that met exclusion criteria were dropped out. Eventually, after including two papers through hand search, 16 studies were selected for the present systematic review. The description of the study selection is illustrated in **Figure 1**.

Table 1 presents the characteristics of the sixteen chosen articles which were published between 2003 and 2017 (Al-Khalidi *et al.*, 2015, Biancuzzo *et al.*, 2010b, Green *et al.*, 2010, Itkonen *et al.*, 2016, Johnson *et al.*, 2005, Levinson *et al.*, 2016, Madsen *et al.*, 2013, Mehrotra *et al.*, 2014, Natri *et al.*, 2006, Neyestani *et al.*, 2012, Nikooyeh *et al.*, 2016, Rich-Edwards *et al.*, 2011, Tangpricha *et al.*, 2003, Tripkovic *et al.*, 2017, Urbain *et al.*, 2011, Wagner *et al.*, 2008). From these articles, eight studies had examined the effect of dairy products fortifications on 25(OH)D (Al-Khalidi *et al.*, 2015, Green *et al.*, 2010, Johnson *et al.*, 2005, Levinson *et al.*, 2016, Madsen *et al.*, 2013, Neyestani *et al.*, 2012, Rich-Edwards *et al.*, 2011, Wagner *et al.*, 2008), three on bread (Itkonen *et al.*, 2016, Natri *et al.*, 2006, Nikooyeh *et al.*, 2016), two on mushrooms (Mehrotra *et al.*, 2014, Urbain *et al.*, 2011) and three on orange juice (Biancuzzo *et al.*, 2010b, Tangpricha *et al.*, 2003, Tripkovic *et al.*, 2017). Four studies were carried out in the United States (Biancuzzo *et al.*, 2010b, Johnson *et al.*, 2005, Mehrotra *et al.*, 2014, Tangpricha *et al.*, 2003), two studies in Canada (Al-Khalidi *et al.*, 2015, Wagner *et al.*, 2008), two in Iran (Neyestani *et al.*, 2012, Nikooyeh *et al.*, 2016), two in Finland (Itkonen *et al.*, 2016, Natri *et al.*, 2006) and one study was conducted in Germany (Urbain *et al.*, 2011), one in Israel (Levinson *et al.*, 2016), one in United Kingdom (Tripkovic *et al.*, 2017), one in Denmark (Madsen *et al.*, 2013), one in Mongolia (Rich-Edwards *et al.*, 2011), and one in New Zealand (Green *et al.*, 2010). All trials were designed as parallel-group studies, and duration of their intervention ranged from two weeks to sixteen weeks.

Risk of bias assessment: The quality assessment

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of the included articles for all domains of Cochrane risk of bias tool is summarized in **Table 2**. Most of the studies (n=12) had good quality (low risk for more than 2 items) (Biancuzzo *et al.*, 2010b, Green *et al.*, 2010, Johnson *et al.*, 2005, Madsen *et al.*, 2013, Mehrotra *et al.*, 2014, Neyestani *et al.*, 2012, Nikooyeh *et al.*, 2016, Rich-Edwards *et al.*, 2011, Tangpricha *et al.*, 2003, Tripkovic *et al.*, 2017, Urbain *et al.*, 2011, Wagner *et al.*, 2008), two of them were fair (low risk for 2 items) (Itkonen *et al.*, 2016, Levinson *et al.*, 2016) and others (n=2) were classified as poor quality (low risk for less than 2 items) (Al-Khalidi *et al.*, 2015, Natri *et al.*, 2006). The articles having weak quality score did not report blinding of outcome assessment, allocation concealment, and random sequence generation.

The effect of bread fortification with vit D on 25(OH) D levels: Three studies investigated the effect of fortified bread with vit D on serum 25(OH)D concentrations (Itkonen *et al.*, 2016, Natri *et al.*, 2006, Nikooyeh *et al.*, 2016). Natri et al. (Natri *et al.*, 2006) observed that bioavailability of vit D from both wheat and rye bread is equal, although rye bread contains more fiber. Their three-week investigation emphasized that the consumption of either fortified wheat or rye bread with vit D (12µg/100g) can significantly improve serum 25(OH)D levels in 41 healthy women. In line with their study, Nikooyeh et al. (Nikooyeh *et al.*, 2016) revealed that over longer intervention among 90 healthy men and women who consumed 50 g bread fortified with 25µg vit D for eight weeks, there was a significant raising in the circulation of 25(OH)D concentrations.

Another study assessed the bioavailability of vit D_2 from UV-irradiated yeast present in bread during eight-week intervention among 33 young adult females (Itkonen *et al.*, 2016). Participants were divided into four groups with different interventions: placebo pill and regular bread; D_2 supplement and regular bread; D_3 supplement and regular bread and placebo pill and D_2-biofortified bread. The results represented that vit D_2 fortified bread (25µg D_2/d) modestly increased serum 25(OH)D_2, but not as much as vit D supplement (6.4 vs. 31.3 nmol/l, respectively).

The effect of mushroom fortification with vit D on 25(OH)D levels: Two studies assessed the effect of consuming fortified mushrooms with vit D on 25(OH)D changes in the body (Mehrotra *et al.*, 2014, Urbain *et al.*, 2011). Twenty-six young adults with low serum 25(OH)D (≤ 50 nmol/l) and normal serum calcium concentration (2.2-2.7 nmol/l) were enrolled in a randomized, placebo-controlled study to determine the bioavailability of vit D_2 from vit D_2-enhanced mushrooms by ultraviolet irradiation (Urbain *et al.*, 2011). An experimental soup was made by fresh mushrooms irradiated with a UV-B dose of 1.5 J/cm^2, increasing vit D_2 content from <1 to 491µg/100g. It was observed that serum 25(OH)D concentrations rose significantly after ingesting 28000 IU of D_2/week for four weeks via experimental soup (3.9 nmol/l) vs. supplement (4.7 nmol/l).

Another research was conducted among pre-diabetic individuals, included 43 nonsmoking participants, with at least two features of metabolic syndrome (Mehrotra *et al.*, 2014). Two groups of participants who consumed entrees made by 100 g of UVB-treated mushrooms containing 600 IU D_2 or 4000 IU D_2 for sixteen weeks had modest or no increase in 25(OH)D_2 or total 25(OH)D.

The effect of orange juice fortification with vit D on 25(OH)D levels: Tangpricha et al. (Tangpricha *et al.*, 2003) carried out a study to determine the bioavailability of vit D_3 in orange juice and vit D_2 in whole milk, skim milk, and corn oil on toast. Eighteen healthy adults were asked to drink 240 ml of whole milk or skim milk that contained 25000 IU ergocalciferol or 25000 IU vit D_2 that had been dissolved in 0.1 ml corn oil and applied to toast. After ingestion of fortified whole milk, skim milk and corn oil on toast, there were not any significant changes in blood vit D_2 concentrations. However, remarkable differences appeared in blood vit D_3 among the participants who consumed fortified orange juice.

In addition, another study was conducted on fortified orange juice with vit D_2 and vit D_3

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(Biancuzzo *et al.*, 2010b). Eighty-six healthy participants were randomly assigned into one of the five groups: 1) placebo capsule + orange juice without vit D, 2) placebo capsule + orange juice containing 1000 IU vit D_3, 3) placebo capsule + orange juice containing 1000 IU vit D_2, 4)1000 IU vit D_3 capsule + placebo orange juice, and 5) 1000 IU vit D_2 capsule + placebo orange juice. After eleven weeks of intervention, analysis of the area under the curved demonstrated that the bioavailability of vit D_2 and vit D_3 in orange juice and capsules were similar and raised 25(OH)D effectively. Also, there were no considerable changes in serum 25(OH)D_2 and 25(OH)D_3 in the placebo groups, which means that sunlight exposure and diet could not significantly affect the vit D status.

Another research was carried out in 2017 by Tripkovic et al. (Tripkovic *et al.*, 2017) indicating that whether vit D_2 or vit D_3 added to juice or biscuit is effective in increasing serum total 25(OH)D. The results showed that 335 women who received 15 µg vit D2 or vit D3 added to juice and biscuit for twelve weeks had improvement in their vit D status.

The effect of dairy products fortification with vit D on 25(OH)D levels: Neyestani et al. (Neyestani *et al.*, 2012) carried out a study to determine the effect of vit D fortification either with or without calcium on certain inflammatory markers among 90 Iranian individuals with type 2 diabetes. All subjects were randomly divided into three groups of 1) receiving two 250-ml bottles of Doogh (Persian yogurt drink) per day (PD, containing 150 mg calcium and no detectable vit D_3/250ml); 2) vit D-fortified Doogh (DD, containing 500 IU vit D_3 and 150 mg calcium/250ml); and 3) calcium + vit D_3-fortified Doogh (CDD, containing 500 IU vit D_3 and 250 mg calcium/250ml). There was a detectable improvement in vit D status of DD and CDD groups following twelve weeks of intervention. Moreover, inflammatory markers and retinol binding protein-4 concentrations significantly decreased in those groups.

Green et al. also demonstrated that 73 women who consumed fortified milk (5µg vit D_3) for twelve weeks had 10 nmol/L higher serum 25(OH)D concentrations compared those consumed the placebo (Green *et al.*, 2010).

In the two researches conducted by Johnson, the bioavailability of vit D from fortified process cheese and its effects on 25(OH)D status in the elderly subjects was assessed (Johnson *et al.*, 2005). One hundred older men and women randomly received 85 g of 600 IU vit D fortified cheese, non-fortified cheese or no cheese during two months of intervention. Unexpectedly, a greater decrease in serum 25(OH)D was observed among the vit D fortified cheese group. The researchers speculate that this decrement may be related to higher baseline serum 25(OH)D concentrations. An additional randomized cross over the trial was also conducted to determine the bioavailability of vit D_2 and its absorption from process cheese and fortified water dilution (Johnson *et al.*, 2005). A total sample of eight people, divided into two groups of young and old, randomly received either vit D-fortified cheese or water. Consistent with the results obtained from serial blood sampling collected during 24-hours after the intervention, there was a similar peak in the serum vit D of younger (23 to 50 yr) and older (72 to 84 yr) adults, and vit D_2 absorbed more significantly from cheese than from water.

Another study was done by Wanger et al. (Wagner *et al.*, 2008) also investigated the bioavailability of vit D from fortified cheese. Eighty adults were randomly assigned to one of six weekly interventions of: 1) fortified cheddar cheese (DC) (34g, n=20); 2) fortified low-fat cheese (DLF) (41g, n=10); liquid vit D supplement (1ml), taken with food (DS+) (n=20) or without food (DS-) (n=10); placebo cheddar cheese (n=10); or placebo supplement (n=10). Over eight weeks of intervention, in the placebo groups, baseline 25(OH) D levels of 55.0±25.3 nmol/l declined to 50.7±24.2 nmol/l. In the vit D-treated groups, the mean increases in 25(OH)D values were as follows: 65.3±24.1 (DC), 69.4±21.7 (DLF), 59.3±23.3 (DS+) and 59.3 ±19.6 nmol/l (DS-) which presents that fortified cheese boost vit D

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status as adequately as a supplement, making it a proper choice for vit D fortification.

The other research was performed to assess the bioavailability and safety of vit D_3 from fortified mozzarella cheese baked on pizza (Al-Khalidi *et al.*, 2015). The research demonstrated that ingesting 200 IU or 28000 IU vit D_3-fortified mozzarella cheese for eight weeks could increase 25(OH)D levels by 5.1± 11 nmol/l in the low-dose group (n=47; P-value=0.003) and by 73±22nmol/l in the high-dose group (n=49; P-value<0.0001).

Levinson et al. (Levinson *et al.*, 2016) also assessed the bioavailability of vit D_3 from fat-free yogurt, in re-assembled casein micelles (rCMs) compared to polysorbate-80 (PS80/Tween80) which is commonly used a synthetic emulsifier. Serum 25(OH)D status of participants consuming fat-free yogurt with 50000 IU of either VD_3-rCM, VD_3-PS8 showed increases of ~ 8 ng/ml after two weeks, and no significant differences were found between mean changes of 25(OH)D among the individuals who consumed rCM yogurt versus PS80.

On the other hand, Madsen et al. (Madsen *et al.*, 2013) investigated the association of fortified milk and bread with vit D status of 782 children and adults. Participants were recruited from 201 families and were randomly assigned to vit D-fortified or non-fortified milk and bread for six months. When comparing from baseline to completion of the intervention, a greater serum 25(OH)D level was seen in the fortification group (67.6 nmol/L) than in the control group (41.7 nmol/L). Similar finding was also reported by Rich-Edwards et al. (Rich-Edwards *et al.*, 2011). There were improvements in 25(OH)D concentrations among 579 children in Mongolia who received 300 IU vit D via fortified milk.

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Table 1. Characteristics of the studies that were included in the systematic review

The first author (year)	Season	Country	Study design	Number of participants (sex ratio)	Age (y) (range or mean±SD)	Study duration (week)	Food fortified	Fortification dose, type of vitamin D	25(OH)D analysis[1]	Baseline 25(OH)D (mean±SD or 95% CIs)	Endpoint 25(OH)D (mean±SD or 95% CIs)
Tripkovic (2017) (Tripkovic *et al.*, 2017)	Two consecutive winters	United Kingdom	Parallel five groups	335 1) Placebo (n=65) 2) vit D2 Juice (n=67) 3) vit D2 biscuit (n=66) 4) vit D3 Juice (n=70) 5) vit D3 biscuit (n=67)	20-64	12	Juice biscuit	15 mg vit D2 15 mg vit D3	HPLC-MS/MS	nmol/L 1) Placebo 44.8 (37.5, 52.1) 2) vit D2 Juice 44.9 (37.8,52.0) 3) vit D2 biscuit 46.1 (38.9,53.4) 4) vit D3 Juice 42.3 (35.4, 49.2) 5) vit D3 biscuit 41.9 (34.9 ,48.9)	nmol/L 1) Placebo 33.5 (27.8,39.3) 2) vit D2 Juice 59.7 (53.9,65.4) 3) vit D2 biscuit 61.9 (56.0,67.7) 4) vit D3 Juice 74 (68.1,79.9) 5) vit D3 biscuit 73 (67.1,78.9)
Nikooyeh (2016) (Nikooyeh *et al.*, 2016)	Winter (February-March)	Iran	Parallel three groups	90 (49 F/ 41 M) 1) Fortified (n=30) 2) Supplement (n=30) 3) Control (n=30)	20-60 Fortified (۳۷,۲±۱۰,۵) Supplement (۳۷,۳±۱۰,۹) Control (۳۹,٤±۱۱,٦)	8	Bread	25 µg vit D3	HPLC	nmol/L 1) Fortified ۳۳,۹±۲۱,۹ 2) Supplement ۳۵,۰±۳۸,۷ 3) Control ۳٤,۷±۳۰,۵	nmol/L 1) Fortified ۷۲,۹±۲۳,۱ 2) Supplement ٦۳,۹±۳۱,۰ 3) Control ۲۵,٤±۲۱,۸
Levinson (2016) (Levinson *et al.*, 2016)	NR	Israel	Parallel three groups	87 1) Enriched with vitD3-rCMs 2) Enriched with vitD3-PS80 3) Placebo group	18-61	2	Fat-free yogurt with vit D3	50000 IU vit D3	Chemiluminescence immunoassay (CLIA)	ng/L Changes: 1) 7.51±1.23 2) 8.01±0.8 3) -0.65±0.74	
Itkonen (2016) (Itkonen *et al.*, 2016)	Winter (February-April)	Finland	Parallel four groups	41 (33 F/ 11 M) 1) Placebo (n=10) 2) D2 bread (n=10) 3) D3 supplement (n=11) 4) D2 supplement (n=10)	20-37	8	Bread (87 g)	۱) 25 µg vit D2 in bread 2) 25 µg vit D۳ supplement ۳) 25 µg vit D۲ supplement	OCTEIA immunoenzymometric assay (IDS) and (DEQAS)	nmol/L 1) Placebo 66.2±18.6 2) D2 bread 64.6±15.1 3) D2 supplement 63·5±11.3	nmol/L Mean changes: 1,2) Placebo and D2 bread (not change) 3) D3supplement +17·0 4) D2 supplement

									4) D3 supplement 66·6±14.8	+9·6
Al-Khalidi (2015) (Al-Khalidi *et al.*, 2015)	NR	Canada	Parallel two groups	96 1) Low-dose (n=47) 2) High-dose (n=49)	NR	8	Pizza (mozzarella cheese)	1) 200 IU vit D3 2) 28000 IU vit D3	NR	NR
Mehrotra (2014) (Mehrotra *et al.*, 2014)	November 2011-April 2012	United States	Parallel four groups	٣٦ 1) Mushrooms 500 IU vit D2 + placebo (n=٨) 2) Mushrooms 2600 IU vit D2 + placebo (n=١٢) 3) 1200 IU vit D3/d capsules (n=٨) 4) 7300 IU vit D3/d capsules (n=٨)	30-90 (٤٩±١٢)	16	Mushroom (100 g)	1) 500 IU D2 2) 2600 IU D2 3) 1200 IU D3 4) capsules 7300 IU	RIA and LC/MS/MS	ng/mL 1) NR 2) 17.0±4.9 3) 16.1±3.5 4) 18.8±4.2	ng/mL 1) Not change 2) 18.5±4.1 3) 28.5±1.1 4) 32.5±3.8
Madsen (2013) (Madsen *et al.*, 2013)	Winter	Denmark	Parallel two groups	726 1) Fortification (n=355) 2) Control (n=371)	Children and adults (4-60)	26	Milk and bread	Children aged 4-17: 1) Fortification 10.2 µg 2) Control 2.2 µg Adults aged 18-60: 1) Fortification 8.1 µg 2) Control 2.2 µg	HPLC	nmol/L Children aged 4-17: 1) Fortification ٧٢,٨ (64.0, 88.9) 2) Control ٧٢,٨ (61.8, 83.9) Adults aged 18-60: 1) Fortification ٧٣,٣ (61.9, 88.3) 2) Control ٧٠,٠ (60.0, 86.7)	nmol/L Children aged 4-17: 1) Fortification ٦٧,٦ (56.2, 79.4) 2) Control ٤٢,٧ (30.9, 58.9) Adults aged 18-60: 1) Fortification ٦٦,١ (56.2, 79.4) 2) Control ٤٠,٧ (28.8, 60.3)
Neyestani (2012) (Neyestani *et al.*, 2012)	NR	Iran	Parallel three groups	90 1) Plain doogh (n=30) 2) Vit D fortified doogh (n=30) 3) Vit D + calcium fortified doogh (n=30)	30-60 1) 50.8±6.7 2) 51.5±5.4 3) 49.9±6.2	١٢	Persian yogurt drink or doogh (wo 250 ml bottle/d)	1) 150 mg ca 2) 500 IU vit D3 and 150 mg ca 3) 500 IU vit D3 and 250 mg ca	HPLC	nmol/L 1) 41.6±44.5 2) 44.4±28.7 3) 44.5±43.7	nmol/L 1) 37.2± 44 2) 77.7±28.6 3) 74.6±39.5
Urbain	Winter (late	Germany	Parallel	27	1) 28.6±4.3	5	Mushrooms	28000 IU (700	Radioimmuno	nmol/L	nmol/L

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(2011) (Urbain *et al.*, 2011)	January-early March 2010)		three groups	1) 28000 IU (700 mg) vit D2 in soup (n=8) 2) 28000 IU vit D2 via a supplement (n=9) 3) placebo (n=9)	2) 31.1±6.7 3) 32.4±6.0		(soup)	mg) vit D2 fortified food 28000 IU vit D2 via a supplement	assay (DiaSorin Inc)	1) 34.0±11.0 2) 28.7±10.0 3) 38.7±14.2	1) 56.7±7.2 2) 58.0±11.2 3) 28.7±8.7
Rich-Edwards Janet (2011) (Rich-Edwards *et al.*, 2011)	Winter	Mongolia	Parallel five groups	579 1) Unfortified Mongolian milk (n=101) 2) Fortified Mongolian milk (n=140) 3) Fortified UHT milk (n=37) 4) Daily vit D supplement (n=109) 5) Seasonal vit D supplement (n=92)	Children (9-11)	from January through March	Milk	1) 300 IU weekly per milk 2) 300 IU supplement	Liquid chromatography–tandem mass spectrometry	ng/mL 1) 8±4 2) 8±4 3) 10±5 4) 7±3 5) 8±4	ng/mL 1) 8±4 2) 20±6 3) 29±10 4) 21±6 5) 12±4
Green (2010) (Green *et al.*, 2010)	January to April	New Zealand	Parallel two groups	73 F 1) Fortified milk (n=37) 2) Placebo milk (n=36)	18-45	12	Milk	75 g of fortified milk powder provided 200 IU vit D3	DiaSorin radioimmunoassay (Stillwater, MN)	nmol/L 1) 76 (66, 87) 2) 74 (65, 85)	nmol/L 1) 65 (57, 73) 2) 53 (46, 62)
Biancuzzo (2010) (Biancuzzo *et al.*, 2010b)	February	United States	Parallel five groups	105 1) Placebo (n=15) 2) vit D3 orange juice (n=18) 3) vit D2 orange juice (n=17) 4) vit D3 in capsules (n=20) 5) vit D2 in capsules (n=16)	18-84 1) 40.8±10.8 2) 41.4±12.6 3) 40.1±15.6 4) 40.1±18.0 5) 38.9±12.3	11	Orange juice	1000 IU vit D^{3} 1000 IU vit D2	Liquid chromatography tandem mass spectroscopy	ng/mL 1) 19.8 ± 9.6 2) 17.9 ± 11.1 3) 15.8 ± 10.0 4) 19.6 ± 11.1 5) 16.6 ± 9.9	ng/mL 1) 18.1 ± 6.4 2) 230.7 ± 8.5 3) 26.4 ± 7.4 4) 28 ± 11.0 5) 27.4 ± 10.5
Wagner (2008) (Wagner *et al.*, 2008)	Began in the fourth week of January and ended in	Canada	Parallel six groups	80 (40 F/ 40 M) 1) Fortified cheddar cheese (34 g; n=20) 2) Fortified low-fat	1) 28.7±11.4 2) 30.6±11.7 3) 31.8±12.5 4) 23.6 6 3.5	8	Cheese	28,000 IU vit D3 weekly (4000 IU/d)	Radioimasay (DiaSorin)	nmol/L 1) 50.7 ±18.9 2) 57.5 ±18.4 3) 55.7 ±21.2	nmol/L 1) 115.62 ± 2.10 2) 126 ± 8.34 3) 115.21 ± 4.50

	the first week of April			cheese (41 g; n=10) 3) vit D supplement with food (n =20) 4) vit D supplement without food (n=10) 5) Placebo cheddar cheese (n=10) 6) Placebo supplement (n=10)	5) 26.2 ±6.5 6) 24.6 ±4.5					4) 53.4 ±40.1 5) 52.4 ±22.7 6) 57.6 ±28.7	4) 111.36 ± 8.55 5) NR 6) NR
Natri (2006) (Natri *et al.*, 2006)	February–March	Finland	Parallel four groups	41 1) Fortified wheat (n=11) 2) Fortified rye (n=10) 3) Control (n=9) 4) vit D supplement control (n=11)	25-45 1) 27.3±0.6 2) 28.8±1.8 3) 29.0±1.7 4) 31.1±1.8	۳	Bread	10 mg vit D in all groups except the control group	Immunoradio metric method (DiaSorin)	nmol/L 1) 29.0±3.0 2) 28.9±3.5 3) 27.1±3.7 4) 29.6±2.6	nmol/L 1) 45.44±3.16 2) 49.31±1.50 3) 27.59±3.0 4) 43.96±3.33
Johnson (2005) (Johnson *et al.*, 2005)	winter	United States	Parallel three groups	110 1) vit D-fortified process cheese (n=۳۵) 2) Non-fortified process cheese (n=۳۷) 3) No process cheese (n=۳۸)	≥ 60	8	Process cheese	600 IU vit D	HPLC	ng/ml 1) 23±1.4 2) 20±1.2 3) 18±1.3	ng/ml 1) 21±1.4 2) 22±1.1 3) 19±1.2
Tangpricha (2003) (Tangpricha *et al.*, 2003)	Began in the second week of March	United States	Parallel three groups	۲۶ 1) vit D fortified juice (n=14) 2) Unfortified juice (n=12)	22-60 (29.0±9.0)	12	Orange juice and skim milk	1000 IU vit D3	The intraassay CV of 8% and an interassay CV of 12%	nmol/L 1) 7.0±8.0 2) 50.0±10	nmol/L 1) 94.0±20 2) 73.0±8.0

[1]Analytical methods for analyzing circulating 25(OH)D levels, F: female, M: male, NR: not reported, HPLC: high-performance liquid chromatography

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Table 2. Risk of bias assessment for included RCTs

	L (2017) (Tripkovic *et al.*, (2016) (Nikooyeh *et al.*, (2016) (Levinson *et al.*, Itkonen (2016) (Itkonen *et al.* Al-Khaldi (2015) (Al-Khaldi *et al.*, 2015) (2014) (Mehrotra *et al.*, Madsen (2013) (Madsen *et al.*, 2013) (2012) (Neyestani *et al.*, Janet (2011) (Rich-Urban (2011) (Urbain *et al.*, 2011) (2010) (Biancuzzo *et al.*, Wagner (2008) (Wagner *et al.* Natri (2006) (Natri *et al.*, 2006) (2005) (Johnson *et al.*, a (2003) (Tangpric haGfeld (2010) (Green *et al.*, 2010)
Random sequence generation **(selection bias)**	+ + ? ? ? + + ? + + + + ? ? + ?
Allocation concealment **(selection bias)**	? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ?
Blinding of participants and personnel **(Performance bias)**	+ + ? ? ? + ? ? ? ? ? + ? ? + +
Blinding of outcome assessment **(Detection bias)**	? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ?
Incomplete outcome data **(Attrition bias)**	+ ? ? + + + + ? + + + + + + + +
Selective reporting **(Reporting bias)**	+ + + + ? + + + + + + + + + + +
Score	4 3 1 2 1 4 3 1 3 3 3 4 2 2 4 3
Overall quality	Good Good Weak Fair Weak Good Good Weak Good Good Good Good Fair Fair Good Good

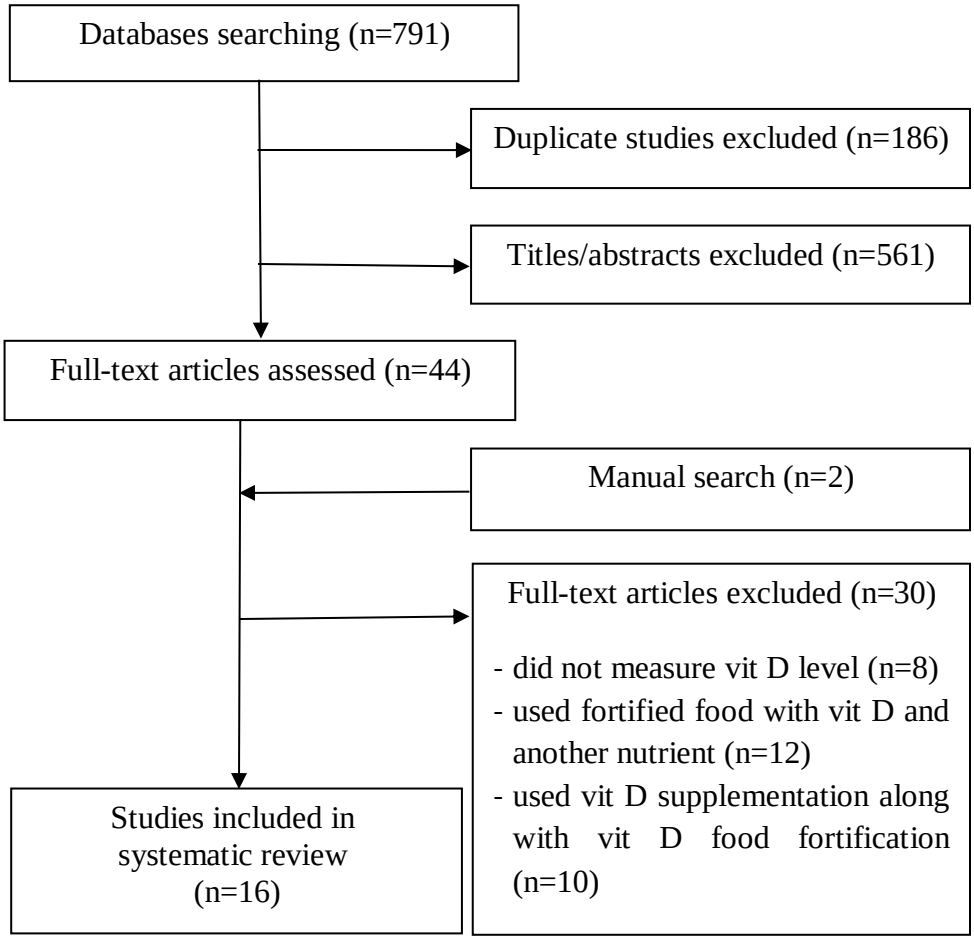

Figure 1: Flow chart of the study selection process

Discussion

The current systematic review was undertaken to evaluate the effect of food fortification with vit D on serum 25(OH)D levels. According to the findings of reviewed studies, vit D food fortification can be an effective and cost-effective approach to provide sufficient 25(OH)D concentrations and reduce the number of people suffering vit D deficiency. It was also observed that vit D_3 fortified foods had better efficacy than vit D_2 fortified foods. Overally, fourteen studies supported the benefits of food enrichment (Al-Khalidi *et al.*, 2015, Biancuzzo *et al.*, 2010b, Green *et al.*, 2010, Johnson *et al.*, 2005, Levinson *et al.*, 2016, Madsen *et al.*, 2013, Natri *et al.*, 2006, Neyestani *et al.*, 2012, Nikooyeh *et al.*, 2016, Rich-Edwards *et al.*, 2011, Tangpricha *et al.*, 2003, Tripkovic *et al.*, 2017, Urbain *et al.*, 2011, Wagner *et al.*, 2008) and only two studies failed to find reasonable changes as a result of food fortification on serum 25(OH)D levels (Itkonen *et al.*, 2016, Mehrotra *et al.*, 2014). Food fortification with vit D significantly increases serum 25(OH)D levels, helping perpetuation of vit D status among the populations.

Different foods have been suggested to be fortified with vit D, such as milk, mushrooms, bread, and orange juice. Dairy products fortification is very common in the United States, but many people avoid consuming milk due to lactose intolerance and vegetation cause (Gibson, 1994, Pawłowska *et al.*, 2016). On the other hand, there was a concern that low PH of orange juice (~4) would limit stability of added vit D. However HPLC analysis indicated that vit D_3 remained unchangeable after storage for 30 days at 4ºC

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(Tangpricha *et al.*, 2003). Therefore, some researchers have suggested that since bread is the primary food and also available in many countries, it is a good choice for fortification (Mocanu and Vieth, 2013, Natri *et al.*, 2006, Nikooyeh *et al.*, 2016).

Vit D is bioavailable from cheddar, low-fat cheese, whole milk and skim milk and also fat content of milk and its products cannot change the bioavailability (Tangpricha *et al.*, 2003, Wagner *et al.*, 2008). In addition, some studies showed that vit D fortified bread, orange juice and mushrooms improved 25(OH)D status in different population groups (Biancuzzo *et al.*, 2010b, Natri *et al.*, 2006, Nikooyeh *et al.*, 2016, Tangpricha *et al.*, 2003, Urbain *et al.*, 2011). Whereas UVB-activated D2 yeast added to bread did not increase total 25(OH)D concentrations which may be results of low bioavailability of vit D from UVB irradiated yeast in bread (Itkonen *et al.*, 2016). On the other hand, in another RCT, vit D2-UVB-mushrooms did not increase total 25(OH)D which may be attributed to cooking loss and probable low absorption of vit D (Mehrotra *et al.*, 2014).

In addition, the efficacy of vit D fortification varied among the included studies, which might be related to differences in doses, type of vit D, type of food, fortification method, age and baseline vit D status of participants. According to the results of eligible studies, the higher 25(OH)D concentrations were achieved among participants with lower baseline 25(OH)D levels and no differences were reported between men and women (Natri *et al.*, 2006, Tangpricha *et al.*, 2003).

Despite beneficial effects of vit D fortification in the prevention of many diseases, it may cause some serious side effects on human health; consequently, it has limitation of consumption for some individuals. Just as some researchers reported the withdrawal of participants from their studies because of gastrointestinal discomfort, especially those who consumed fortified dairy products (Daly *et al.*, 2006, Johnson *et al.*, 2005, Lau *et al.*, 2001).

The limitations of this systematic review are the lack of information on dietary intake of vit D of the participants,the baseline vit D status of participants that varied in the included studies which may impact on the 25(OH)D responses to fortified foods, thethe power of detecting small changes in 25(OH)D is different between laboratories, and the results varied by countries depending on their lifestyle, dietary habits and genetic background which are all being involved in responses to vit D fortification.

The current study comprehensively investigated the effect of food fortification with vit D on 25(OH)D levels based on all available RCTs to date, which have high levels of credibility. Cochrane's risk of bias tool was also used to investigate the methodological quality of the trials which is considered as the strength of the present review.

Conclusion

The present systematic review of RCTs demonstrated that fortification of foods with vit D has significantly improved 25(OH)D serum status and has similar efficacy with vit D supplements. Moreover, it was observed that food fortification has a greater impact on the people with lower 25(OH)D serum levels. Therefore, food enrichment is an economical and effective approach for different populations to prevent vit D deficiency. Further studies are still needed to determine the best food and optimal dosage of vit D for fortification.

Conflict of Interest

The authors declare that there is no conflict of interest.

Author Contributions

Mohammadi M designed the search strategy; Mohammadi M and Talenezhad N performed electronic search and study selection; Talenezhad N and Ramezani-Jolfaie N extracted the data; Sakhaei R and Ramezani-Jolfaie N wrote the manuscript, and all authors read and approved the final manuscript.

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