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Lipid-modifying Effect of Vitamin D Fortified Products: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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ABSTRACT

Introduction: Various fortification strategies have been proposed to account to treat or prevent vitamin D deficiency. However, the optimum fortification approach, and the effect of these on health is not widely understood. There have been controversial reports regarding the effect of vitamin D fortification on the lipid profile. The aim of present systematic review is the evaluation of administration of vitamin D fortified products on lipid profile.

Methods: We used databases including PubMed/Medline, Web of Knowledge, Science Direct, Scopus and Cochrane Library. A search was conducted until 2020. Randomized controlled trials that have assessed the relationship between consumption of vitamin D fortified products and serum lipid profile were included. The relationship between fortification dose, dairy or non-dairy fortification as well as duration of intervention and plasma lipid profiles evaluated in separate sub-groups.

Results: Among serum lipids including total cholesterol(TC), triglyceride(TG), low density lipoprotein(LDL) and high density lipoprotein(HDL), fortification of vitamin D was reported to have a significant effect on reducing TC (pooled estimate: -0.089 mmol/L, 95%CI: -0.134 to -0.044, p<0.001). Its effect on other lipid profiles were not significant (LDL pooled estimate:-0.115 mmol/L, 95%CI:-0.238 to 0.008; HDL pooled estimate:0.024 mmol/L, 95%CI:-0.024 to 0.071; TG pooled estimate:-0.176mmol/L, 95%CI:-0.499 to 0.148).

Conclusion: This meta-analysis demonstrated that vitamin D fortification could significantly reduce TC both in long and short term interventions and in different products. However this reduction, whilst statistically significant, may not be clinically important. The effect of fortification on other lipid profile components vary depending on dose and duration.

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Introduction

Vitamin D is an important micronutrient that functions as a hormone and is a crucial factor in the metabolism of calcium and phosphate, bone development and health, but is also involved in other cellular processes (1).

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The sources of vitamin D2 and D3 include diet and ambient sun exposure (1). Vitamin D2 is found in plants, while vitamin D3 is found in fish, eggs, etc. Vitamin D3 (cholecalciferol) is also produced from the photochemical transformation of 7-dehydrocholestrol within the epidermis (2, 3). Vitamin D is metabolized to 25-hydroxyvitamin D3 under the action of 25-hydroxylase enzyme (cytochrome P450 2R1) in the liver, and subsequently to 1,25-dihydroxyvitamin D3 under the action of 1-alpha-hydroxylase enzyme (cytochrome P27B1) in the kidney (4).

The biological activity of the different supplemental forms of vitamin D (D2 vs. D3) vary (5). Most studies indicate that vitamin D3 can raise the concentration of serum 25(OH)D more effectively (6-8).

Insufficiency and deficiency of this fat-soluble vitamin is an important global health problem but the exact cut off point for the classification of vitamin D insufficiency and deficiency remain controversial (1, 9-11). A vitamin D concentration between 75-125 nmol/L (30-50 ng/ml) has been suggested to be the optimal range for overall human health (12).

To maintain the desirable level of vitamin D, supplementation and a diet containing vitamin D enriched foods are useful sources. Both dairy and non-dairy foods have been widely used as matrices for vitamin D fortification (13). Globally there are different vitamin D supplementation guidelines dependent on the overall vitamin D status of the population concerned (12). Different policies have been implemented to manage vitamin D deficiency in different countries. Some have used mandatory policies for food fortification, while most have implemented voluntary fortification policies (14, 15). Because of the variations in levels of vitamin D fortification in foods, and the differences in enforcement of implementation in different countries, it is difficult to assess what has been the most successful strategy (14, 15). For example, although vitamin D food fortification is not mandatory in Finland, most companies have complied with this voluntary policy, resulting in a significant reduction in vitamin D deficiency and insufficiency in the general population of Finland (14, 16).

Vitamin D insufficiency is associated with several conditions, including insulin resistance, diabetes mellitus, cardiovascular, pulmonary, hepatic and renal diseases, autoimmune disorders and various cancers (1). It has also been reported that vitamin D status has an effect on the lipid profile, but studies have been inconsistent. It is well established that dyslipidemia is associated with an increased risk of cardiovascular diseases (CVD) (17). Today it is estimated that this disease is responsible for one-third of deaths worldwide (18). A review of cross sectional studies showed a positive association between serum 25 (OH) D and high density lipoprotein-cholesterol (HDL-C), and an inverse association with serum triglycerides (TG) (19). Some studies have reported an improvement in serum total cholesterol (TC), triglycerides (1), high density lipoprotein-cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C) after treatment with vitamin D supplements (1, 20, 21), however other trials have not shown these effects (22, 23). These results may be due to differences in baseline vitamin D status, sample size, or the dose and formulation of the vitamin D used. We therefore aimed to evaluate the effects of using vitamin D fortification on the serum lipid profile by undertaking a meta-analysis of all relevant randomized controlled trials investigating the effect of this intervention compared to a regular dietary intake.

Materials and Method

This systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) guidelines (24).

Five scientific databases were searched for suitable articles published before the end of December 2019, and included: PubMed/Medline, Web of Knowledge, Science Direct, Scopus, Cochrane Library and the Google Scholar. The key search terms used were: “fortification” or “fortified” or “fortified food” or “fortifi*” in combination with “vitamin D” or “vit D” or “25-hydroxyvitamin D”. Only articles published in English language were included.

Inclusion Criteria

The PICOS (participants, interventions, comparisons, outcomes, and study design) criteria of the study are listed below:

a) Study types: Randomized controlled trials lasting for at least one month were entered.
b) Types of participants: Human subjects without any restriction on their age, gender and health status were included.
c) Type of interventions: Food products fortified with different forms of vitamin D (i.e. D2 or D3) or Calcium-vitamin D were included.
d) Type of control: Only studies that used unfortified food product similar to the intervention group; or those which used regular diet as the control group, were included in this review.
e) Types of outcome measures: Lipid profiles

[including total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL) and very low density lipoprotein cholesterol (VLDL)]; data on lipoprotein (a) (Lp(a)) and Apolipoprotein A1 (ApoA1) and Apolipoprotein B (ApoB), (if mentioned in the articles) were also extracted.

Exclusion criteria

All review articles, studies published as poster presentations, fortified food products with other nutrients or vitamin D supplementation as interventions, were excluded. If the control group received fortified food, we excluded the article. Articles focusing on different fortification methods or genetic reports were also excluded.

Data Extraction and Analysis

Two authors (ME and RS) extracted the data from articles. The information extracted was as follows: First author's name and publication year, country, population, intervention (type, dose), sample size in each group, outcome measures and duration of intervention.

Quality Assessment (risk of bias)

The quality of all studies included in this review was assessed using the Jadad scale (25). According to this scale, the major items leading to risk of bias were randomization, blinding and dropouts. The score for this vary from zero to five. Articles with a score of three, or more indicates adequate quality (26). All studies that obtained the minimum score of 3 entered to meta-analysis. The quality of studies was evaluated by two authors, independently (ME and RS). Any disagreement was solved by consensus.

Data Synthesis and Analysis

Comprehensive Meta-analysis software (Version 2) was used for meta-analysis (27). The mean difference with 95% confidence intervals was calculated for all continuous data. Heterogeneity was tested using the I^2 statistic. In case of I^2 statistics less and more than 50%, fixed or random-effects models were used respectively. To determine the influence of variables such as type of food (dairy or non-dairy type), fortification dose, fortification with vitamin D or calcium-vitamin D, and duration of use of the fortified product, a subgroup analysis was conducted. P-values <0.05 were considered statistically significant. Publication bias was assessed by Egger's test and by using a funnel plot.

Results

Study selection

A total of 4437 studies were found following the literature search. A total of 2279 duplicate publications were removed from these articles. After reviewing the title and abstract of the remaining 2158 articles, 1997 articles did not meet the criteria for entry into the review due to irrelevant study type (non-RCTs, animal studies) or because of studying the effect of supplementation or products fortified with other micronutrients. The remaining 161 eligible studies were then evaluated for study types;

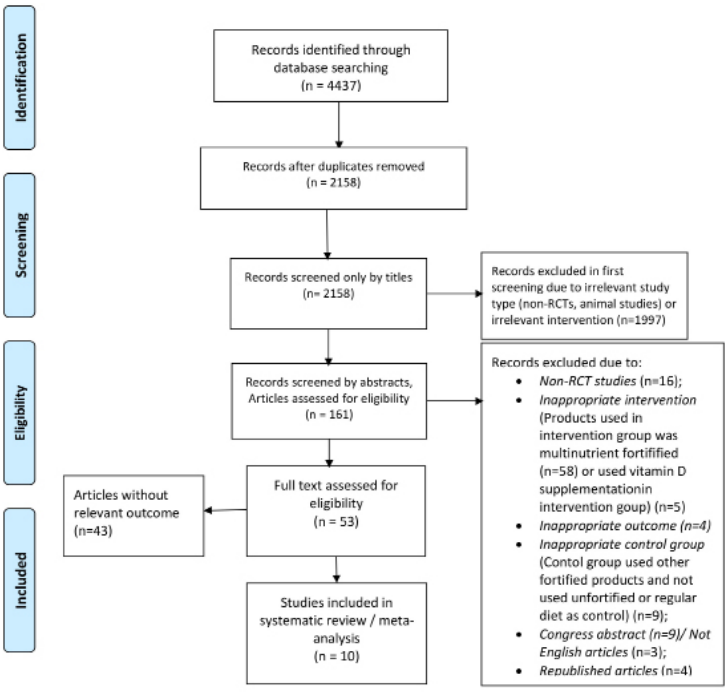

Figure 1: Flow diagram of the study selection

non-clinical trials, those with inappropriate fortification, or those articles without full text were excluded. The remaining 10 articles were then included in the systematic review and meta-analysis. Figure 1 summarizes the present study protocol.

Characteristics of Included Studies

The characteristics of the 10 studies that were used in the present meta-analysis are summarized in table 1 (13, 22, 23, 28-34). As shown in this table, six studies were from Iran, two from the United States and one study each from Australia and Canada. The number of participants in intervention groups of each country were 283, 110, 73 and 36, respectively (total: 502). Studies were conducted on participants who were either healthy, or who were diabetic patients. Three articles, that had more than one type of intervention group, have been labeled with different numbering and included separately in the data analysis (23,

Table 1: Characteristics of included studies

Nikooyeh et al., 2011* [21]	Iran	double-blind, randomized, controlled trial	Diabetic patients (30-60 year old)	Control (41.6±44.5nmol/L); intervention (44.4±28.7nmol/L)	1	500 cc/d vitamin D3–fortified yogurt drink (containing 1000 IU vitamin D3); n=30	plain yogurt drink; n=30	3 months
				Control (41.6±44.5nmol/L); intervention (44.5±43.7nmol/L)	2	500 cc/d Ca-D3–fortified yogurt drink (containing 1000 IU vitamin D3 and 500 mg Ca); n=30	plain yogurt drink; n=30	3 months
Rosenblum et al., 2012* [27]	US	parallel, double-blind, placebo-controlled trials	Healthy overweight and obese men and women (18-65 years)	Control (67.5±32.5nmol/L); intervention (65±25nmol/L); baseline serum 25(OH) D in all subjects were >25nmol/L.	1	720 cc/d CaD3 fortified regular orange juice (containing 350 mg Ca and 100 IU vitamin D); n=33	Unfortified regular orange juice; n=38	4 months
				Control (82.5±32.5nmol/L); intervention (77.5±30nmol/L); baseline serum 25(OH)D in all subjects were >25nmol/L.	2	720 cc/d CaD3 fortified lite orange juice (containing 350 mg Ca and 100 IU vitamin D); n=42	Unfortified lite orange juice; n=41	4 months
Heravifard et al., 2013* [28]	Iran	double-blind, randomized, controlled trial	Type 2 diabetic patients (30-60 years)	Control (41.6±44.5nmol/L); intervention (44.4±28.7nmol/L); Suboptimal vitamin D status at baseline observed in 80% of control and 70%of intervention group.	1	500 cc/250 ml D3-fortified doogh (containing 1000 IU vitamin D3); n=30	plain doogh; n=30	3 months
				Control (41.6±44.5nmol/L); intervention (44.5±43.7nmol/L); Suboptimal vitamin D status at baseline observed in 80% of control and 70%of intervention group.	2	500 cc Ca D3/250 ml-fortified doogh (containing 1000 IU vitamin D3 and 500 mg Ca); n=30	plain doogh; n=30	3 months

[a]UHT: ultra-heat-treated; [b]IFG: impaired fasting glucose; [#] doogh: Persian yogurt drink; * These studies had different fortified intervention groups. Each intervention group counted as an independent study.

Note that the cut-off values used to define vitamin D status have been reported as follows: severely deficient: a serum 25-(OH) D <30 nmol/L; moderately deficient: <50 nmol/L; mildly deficient: <75 nmol/L; beneficial range: 75-125 nmol/L.

[¶] Note that there are mandatory fortification policies in the US, Canada and Australia for some products. In these countries vitamin D is added to margarine. In the US, fortification of cow`s milk is also mandatory. The fortified products used in mentioned trials were not part of mandatory policies (e.g. cheese in Canada and the US, and milk in Australia). In Iran there is no mandatory legislation for vitamin D fortification

29, 30). The vitamin D consumed in fortified foods ranged from 100 to 4000 IU per day. Only on999e study evaluated the effect of vitamin D fortification on serum Lp(a), ApoA1 and ApoB, however the other nine studies measured lipid profile including TC, TG, LDL-C and HDL-C. Eight studies evaluated the effect of dairy products (13, 22, 23, 28, 30, 31, 33, 34) and two studies assessed non-dairy products including orange juice and bread (29, 32). Six studies administered

Table 2: Quality of included studies based on Jadad scale

Study	Was the study described as randomized?*	Was the study described as a double *?blind	Was there a description of withdrawal and drop-*?outs	The randomization scheme described and *appropriate	The method of double blinding described and appro-*priate	The randomization scheme described and inappropri-**ate	The method of double blinding described and inappropri-**ate	Total score
Johnson, J. L.,2005 [11]	1	1	1	0	0	0	0	3
Daly, Robin M.,2009 [20]	1	0	1	1	0	0	0	3
Nikooyeh, B., 2011 [21]	1	1	1	0	0	0	0	3
Shab-Bidar, S., 2011 [26]	1	1	0	0	1	0	0	3
Rosenblum, J. L., 2012 [27]	1	1	1	1	1	0	0	5
Heravifard, S., 2013 [28]	1	1	1	0	0	0	0	3
Jafari, T., 2016 [29]	1	1	1	1	1	0	0	5
Nikooyeh, B., 2016 [30]	1	1	0	1	1	0	0	4
Moreira-Lucas, T. S., 2017 [31]	1	1	1	1	1	0	0	5
Salehi, S., 2018 [32]	1	1	1	1	1	0	0	5

* yes:+1 ; no: 0
** yes:-1 ; no: 0
Note that inappropriate in case of randomization refers to studies which declare that they use randomization sequences, but in the description they express that the patients are allocated alternately, or according to date of birth, hospital number, etc).
Note that inappropriate in case of blinding refers to studies that the method was described as double-blind but the method of blinding was inappropriate (e.g., different packaging type in intervention and placebo group)

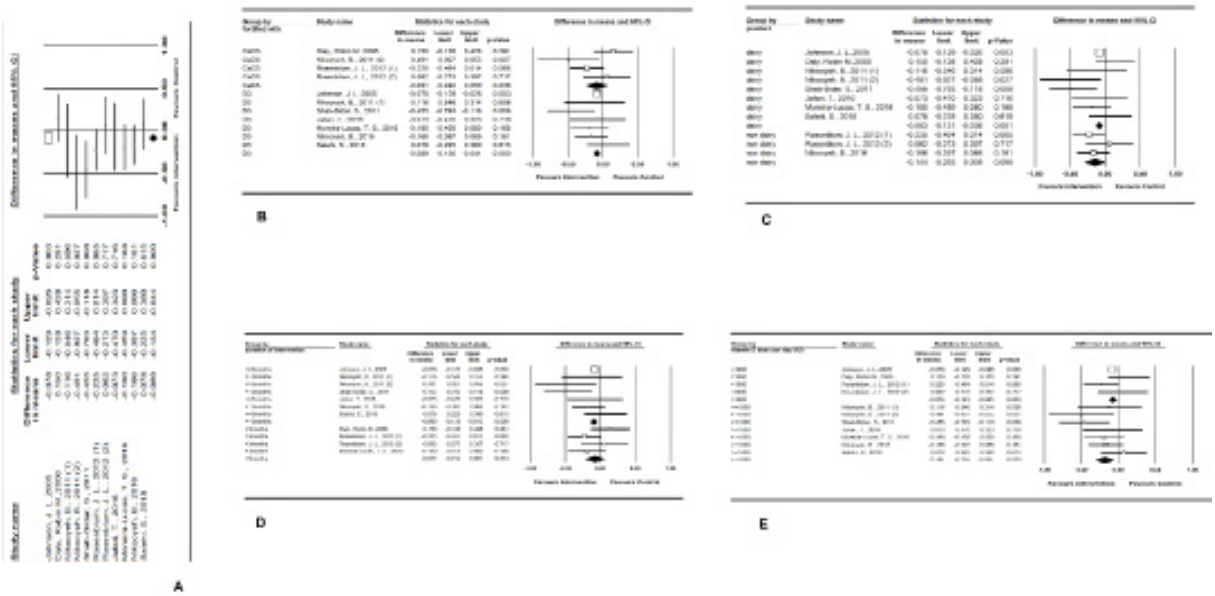

Figure 2. a: Forest plot for the assessing the relationship between using vitamin D fortified food and total cholesterol level and subgroup analysis according to b)fortification substance, c)fortified product, d)duration of intervention and e)dose of vitamin D (Note that numbers written in front of some studies indicate two different fortified intervention groups (based on table 1). Each intervention group counted as an independent study and marked with a number)

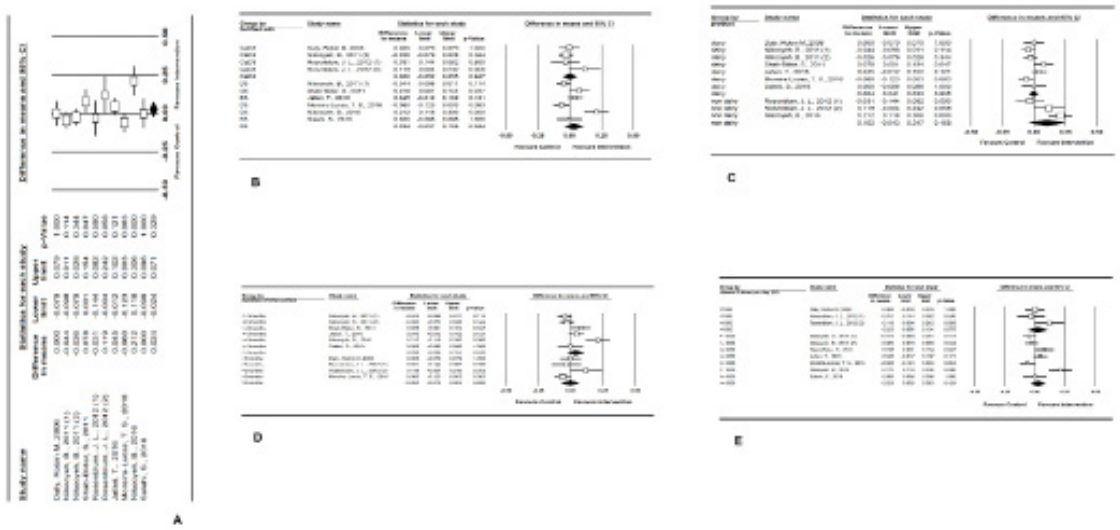

Figure 3. a: Forest plot for the assessing the relationship between using vitamin D fortified food and high density lipoprotein level and sub-group analysis according to b)fortification substance, c)fortified product, d)duration of intervention and e)dose of vitamin D. (Note that numbers written in front of some studies indicate two different fortified intervention groups (based on table 1). Each intervention group counted as an independent study and marked with a number)

products fortified with only vitamin D and three studies used products fortified with vitamin D plus calcium. One study compared both types of products (both vitamin D and calcium plus vitamin D fortified foods). The duration of most interventions ranged from 2-6 months, with a single study having a duration of 24 months (22). The dairy or non-dairy type, fortification dose, fortification with vitamin D or calcium-vitamin D as well as duration of using fortified product were evaluated in separate sub-groups in all studies and their association with different plasma lipid profile components was evaluated.

Risk of Bias of Included Studies

As shown in table 2, only four studies obtained a complete Jadad score (complete 5 score), but all of the studies had the minimum acceptable score (≥3). So, the quality of all the included studies was appropriate.

Effect of vitamin D fortification on serum lipids

TC was reduced by fortification regardless of source; whether dairy or non-dairy products,

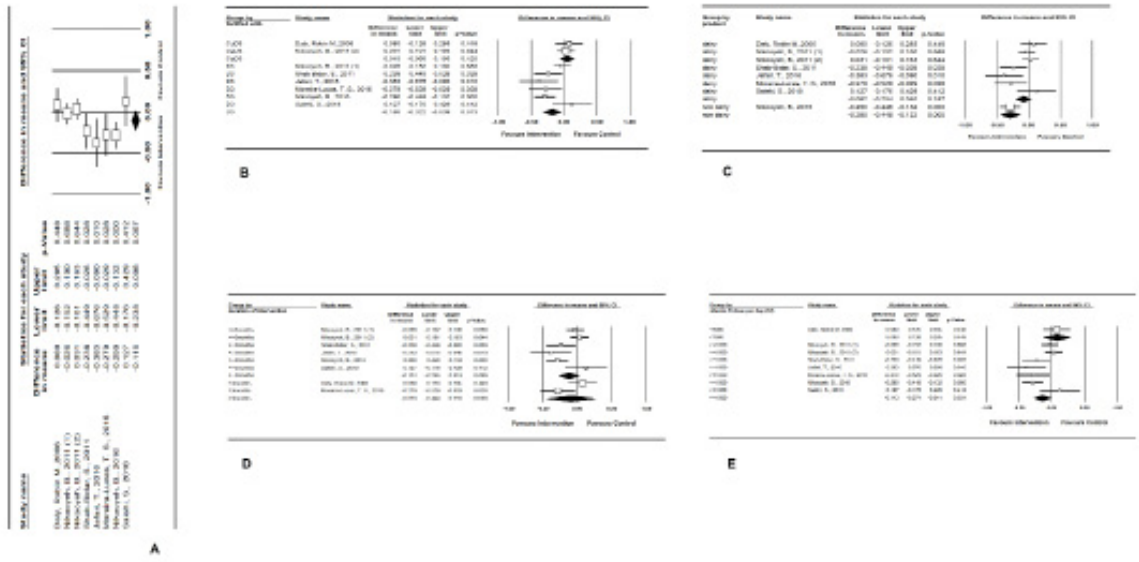

Figure 4. a: Forest plot for the assessing the relationship between using vitamin D fortified food and low density lipoprotein level and sub-group analysis according to b)fortification substance, c)fortified product, d)duration of intervention and e)dose of vitamin D (Note that numbers written in front of some studies indicate two different fortified intervention groups (based on table 1). Each intervention group counted as an independent study and marked with a number)

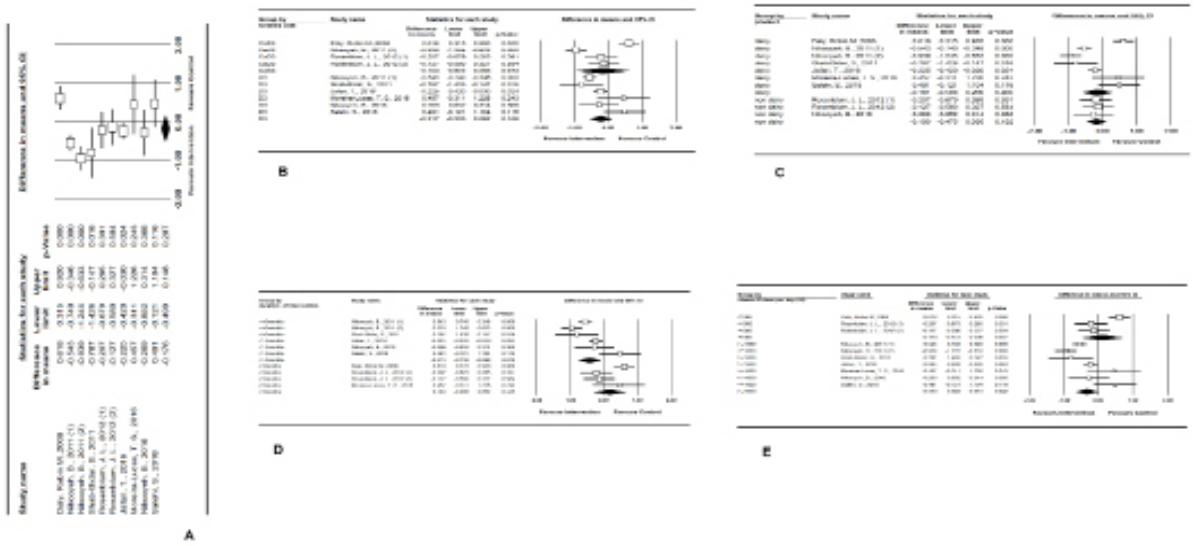

Figure 5. a: Forest plot for the assessing the relationship between using vitamin D fortified food and triglyceride level and sub-group analysis according to b)fortification substance, c)fortified product, d)duration of intervention and e)dose of vitamin D (Note that numbers written in front of some studies indicate two different fortified intervention groups (based on table 1). Each intervention group counted as an independent study and marked with a number)

dose, duration of using fortified product and fortification with vitamin D or calcium-vitamin D (Difference in means: -0.089 mmol/L, 95%CI: -0.134 to -0.044, p<0.001). A vitamin D fortification duration of >3 months was not associated with a significant improvement in serum TC, TG, LDL-C and HDL-C. Using fortified products for less than 3 months was associated with a significant reduction in serum TC and TG. Figures 2 to 5 show the relationship between different lipid profile components and fortification characteristics.

Fortification with calcium-vitamin D did not significantly affect lipid profile components. Fortification with vitamin D in contrast to fortification with Calcium-vitamin D was associated with a significant reduction in serum TC (Difference in means: -0.089 mmol/L, 95%CI: -0.136 to -0.041, p<0.001) and LDL-C (Difference in means:-0.18 mmol/L, 95%CI: -0.322 to -0.039, p=0.013). Furthermore, fortification with doses of vitamin D greater than 1000 IU was associated with a significant reduction in serum TC (Difference in means: -0.181 mmol/L, 95%CI: -0.301 to -0.061, p=0.003), LDL-C (Difference in means: -0.143 mmol/L, 95% CI:-0.274 to -0.011, p=0.034) and TG (Difference in means: -0.33 mmol/L, 95% CI: -0.648 to -0.013, p=0.042); while fortification with doses lower than 1000 IU could not reduce TG and LDL-C but it reduced TC significantly (Difference in means: -0.074 mmol/L, 95%CI: -0.123 to -0.025, p=0.003).

According to the search strategy, only one

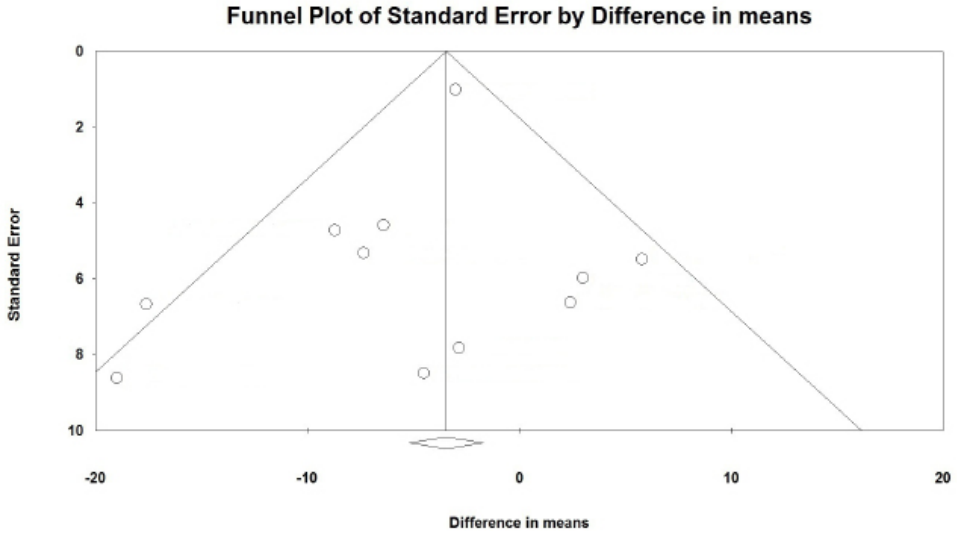

Figure 6: Funnel plot for included studies of total cholesterol

clinical trial which investigated lipoprotein (a) and Apolipoprotein A1 and Apolipoprotein B reported that fortification could significantly improve level of lipoprotein (a) and Apolipoprotein A1 in type 2 diabetic patients (30).

Publication bias

Publication bias was evaluated by Egger`s test. There was no evidence of publication bias for the outcomes: serum total cholesterol (0.43), HDL-C (0.14), LDL-C (0.42) and TG (0.48). A funnel plot of the impact on serum total cholesterol is shown in figure 6.

Discussion

To the best of our knowledge, the current systematic review and meta-analysis is the first that assesses the effect of vitamin D fortification on lipid profile in RCTs.

In the current review, consuming vitamin D fortified foods was associated with a slight but significant reduction in serum TC, but had no significant effects on other components of the lipid profile. The possible association between lipid profile and vitamin D status has been established in cross sectional studies (19), however recently, some studies including that of Faridi et al. have demonstrated this possible relationship in a community based follow up study on 13,039 participants (20) and showed that vitamin D deficiency was correlated with lower HDL-C and TC. They also found that in comparison with normal vitamin D level, participants with vitamin D deficiency had higher risk of dyslipidemia.

Regarding the treatment of vitamin D deficiency in the general population, two strategies have been reported; supplementation and fortification. Vitamin D supplementation was found to be associated with an improvement in serum lipid levels. However, a meta-analysis on the effect of vitamin D supplementation on blood lipids in 2012 showed that there was no significant relationship between supplementation and TC, HDL-C and TG. According to the results of 12 clinical trials, vitamin D supplementation significantly increased LDL-C levels (35). This current meta-analysis has addressed some shortcomings of randomized clinical trials, because many of the evaluated studies were of limited sample size. Wang et al. stated that further large scale randomized trials could affect the results of their meta-analysis in near future (35). Moreover, they concluded that the lack of sufficient randomized trials evaluating the higher doses of supplementation is evident and future randomized studies with adequate doses of vitamin D supplementation could also provide valuable results (35).

With respect to vitamin D fortification there have been few well designed RCTs and their results are heterogeneous due to different vitamin D doses, duration of intervention, fortified products and characteristics of participants. Most of the studies in this analysis used a high dose of vitamin D (>1000 IU/day) for a short duration (≤3months). It should be also noted that in the current meta-analysis, there were RCTs from countries with both mandatory and non-mandatory fortification policies. There are mandatory fortification policies in the US, Canada and Australia for some products. In these countries vitamin D is added to margarine. In the US, fortification of cow`s milk is also mandatory (14). But the fortified products used in the included trials were not part of mandatory policies (e.g. cheese in Canada and the US, and milk in Australia).

In the sub-group analysis, doses of vitamin D, either greater, or lower than 1000 IU, were both shown to significantly reduce serum TC, while for serum TG, only the higher dose had a significant effect in reducing TG. The duration of the intervention (more or less than 3 months) had no significant effect in LDL-C and HDL-C, whilst a duration of <3 months (vs. >3 months) could reduce TG and TC significantly. These results were similar in some respects to the meta-analysis of Wang in 2012 (35). In this current systematic review vitamin D supplementation had obvious effect in the shorter duration studies, but its effect were only shown on LDL-C, while in the present study the effect was only on total cholesterol. A greater effect in the short term studies could be due to poor compliance of the subjects in the longer term.

Nikooyeh et al. demonstrated that plain yogurt without vitamin D can significantly increase TG; whilst fortification with 300 mg of calcium plus 1000 IU vitamin D3 significantly decrease TG level (23). Shab-Bidar et al. demonstrated that after intervention (500 ml/d vitamin D3-fortified doogh containing 1000 IU vitamin D3) serum TG and LDL-C decreased while HDL-C increased significantly (28). Nikooyeh et al. demonstrated that both HDL-C and LDL-C levels could be significantly affected by consuming vitamin D fortified bread (1000 IU/day vitamin D) (32). The only study which used fortified yogurt demonstrated that this fortification did not affect serum lipid profile (31). Fortified orange juice which was used in the study of Rosenblum et al. did not significantly affect serum HDL-C, TC and TG levels (29).

Kumaratne et al. have reported that overweight and obese participants with vitamin D deficiency

had significantly higher serum levels of TC, LDL-C and TG (21). In contrast, in participants with normal body mass index or underweight no significant association was found between vitamin D and serum lipid concentrations (21). A meta-analysis of the effects of vitamin D supplementation on lipid profile in women with gestational diabetes, demonstrated that supplementation could only reduce LDL-C level (36).

An earlier meta-analysis regarding the effect of vitamin D on serum lipid profile of diabetic patients has shown some interesting results. This meta-analysis evaluated both vitamin D supplementation and fortification (37). According to their search strategy, they evaluated 4 clinical trials which used fortification and 16 clinical trials using supplementation. Their study demonstrated that vitamin D had minor effect on serum lipids of diabetic patients and could not be considered as a useful therapeutic modification in such patients. Vitamin D improved TG, TC and LDL-C levels in diabetic patients and did not alter HDL-C levels significantly. According to their results, in contrast to vitamin D supplementation, fortification had a greater impact in patients with type 2 diabetes. Our meta-analysis shows that as reported by Jafari et al. (37), fortification did not significantly affect HDL-C levels. Moreover, we could not find any positive relationship between serum HDL-C, LDL-C and TG levels and vitamin D fortification in our study. A possible explanation for the differences in the results of these meta-analysis may relate to the inclusion criteria. Jafari et al. considered both food fortification and supplementation while we have only considered fortification (37). Moreover, regardless of differences in inclusion criteria, since 2012, six clinical trials have been conducted about vitamin D fortification in diabetic patients.

The relationship between vitamin D fortification and serum lipid profile is addressed in several articles (1, 19, 20). However, the exact mechanism behind this relation is not fully understood. A possible explanation may be the relationship between vitamin D level and parathyroid hormone (PTH) (38). PTH has been shown to raise serum TG and vitamin D can regulate PTH levels (39). Increased concentration of vitamin D can reduce serum PTH and therefore reduce TG levels (39). Another possible association may be the relationship between the effects of calcium on lipid hemostasis. Vitamin D3 can increase the intestinal absorption of calcium and reabsorption by kidneys (40). The increased absorption of calcium from intestine induced by increased level of vitamin D can increase the insoluble complexes of calcium-fatty acid and decrease fatty acid absorption from bowel. Moreover, calcium may increase the conversion of cholesterol to bile acids (41, 42). This should however be interpreted with caution as increased level of calcium may even end up in hypertriglyceridemia. A large Italian cohort study demonstrated that progressive increase of calcium level is related to worsening of lipid profile and suggested controlled use calcium and vitamin D supplementation especially in those who have higher risks of cardiovascular adverse events (43). Furthermore, some studies have demonstrated that vitamin D may be negatively associated with LDL-C and positively with TC concentrations (44, 45). As TC comprises of different components including HDL-C and LDL-C, the effect of vitamin D on TC may not be so specific for all of its components. So, it is possible that the relation between vitamin D and a cholesterol component may be inverse from its relation with TC (45).

Fortified foods are the major source of vitamin D in Canada and the US but the fortification practices in these two countries are different (46). Hennessy and his colleagues in the review of the effect of voluntary food fortification on micronutrient intakes in European countries found that voluntary fortification can improve the status of some micronutrients such as vitamin D and folate in both children and adults. The result of Laaksi et al. study in Finland was highlighted in the mentioned review article because it was one of the most specific study on vitamin D fortification. The prevalence of vitamin D insufficiency decrease from 78% to 35% and the prevalence of vitamin D deficiency decrease from 19% to 5% only one year after the vitamin D fortification policy (46).

Another review conducted by Chadare et al. concluded that although food fortification is necessary for both developed and developing countries, it is not the only way to overcome the widespread nutritional deficiencies. In this review there are some examples of both classical food fortification and food-to-food fortification interventions. It should be noted that none of the examples on food-to-food fortification addressed vitamin D deficiencies (47).

With respect to cost-effectiveness, there are few studies which evaluate the economic value of different products fortified with vitamin D in various status (48). Ethgen et al. confirmed the cost-effectiveness of vitamin D fortified dairy products in patients with osteoporotic fractures (49). A modelling study using data from Wales and England also strongly recommend fortifying wheat flour with Vitamin D (50).

The current review has some limitations.

First, data of the participants` weights were not mentioned in most of the included studies. Obesity is associated with dyslipidemia, and it may have an effect on vitamin D metabolism too. Second, only studies published in English were included in this review and it could influence our results. Third, as the mean baseline serum vitamin D level was in beneficial range only in two studies (22, 29), the participants` response to the intervention could not be evaluated based on this factor. Finally, as there were few studies with non-dairy fortified products, the results derived from this meta-analyses should be interpreted with considerable caution.

Conclusion

Our systematic review and meta-analysis showed that only TC was significantly reduced by using vitamin D fortified foods. It reduces regardless of using different dairy or non-dairy product with various doses and duration of using fortified product and fortification with vitamin D or calcium-vitamin D. However this reduction, whilst statistically significant, may not be clinically important. According to this study results, among serum lipids including TC, TG, LDL-C and HDL-C, fortification of vitamin D may have significant effect on reducing total cholesterol. Our results also suggests the need for further robust randomized controlled trials with greater populations to provide conclusive evidence. Moreover, more variable doses of vitamin D fortification can be used in further trials in order to reevaluate the effects of fortifications on other plasma lipid parameters which are not considered to take effect from vitamin D fortifications.

Conflict of interest

The authors have no conflicts of interest to declare.

Declaration of interest

The authors report no declarations of interest.

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