

REVIEW ARTICLE

A systematic review and meta-analysis of the effect of Vitamin D-fortified food on glycemic indices

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Abstract

Some reports indicated that Vitamin D may improve glycaemia indices in diabetic patients. The aim of this systematic and meta-analysis was to evaluate effects of Vitamin D fortification on indices of glycemic control. Six databases (PubMed/Medline, ISI Web of Knowledge, Cochrane Library, Science Direct, Scopus, and Google Scholar) were searched, for randomized controlled trials that were published up to September 2018 and that compared the effect of Vitamin D-fortified food versus regular diet in relation to glycemic control. Of the 4,379 studies originally found, 11 articles remained to be assessed for meta-analysis. Vitamin D fortification was associated with a significant improvement in fasting serum glucose (mean difference [MD]: -2.772; 95% confidence interval [CI]: -5.435 to -0.109) and fasting serum insulin (MD: -2.937; 95% CI: -4.695 to -1.178) in patients with Type 2 diabetes mellitus. A diet with food enriched with Vitamin D was associated with a significant improvement in homeostatic model assessment of insulin resistance (MD: -1.608; 95% CI: -3.138 to -0.079) but was not associated with a significant reduction in hemoglobin A1C (MD: 0.034; 95% CI: -0.655 to 0.069). This meta-analysis indicates that Vitamin D fortification improves indices of glycemic control. Hence, food fortified with Vitamin D may be of potential therapeutic value in diabetic patients, as an adjuvant therapy.

Abbreviations: FSG, fasting serum glucose; FSI, fasting serum insulin; HbA1C, hemoglobin A1C; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement; PTH, parathyroid hormone; RCT, randomized controlled trial; T2DM, Type 2 diabetes mellitus; VAT, visceral adipose tissue; 25(OH)D, 25-hydroxy Vitamin D.

Maryam Emadzadeh and Reza Sahebi contributed equally as first author to this study.

KEYWORDS

diabetes, fasting serum glucose, fortification, glycemic indices, vitamin D

1 | INTRODUCTION

Vitamin D is an essential fat-soluble nutrient.¹ Vitamin D deficiency is very common in populations around the world,² and this affects economic and public health,³ including the development of children.⁴ Previous research has suggested that Vitamin D deficiency is linked with increased risks of cardiovascular disease, autoimmune disorders and diabetes mellitus.⁵

According to the International Diabetes Federation, there are 425 million diabetic patients globally.⁶ Many reports indicate that Vitamin D has an antioxidant role in diabetes mellitus⁷ and may also improve glycaemia index such including fasting blood glucose (FBG), homeostatic model assessment of insulin resistance (HOMA-IR), and hemoglobin A1C (HbA1C).⁵ The Institute of Medicine has published the dietary reference intakes for Vitamin D and proposed that the appropriate serum level concentration of 25(OH) D is 50 nmol/L, and this is required for all normal health.⁸ Although the main source of Vitamin D is by dermal synthesis following sun exposure (wavelength between 290 and 315 nm), people living at $\geq 40^\circ$ latitude are exposed to insufficient UV light for adequate Vitamin D synthesis.⁹ Hence, these people may require Vitamin D from the diet.¹⁰ Dietary sources rich in Vitamin D include egg yolk, fish liver oil, and nuts, and dietary fortification could be supply large amounts of Vitamin D.¹¹ In some countries such as the United States, Vitamin D-fortified foods include juice, yoghurt, cheese and butter¹² than can provide approximately 60% of Vitamin D requirement.¹³ In the United States, Vitamin D-fortified foods have been used for many years.¹⁴

Nowadays, there are voluntary and mandatory Vitamin D-fortified food policies in many industrial countries across the world.¹⁵ For example, the Ministry of Trade and Industry of Finland in 2003 suggested Vitamin D fortification of margarines and fluid milks spreads on a voluntary.¹⁶ Although in many countries Vitamin D food fortification is voluntary¹⁷ but in several countries such Germany, national laws restricting addition of Vitamin D to food including margarine.¹⁵ A study in Finland demonstrated that adding Vitamin D at a dose of 10 μ g to all fat spreads increased mean serum 25(OH) D concentrations from 47.6 in the 2000 nmol/L to 65.4 nmol/L in 2011.¹⁶ These data suggested that Vitamin D food fortification could be improved the level concentration of serum 25(OH) D. Shab-Bidar et al. in a randomized

controlled trial (RCT) in 2011 reported that improving the Vitamin D status could improve glycemic status in type 2 diabetic subjects.¹⁸ Also Nasri suggested supplementary Vitamin D affected glycemic parameters and reduce HbA1C in male type 2 diabetic patients.¹⁹ In line with the research of Nasri, Vahedian concluded consumption of Vitamin D decreased insulin resistance and fasting blood sugar in patients with type II diabetes.²⁰

To gather and pool the results of the related RCTs, in the present study we aimed to assess the effect of consuming Vitamin D-fortified food on serum glycaemic indices by systematically reviewing the literature and conducting meta-analysis on all randomized controlled trials investigating the effect of this intervention vs. regular diet.

2 | METHODS

In the current study we used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) guidelines.²¹

2.1 | Search strategy

PubMed/Medline, ISI Web of Knowledge, Cochrane Library, Science Direct, Scopus and Google Scholar were searched using the appropriate key words. To avoid missing relevant articles, the search key words were carefully selected. The main key words were "Vitamin D" or "vit D" combined with "fortification" or "fortified" or "fortified food" or "fortifi*." The search strategy was adapted for each database. Randomized controlled trials comparing the effect of Vitamin D-fortified food versus regular diet in the improvement of glycemic status were included. Indices of glycemic status include HbA1C, fasting serum glucose (FSG), fasting serum insulin (FSI) and homeostatic model assessment-insulin resistance (HOMA-IR). Only articles published in English were entered. The last search was done on November 25, 2018 and articles published prior to September 30, 2018 were searched.

2.2 | Data extraction and quality assessment

Two reviewers (M. E. and R. S.) extracted the data. First authors' name, publication year, type of studies, name of

the country, population characteristics, type of fortified food, the dose of Vitamin D used in fortification, and duration of the intervention were extracted.

Two reviewers (M. E. and R. S.) separately assessed the quality of the included studies using the Jadad scale.²² This scale included five questions about randomization, blinding, and dropouts. It ranges between 0 and 5, while higher score shows the higher quality.²³ Scores of 3 and more is considered appropriate.

2.3 | Selection criteria (inclusion and exclusion criteria)

All randomized controlled trials (RCTs) comparing the effects of Vitamin D-fortified food or calcium–Vitamin D (Ca–D)-fortified food versus regular diet (or using non-fortified food) on glycemic status in adult patients were included. Foods fortified with multinutrients or those

which fortified with nutrients other than Vitamin D or Ca–D were excluded. We included only original articles, while other search results such as conference papers, book chapters and reviews were excluded. We removed duplicate studies by title and abstract screening (Figure 1).

2.4 | Statistical analysis and data synthesis

To calculate the effect size, we used the mean change from baseline to the last follow-up time for all quantitative outcomes in both intervention and control groups. If needed, we converted the measurement units in order to pool the data with the same units of measurements.

To compensate for the heterogeneity of studies regarding different population and various fortified products, we used the random effects model. Effect size

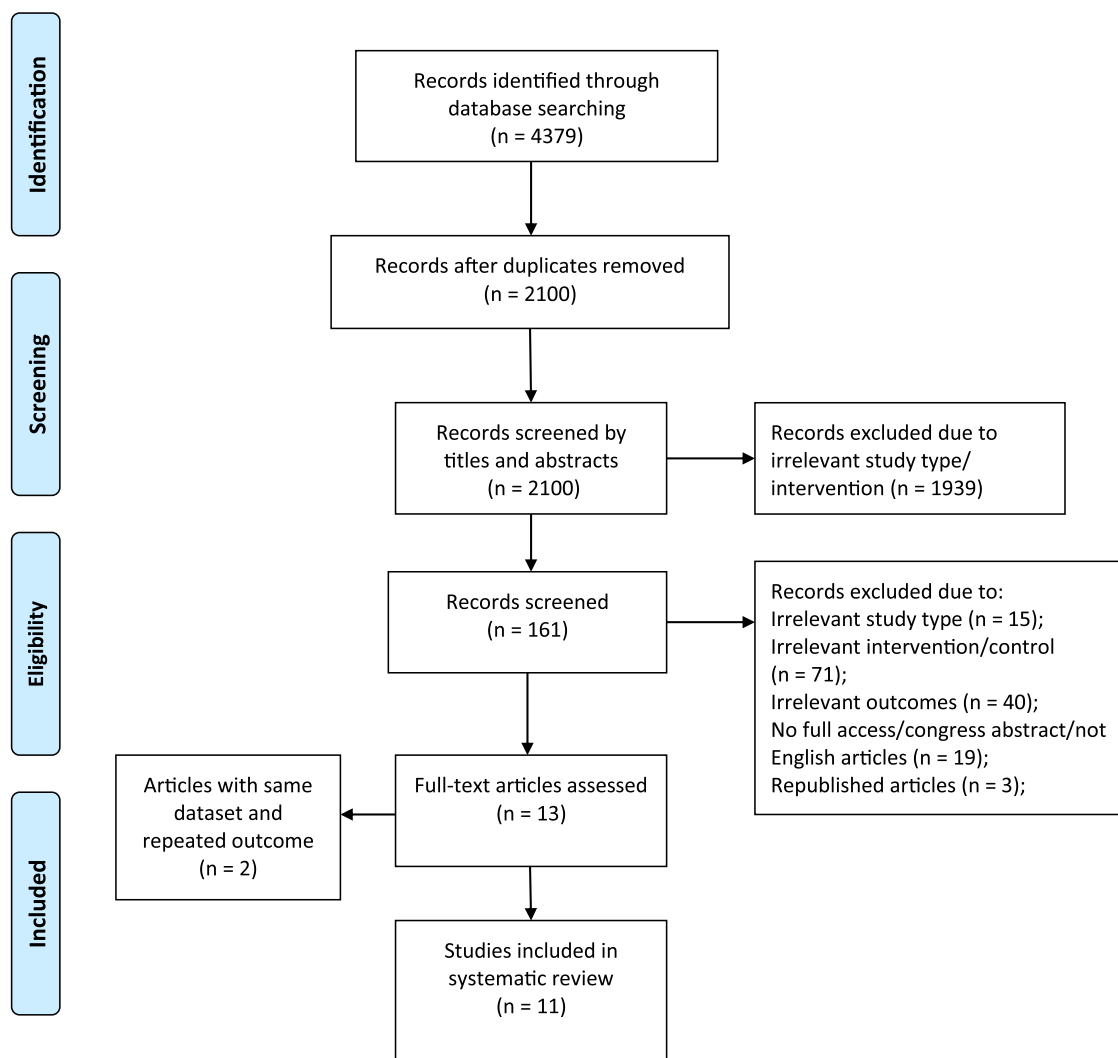


FIGURE 1 PRISMA flow chart for the selection of studies. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

TABLE 1 Jadad score of the included studies

ID	Was the study described as randomized? ^a	Was the study described as a double blind? ^a	Was there a description of withdrawal and dropouts? ^a	The randomization scheme described and appropriate ^a	The method of double blinding described and appropriate ^a	The randomization scheme described and inappropriate ^b	The method of double blinding described and inappropriate ^b	Total score
Nikooyeh et al. ²⁶	1	1	1	0	0	0	0	3
Shab-Bidar et al. ¹⁸	1	1	0	0	1	0	0	3
Neyestani et al. ²⁷	1	1	1	0	0	0	0	3
Rosenblum et al. ²⁸	1	1	1	1	1	0	0	5
Shab-Bidar et al. ²⁹	1	1	0	0	1	0	0	3
Heravifard et al. ³⁰	1	1	1	0	0	0	0	3
Jafari et al. ³¹	1	1	1	1	1	0	0	5
Moreira-Lucas et al. ³²	1	1	1	1	1	0	0	5
Nikooyeh et al. ³³	1	1	0	1	1	0	0	4
Mostafaei et al. ³⁴	1	1	1	0	0	0	0	3
Salehi et al. ³⁵	1	1	1	1	1	0	0	5

^aYes: +1; no: 0.^bYes: -1; no: 0.

presented as mean difference (MD) and 95% confidence intervals (CIs). If the *SD* of means was not reported in the studies, we calculated them using imputing *SD* based on the Cochrane handbook.²⁴ To determine the influence of variables such as being diabetic or not and type of the substance which the product have been enriched with (Vitamin D or Ca-D), we conducted subgroup analysis.

2.5 | Publication bias

We used Funnel plots and Egger's test to identify publication bias. We conducted the meta-analysis with comprehensive meta-analysis V3 software.²⁵

3 | RESULTS

3.1 | Summary of searches and study selection process

We identified 4,329 articles through database searching. After excluding duplication 2,100 studies were remained. From the remaining 2,100 publications, 1939 studies were ruled out because they had irrelevant study type/intervention. The remaining 161 papers were screened for eligibility and 148 articles excluded because of irrelevant study type, irrelevant intervention/control, irrelevant outcomes, no full access/congress abstract/not English articles, republishing articles. Finally, 13 full-text articles assessed and by removing two other articles with repeated outcomes and same datasets, 11 studies were used in a systematic review.

3.2 | Risk of bias assessment

The quality evaluation of all studies which we used was performed with high scores (>3) according to Jadad scale. The results of the quality study are shown in Table 1.

3.3 | Characteristics of the eligible studies

Table 2 shows first author's name, reference number, country (city), population, and the type of interventions and control. Population includes patients with diabetes and healthy group. Age range and type of diabetes are also included. From 11 studies, 9 studies were based in Iran, 1 in the United States, and 1 in Canada. All studies were conducted on diabetic subjects except 2 studies which addressed healthy and prediabetic subjects.^{7,34} In 7 studies, the intervention period was 3 months or less

TABLE 2 Characteristics of included studies

Author	Country (city)	Population	Intervention (type, dose, sample size)	Control (type, sample size)	Duration of intervention	Confounding factors adjusted in each study
Nikooyeh et al. ²⁶	Iran (Tehran)	Diabetic subjects (30–60 years old)	1 500 cc/day Vitamin D3-fortified yogurt drink (containing 1,000 IU Vitamin D3); <i>n</i> = 30	Plain yogurt drink; <i>n</i> = 30	3 months	Fat mass
			2 500 cc/day Ca-D3-fortified yogurt drink (containing 1,000 IU Vitamin D3 and 500 mg ca); <i>n</i> = 30	Plain yogurt drink; <i>n</i> = 30	3 months	
Shab-Bidar et al. ¹⁸	Iran (Tehran)	Patients with T2D (29–67 years)	500 mL/day Vitamin D3-fortified yogurt drink (doogh) (containing 1,000 IU Vitamin D3); <i>n</i> = 50	Plain doogh; <i>n</i> = 50	3 months	Fat mass and waist circumference
Neyestani et al. ²⁷	Iran (Tehran)	Type 2 diabetic patients (30–60 years)	1 500 cc Vitamin D3-fortified doogh (containing 1,000 IU vitamin D3); <i>n</i> = 30	Plain Persian yogurt drink (doogh); <i>n</i> = 30	3 months	ND
			2 500 cc Ca-D3-fortified doogh (containing 1,000 IU Vitamin D3 and 500 mg ca); <i>n</i> = 30	Plain Persian yogurt drink (doogh); <i>n</i> = 30	3 months	
Rosenblum et al. ²⁸	United States (Boston, MA)	Healthy overweight and obese men and women (18–65 years)	1 720 cc/day Ca-D-fortified regular orange juice (containing 350 mg ca and 100 IU Vitamin D); <i>n</i> = 33	Unfortified regular orange juice; <i>n</i> = 38	4 months	ND
			2 720 cc/day Ca-D3-fortified lite orange juice (containing 350 mg ca and 100 IU Vitamin D); <i>n</i> = 41	Unfortified lite orange juice; <i>n</i> = 42	4 months	
Shab-Bidar et al. ²⁹	Iran (Tehran)	Patients with T2D (29–67 years)	500 mL/day Vitamin D3-fortified yogurt drink (doogh) (containing 1,000 IU Vitamin D3); <i>n</i> = 50	Plain doogh; <i>n</i> = 50	3 months	ND

(Continues)

TABLE 2 (Continued)

Author	Country (city)	Population	Intervention (type, dose, sample size)	Control (type, sample size)	Duration of intervention	Confounding factors adjusted in each study
Heravifard et al. ³⁰	Iran (Tehran)	Type 2 diabetic patients (30–60 years)	1 500 cc Vitamin D3-fortified doogh (containing 1,000 IU Vitamin D3); <i>n</i> = 30	Plain Persian yogurt drink (doogh); <i>n</i> = 30	3 months	ND
			2 500 cc Ca–D3-fortified doogh (containing 1,000 IU Vitamin D3 and 500 mg ca); <i>n</i> = 30	Plain Persian yogurt drink (doogh); <i>n</i> = 30	3 months	
Jafari et al. ³¹	Iran (Tehran)	Postmenopausal women with Type 2 diabetes	100 g/day Vitamin D-fortified yogurt (containing 2000 IU Vitamin D); <i>n</i> = 32	Plain yogurt; <i>n</i> = 32	3 months	ND
Moreira-Lucas et al. ³²	Canada (in three centers: Toronto, Guelph, Montreal)	Men and women with IFG (18–75 years)	30 g/w Vitamin D3-fortified low-fat cheddar cheese (containing 28,000 IU Vitamin D3); <i>n</i> = 35	Usual low-fat cheddar cheese; <i>n</i> = 36	6 months	Adjusted for baseline values, age, baseline BMI, sex, and recruitment season
Nikooyeh et al. ³³	Iran (Tehran)	Healthy subjects (20–60 years)	50 g Vitamin D3-fortified bread (containing 25 µg Vitamin D3) + placebo/day; <i>n</i> = 30	50 g plain bread + placebo/day; <i>n</i> = 30	2 months	Adjusted for changes of BMI, waist circumference, and visceral fat
Mostafai et al. ³⁴	Iran (Tehran)	Prediabetic individuals (25–65 years)	200 g/day Vitamin D-fortified yogurt (containing 2000 IU Vitamin D); <i>n</i> = 30	Plain yogurt; <i>n</i> = 30	3 months	ND
Salehi et al. ³⁵	Iran (Tehran)	Type 2 diabetic patients (31–74 years)	250 cc/day Vitamin D3-fortified yogurt (containing 1,000 IU vitamin D3); <i>n</i> = 51	Plain yogurt; <i>n</i> = 50	2 months	Adjusted for age, sex, BMI, and corresponding baseline values

Note: The studies of Nikooyeh et al.,²⁶ Neyestani et al.,²⁷ Rosenblum et al.,²⁸ and Heravifard et al.³⁰ had different fortified intervention groups. Each intervention group counted as an independent study.

Abbreviations: BMI, body mass index; IU, International Unit; IFG, Impaired Fasting Glucose; ND, not determined; T2D, Type 2 Diabetes.

and only 2 report the intervention period was more than 3 months.^{28,32} In all studies, the enriched product was a dairy product, except study conducted by Rosenblum et al that used juice.²⁸ All research studies used high-dose

Vitamin D (more than 1,000 IU per day). In 7 studies, the product used in the intervention was enriched only with Vitamin D^{7,18,29,31,32,34,35} and in one study with Ca–D.²⁸ Three studies had two different interventional groups,

FIGURE 2 Forest plots of the association between intake of fortified food with Vitamin D and FSG. FSG, fasting serum glucose

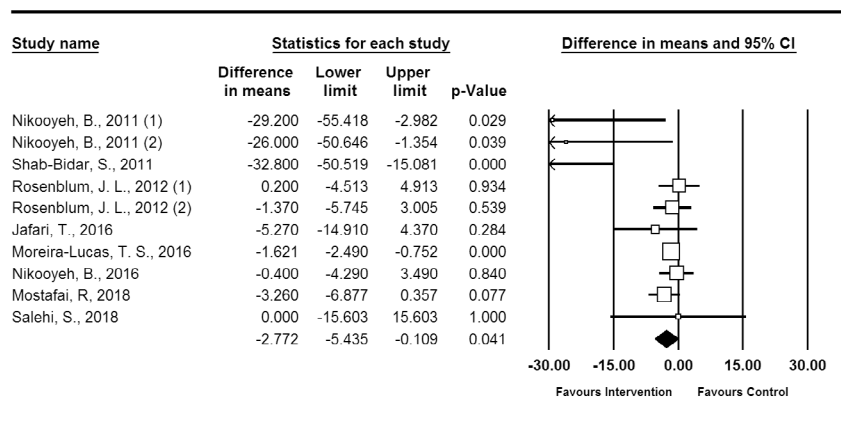
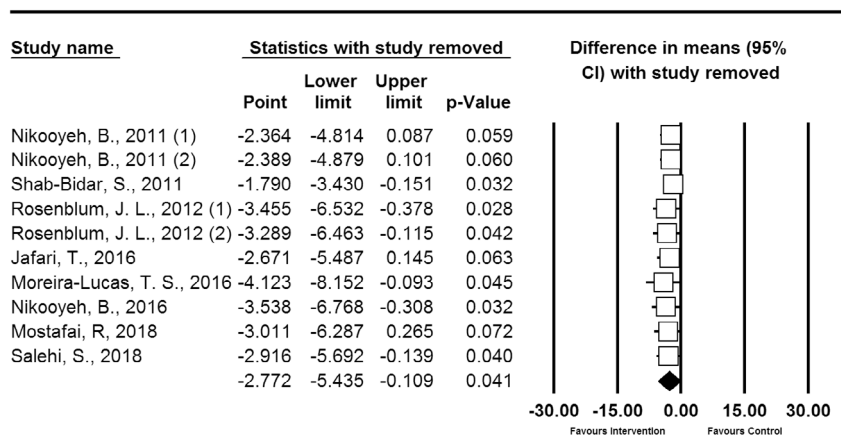
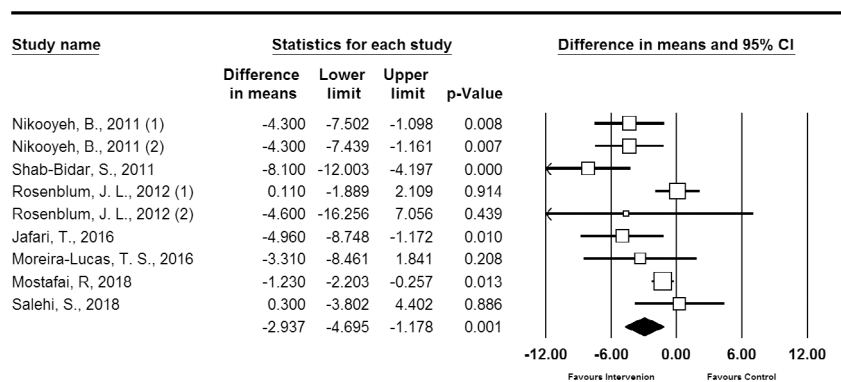


FIGURE 3 Sensitivity analysis plot of FSG. FSG, fasting serum glucose



Meta Analysis

FIGURE 4 Forest plots of the association between intake of fortified food with Vitamin D and FSI in RCTs. FSI, fasting serum insulin; RCTs, randomized controlled trials



Meta Analysis

that both products fortified with Ca-D and Vitamin D alone were studied.^{26,27,30}

3.4 | Pooled estimate of the effect of diabetes-related outcomes

Figure 2 shows the results of the meta-analysis for RCTs for FSG. The pooled results for the effects of enriched

food with Vitamin D on FSG in diabetics were significant (MD: -2.772 , $p = .041$, and 95% CI: -5.435 to -0.109). After subgroup analysis according to the *type of intervention* (Vitamin D or Ca-D), we found that Vitamin D alone significantly reduced FSG more than Ca-D group (pooled effect in Ca-D subgroup: -1.8 , 95% CI: -7.344 to 3.741 ; in the *Vitamin D* subgroup: -3.641 , 95% CI: -7.229 to -0.053). Subgroup analysis according to *duration of intervention* (less or more than 3 months) indicated that

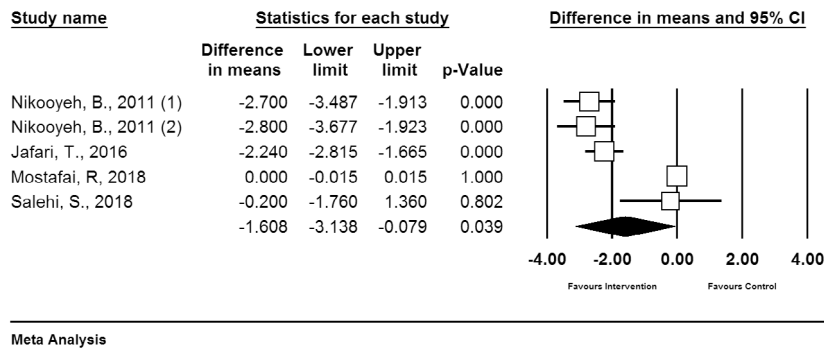


FIGURE 5 Forest plots of the association between intake of fortified food with Vitamin D and HOMA-IR in RCTs. HOMA-IR, homeostatic model assessment of insulin resistance; RCTs, randomized controlled trials

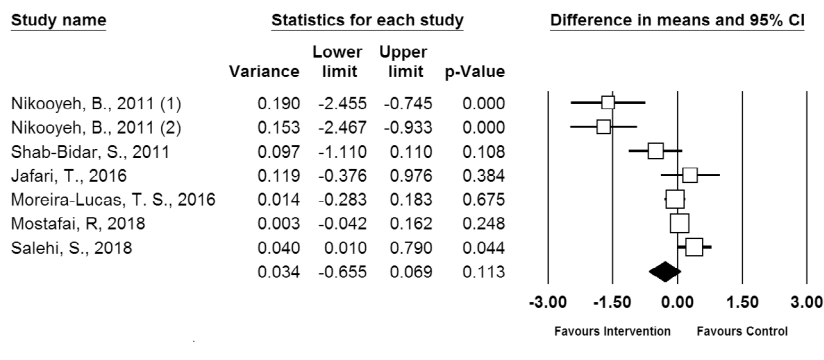


FIGURE 6 Forest plots of the association between intake of fortified food with Vitamin D and HbA1C in RCTs. HbA1C, hemoglobin A1C; RCTs, randomized controlled trials

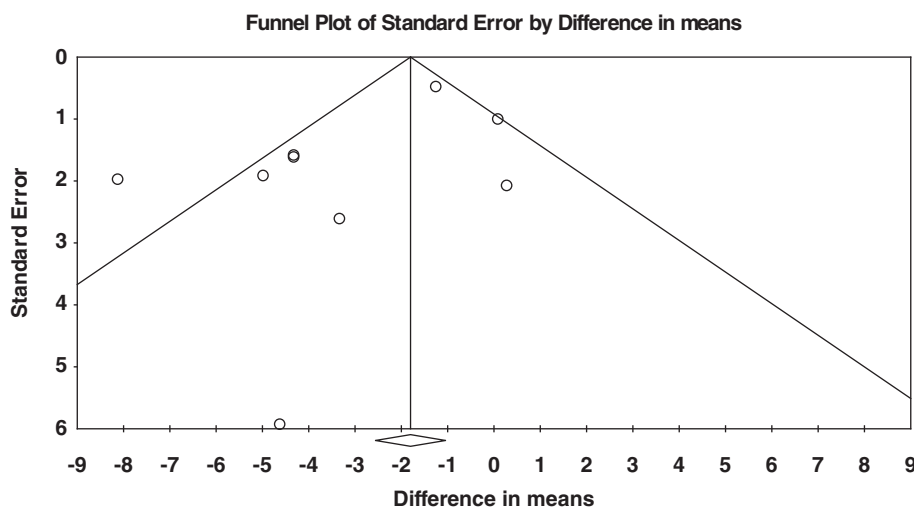


FIGURE 7 Funnel plot for included studies of FSI. FSI, fasting serum insulin

both short and long durations significantly reduced FSG, whilst for shorter duration interventions the reduction was greater (in <3 months of intervention: MD equals to -7.677 [95% CI: -14.067 to -1.296]; in >3 months of intervention: MD equals to -1.554 [95% CI: -2.393 to -0.716]).

As can be seen in Figure 3, the first three studies are the cause of significant results. Sensitivity analysis indicated by removing the study of Nikooyeh,²⁶ the *P* value

became greater than statistically significance level of .05 (Figure 3).

Figure 4 shows Vitamin D fortification is associated with a significant effect on FSI in diabetics (MD: -2.937 , $P = .001$ and 95% CI: -4.695 to -1.178).

Subgroup analysis for FSI according to type of intervention showed the same result as FSG (pooled effect in Ca-D subgroup: -2.122 , 95% CI: -5.865 to 1.61 ; in Vitamin D subgroup: -3.432 , 95% CI: -5.83 to -1.035). From

the intervention duration point of view, the significant reduction is seen in short versus long duration (MD: -3.589 , 95% CI: -5.9 to -1.278 vs. MD: -0.444 , 95% CI: -2.284 to 1.396 , respectively).

In line with FSG and FSI, Figure 5 shows that Vitamin D-fortified food has a significant effect on HOMA-IR (MD: -1.608 , $p = .039$ and 95% CI: -3.138 to -0.079). Unlike FSG, FSI, and HOMA-IR, food fortified with Vitamin D did not reduce HbA1C significantly (MD: 0.034 , $p = .113$ and 95% CI: -0.655 to 0.069) (Figure 6).

3.5 | Publication bias

Publication bias was evaluated by both the visual inspection of funnel plot and Egger's test. There was no evidence of publication bias for the main outcomes: FSG (0.07), FSI (0.11), HbA1C (0.17). Funnel plot of the FSI is shown in Figure 7.

4 | DISCUSSION

We have undertaken a systematic review and meta-analysis of the effects of Vitamin D-fortified food on glycemic control and insulin resistance. To the best of our knowledge, this study was the first systematically review of the effect of Vitamin D fortification on glycemic indices, and suggests that Vitamin D-fortified products improve control of glycemic indices like FSG, HOMA-IR, and FSI in individuals suffering from Type 2 diabetes.

The main source of Vitamin D in man is from dermal synthesis. Factors such as the duration of exposure, latitude, season, senescence, skin pigmentation, and the continued use of sunscreens can affect the synthesis of Vitamin D.³⁶ Some research has led to the proposal that the daily intake of a Vitamin D, either with or without added calcium, improves glycemic status in Type 2 diabetes mellitus (T2DM) patients.^{26,29,31} Furthermore, Vitamin D-fortified products were found to be associated with a significant reduction in HOMA-IR,^{31,34} FSG,³⁴ insulin,^{31,34} IL-6, and TNF- α ; and an increase in quantitative insulin-sensitivity check index³¹ and sensitivity to insulin and anti-inflammatory cytokines like IL-10.²⁹ In agreement with previous studies, Nikooyeh et al demonstrated, Vitamin D fortification intake has potentially beneficial effects as assessed by an improvement in glucose tolerance test and reduction in the prevalence of T2D.²⁶

Furthermore, Nikooyeh's²⁶ research indicated Vitamin D-fortified yogurt with or without calcium is effective on glycaemia indices such as FSG and FSI in comparison with Rosenblum,²⁸ which fortified Vitamin D with or without calcium in orange juice contribute to a

beneficial reduction of visceral adipose tissue (VAT). The pooled effect of the current meta-analysis was in line with Nikooyeh's research.

As shown in FSG funnel plot, only a limited number of studies have shown a *significant* decrease in FSG.^{26,29,32} It is also important to note that Mostafai³⁴ and Nikooyeh,⁷ which both did not show a significant reduction in FSG levels, investigated the effects of Vitamin D fortification in prediabetic/healthy subjects.

Because of two different intervention groups in Nikooyeh study,³³ this article is presented as two separate studies in the first two lines of the FSG funnel plot. This study could be responsible for the significant results in FSG meta-analysis. Sensitivity analysis also showed that by removing each intervention in this article (first or second line in FSG funnel plot) the results became insignificant. It should be noticed that in this article participants monitored strictly and the compliance rate was about 100%.

A low-serum 25-hydroxy Vitamin D [25(OH)D] has been associated with impaired glucose tolerance in T2DM.²⁶ The concentration of serum Vitamin D is reported to be lower in diabetic patients than in healthy people.^{37–40} In some studies, Vitamin D supplementation did not affect fasting plasma glucose^{31,35} or insulin resistance³² and there was no significant relationship between T2D with serum Vitamin D levels.^{41,42} Overall, according to Yazdchi study, Vitamin D consumption in subjects with T2D improved measures of glycemic status^{32,43} and HbA1C levels and no complications have been reported.⁴⁴

Vitamin D plays a potentially important role in T2D by suppressing activation of T cells and systematic inflammatory markers.^{29,31} Although Ford and coworkers report that FSG and HbA1C were higher in patients with T2DM compared to healthy control, serum Vitamin D did not differ significantly between the subjects and unrelated nondiabetic controls.⁴⁵ Consumption of Vitamin D supplements has a beneficial effect on HbA1C and FBG in patients with T2DM and Vitamin D insufficiency.^{29,33} Nikooyeh and Shab-bidar showed serum glucose, HbA1C, HOMA-IR, oxidative stress^{29,33} and insulin improved after Vitamin D-fortified yogurt drink and Ca-D-fortified yogurt drink intake in the intervention group.²⁶ Furthermore, Shab-bidar et al have suggested Vitamin D3-fortified doogh compared with plain doogh leads to a reduction in serum high-sensitivity C-reactive protein (hs-CRP) and parathyroid hormone (PTH) concentrations.^{29,31,33}

Esteghamati et al showed that Vitamin D deficiency is associated with reduced serum level of insulin in T2DM.⁴⁶ RCTs indicate that Vitamin D fortification can improve serum Vitamin D level,³² glycemic indicator,^{26,30,32,34,35} serum hs-CRP,^{27,29} lipid profile, and anthropometric indices.^{26,28,30,31,33,35} Furthermore, several studies have shown

that HbA1C is reduced in intervention group compared to control group.^{26,31,34,35} In the current meta-analysis, reduction in HbA1C is seen but the reduction was not significantly. This may be due to the short duration of the intervention periods to affect the HbA1C. As HbA1C reflects the long-term glycemic control, long-term interventions could affect this index. In some studies, HbA1C was reduced in both groups. It is possible that the improvement in the control group was due to dietary change and taking plain dough that contains calcium without Vitamin D and it is a kind of food and it is replaced instead of some other food groups like carbohydrates.³⁵ Jafari et al have shown that daily consumption of 2000 IU Vitamin D fortified yogurt for 12 weeks had not improved HbA1C in postmenopausal woman,³¹ which we can relate it to other changes in hormonal status and they might need more amount of Vitamin D fortified as a result of Vitamin D deficiency.

It has to be pointed that some previous studies^{47,48} even with high dosages and longer interventional period performed on Vitamin D deficient patients, did not find a significant improvement in glycemic control. In addition, Heravifard et al have demonstrated that consumption of Ca-D is more effective compared with intake Vitamin D only to decrease the risk of T2DM and ameliorates-related factors, glycemic and inflammatory, better,³⁰ while in the current review it is shown that Vitamin D alone significantly reduced FSG and FSI and these reduction is not statistically significant in Ca-D group. Following some previous studies, Nikooyeh showed that Vitamin D fortification leads to a significant reduction to insulin resistance, FSG, waist circumference, and body mass index in the intervention group.²⁶ Moreira et al. observed that the intake of Vitamin D fortification did not effect on insulin sensitivity, B-cell function and fasting glucose; however, it caused an increase in serum Vitamin D levels.³²

In contrast to these studies, Mostafai³⁴ and Nikooyeh³³ showed that fortification of yogurt and bread is more beneficial for improvement of diabetic patients status compare with similar amount of supplementation. Mostafai et al. have shown that 1,000 IU Vitamin D-fortified yogurt decrease FSG and HOMA-IR better compared with the exact amount of Vitamin D supplementation FSG and HOMA-IR.³⁴ In an another study, Nikooyeh et al have demonstrated that 25 mcg fortified-bread compares with the exact amount of Vitamin D supplementation reduced visceral fat and low-density lipoprotein (LDL), while both of them increase HDL equally and decrease TG.³³

Nowadays, most of the Vitamin D fortification projects focus on dairy products like milk, cheese, and yogurt. While, Nikooyeh et al. in a study by fortification of *bread* in healthy people for 8 weeks have shown that Vitamin

D-fortified bread increase Vitamin D concentration, decrease PTH and ameliorates lipid profile.³³ Rosenblum et al. have demonstrated that juice fortification of 950 mg Ca and 300 IU Vitamin D reduce VAT significantly and have a not significant effect on weight loss.²⁸ In the current meta-analysis, only these two trials worked on non-dairy products and other studies used dairy products as intervention. In addition, it should be noticed that all the included studies were in English language and studies published in other languages did not enter in this review. These make the results be interpreted with caution.

5 | CONCLUSIONS

This systematic review and meta-analysis demonstrated that Vitamin D has significant effects on FBG in Type 2 diabetics. Also, Vitamin D fortification leads to an improvement in HOMA-IR, FBG, and HbA1C. But these results are driven by a small number of positive studies. It is therefore unclear whether, Vitamin D could be used as an adjuvant therapy along with the other treatments for those patients. Further studies are required to better understand the relationship between Vitamin D fortification, in both dairy and not-dairy products, and glucose homeostasis indexes in Type 2 diabetes patients. More trials are needed to find out the effect of non-dairy products fortification (vs. dairy-fortified foods) and also the effect of the season of intervention and its simultaneous effect with sun exposure.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Maryam Emadzadeh conducted the primary search, extracted data, and assessed the quality of the included articles with collaboration of Ramin Sadeghi. Ramin Sadeghi, Hamed Khedmatgozar, and Payam Sharifan wrote the draft of the article. RS involved in meta-analysis. Maryam Emadzadeh and Yalda Ravanshad involved in data extraction. Majid Ghayour-Mobarhan designed the research and developed the overall research plan, final review and approved the draft. Gordon A. Ferns collaborated in final review and approval of the draft, English edition and critical review of the draft. Majid

Ghayour-Mobarhan had primary responsibility for final content. All authors have read and approved the final version of this manuscript.

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