Special Article

Effect of vitamin D supplementation on serum lipid profiles: a systematic review and meta-analysis

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Context: *Vitamin D deficiency is highly prevalent across the world. The existing evidence suggests vitamin D may have beneficial effects on serum lipid profiles and thus cardiovascular health.* ***Objective:*** *The objective of this systematic review and meta-analysis was to examine the effect of vitamin D supplementation on serum lipid profiles.* ***Data Source:*** *Original randomized controlled trials (RCTs) examining the effect of vitamin D supplementation on serum lipid profiles and published before July 2018 were identified by searching online databases, including PubMed, Google Scholar, and ScienceDirect, using a combination of relevant keywords.* ***Data Extraction:*** *Data on study characteristics, effect size, measure of variation, type of vitamin D supplementation, and duration of follow-up were extracted by the author.* ***Data Analysis:*** *PRISMA guidelines for systematic reviews were followed. Random effects (DerSimonian and Laird [D-V)] models were used to pool standardized mean differences in total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides between the active and the placebo arms of RCT studies. Between-study heterogeneities were assessed using Cochrane Q and I^2, and publication bias was assessed using Begg's test, Egger's test, and funnel plot.* ***Results:*** *A total of 41 RCTs comprising 3434 participants ($n = 1699$ in the vitamin D supplementation arm and $n = 1735$ in the placebo arm) were identified and included in the meta-analysis. Approximately 63.4% of study participants were women, with 14 studies conducted entirely among women. Approximately 24% of the trials had follow-up duration >6 months, whereas the remaining 76% had follow-up duration of <6 months. The standardized mean differences (SMDs) and 95% confidence intervals (CIs) for comparing the change from baseline to follow-up between the vitamin D supplementation arm and the placebo (control) arm were as follows: total cholesterol = –0.17 (–0.28 to –0.06); LDL cholesterol = –0.12 (–0.23 to –0.01); triglycerides = –0.12 (–0.25 to 0.01); and HDL cholesterol = –0.19 (–0.44 to 0.06). After removing a trial that was an outlier based on the magnitude of the effect size, the SMD for triglycerides was –0.15 (–0.24 to –0.06) and that for HDL cholesterol was –0.10 (–0.28 to 0.09). The improvements in total cholesterol and triglycerides were more pronounced in participants with baseline vitamin D deficiency.* ***Conclusions:*** *Vitamin D supplementation appeared to have a beneficial effect on reducing serum total cholesterol, LDL cholesterol, and triglyceride levels but not HDL cholesterol levels. Vitamin D supplementation may be useful in hypercholesterolemia patients with vitamin D insufficiency who are at high risk of cardiovascular diseases.*

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INTRODUCTION

The prevalence of vitamin D deficiency (serum vitamin D $\leq$ 20 ng/mL) in the United States was estimated to be around 40% in general and higher among blacks, Hispanics, Asians, children, and elderly populations.[1,2] Globally, however, vitamin D deficiency is highly prevalent even in those living in low altitudes assumed to have enough ultraviolet (UV) radiation and in developed countries where vitamin D fortification has been implemented.[3–6] Low serum vitamin D is associated with several chronic diseases, including cardiovascular diseases, stroke, and diabetes.[7–11] The results of intervention studies examining the effect of vitamin D on serum lipid profiles are inconsistent. Some studies have shown favorable lipid profiles in those supplemented with vitamin D[12–14] and in those supplemented with calcium and vitamin D[14,15] compared with the control (placebo) arms. However, some of these studies also found unfavorable outcomes for high-density lipoprotein (HDL) cholesterol after vitamin D[13,16] or calcium and vitamin D[15] supplementation. Many other intervention studies have documented favorable but statistically nonsignificant effects of vitamin D[16–19] on serum lipid profiles. A 2012 meta-analysis documented statistically nonsignificant effects of vitamin D supplementation on total cholesterol, low-density lipoprotein (LDL) cholesterol, HDL cholesterol, and triglycerides.[5] Since then, several more RCTs have been conducted to further evaluate the association between vitamin D supplementation and serum lipid profiles. Thus, the current study aimed to examine the effect of vitamin D supplementation on serum lipid profiles among participants in published RCTs using a systematic review and a large meta-analysis. The study was conducted according to the PRISMA guidelines, and the PRISMA checklist is included in the Supporting Information online.

METHODS

Data source and study selection

The author searched for original RCT studies relating vitamin D to serum lipid profiles published before July 2018 in PubMed, ScienceDirect, Google Scholar, and ClinicalTrials.gov using the medical subject header (MeSH) terms "vitamin D" or "VitD" or "25-hydroxy vitamin D" or "25(OH)D3" or "OH25D" or "(OH)25D2" or "(OH)25D3" or "cholecalciferol" and "serum lipid profiles" or "HDL" or "LDL" or "cholesterol" or "total cholesterol" or "TG" or "TAG" or "triglyceride" or "triacylglycerol". Additional RCTs were identified from reference lists of relevant full-text articles retrieved.

To be included studies had to 1) examine the effect of vitamin D on serum lipid profiles, 2) be conducted in a human population aged $\geq$18 years, 3) be an original study, 4) report mean and standard deviations of the lipid profiles, and 5) be a randomized placebo-controlled clinical trial or compare the supplementation arm to a control arm.

The exclusion criteria included 1) nonhuman study, 2) non-RCT study, 3) studies without clear control arm or placebo arm, 4) study duration <1 month, and 5) studies without baseline and end-of-trial serum lipid profiles or without changes in lipid profiles with a related measure of variation. The participant, intervention, comparisons, outcome, and study design (PICOS) criteria are presented in Table 1. The database search resulted in the identification of 8269 studies, and after exclusion of the studies that did not meet the inclusion criteria and duplicate results, a total of 41 RCTs were included in the meta-analysis (Figure 1). Study quality was evaluated using the Jadad scales.[20] An emphasis was put particularly on items directly related to bias, including randomization, double-blinding, and reporting of dropout rates/loss to follow-up (*see Table S1 in the Supporting Information online*). Each of the 3 items was given a score from 0 to 5 points with the maximum total adding to 15 if all 3 items were mentioned and the method was described and appropriate. A score of 0 was given if an item was not mentioned, and points were subtracted from the maximum 5 for each item if the item was mentioned but the method was not appropriate.

Data extraction

The author extracted the data. The extracted data included first author's last name, year of publication, sample sizes in the active arm and control arm, changes in mean from baseline to the end of the study of HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides, and related pooled standard deviations. The name of supplemented vitamin D, treatment dose, treatment duration (months), general health status of participants, percentage female, and vitamin D status (Table 2 and *see Table S1 in the Supporting Information online*) were also extracted.

Data synthesis

For studies for which the lipid profiles were reported as mean changes and associated 95% confidence intervals (CIs), the CIs were converted into SD using $\sqrt{n}$ *(UCI − LCI)/3.92, where n is the sample size and UCI and LCI are upper and lower confidence intervals, respectively. Data reported in millimoles per liter were converted to milligrams per deciliter by multiplying with

Table 1 **PICOS criteria for inclusion and exclusion of studies**

Parameter	Inclusion criteria	Exclusion criteria
Participants	Studies with adult human population aged >18 y	Nonhuman studies (animal studies), studies among children
Intervention	Studies with vitamin D supplementation	Studies with follow-up duration <1 month
Comparison	Studies with placebo or control arm	Studies without a clear comparison group
Outcomes	Studies with mean and standard deviation in total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides at baseline and end of trials or mean changes and standard deviations in the serum lipid profiles in both the vitamin D supplementation and placebo or control arms	Studies not reporting mean and standard deviation in the serum lipid profiles or not reporting mean changes and standard deviations in serum lipid profiles
Study Design	Randomized controlled trials with parallel design	Observational studies, pre/post and cross-over randomized control trials (excluded from the meta-analysis but reviewed), studies without a placebo or control arm, editorials and opinion pieces

38.67 for HDL, LDL, and total cholesterol and by 88.57 for triglyceride.[21] For studies for which the medians and the first and the third quartiles were reported, the medians were converted to mean using, $\bar{x} \approx \frac{X_{Q3} + X_{Q2} + X_{Q1}}{3}$, where X_{Q3} is the 3rd quartile, X_{Q2} is the median, and X_{Q1} is the 1st quartile, and the interquartile range was converted to standard deviation (SD) using $S \approx \frac{X_{Q3} - X_{Q1}}{2 * \Phi^{-1}\left(\frac{0.75 * n - 0.125}{n + 0.25}\right)}$, where n is the sample size and Φ^{-1} is the inverse of the cumulative standard normal distribution.[22] When not given in the original study, change from the baseline was computed for each lipid profile by subtracting the baseline from the end-of-trial values. When the SD in changes in the lipid profile from baseline to the end of trial was not reported, the SD was computed using $\sqrt{S_b^2 + S_e^2 - 2 * 0.5 * S_b * S_e}$, where S_b is baseline SD, S_e is SD at the end of trial, and the correlation between the baseline and the end of trial was assumed to be 0.5 for the given lipid profile.[23]

Statistical analysis

Random effects (DerSimonian and Laird [D-V])[24] meta-analysis models were conducted to pool standardized mean differences (SMDs) between the active arm and the placebo arm of the trials. The SMD was calculated using $\frac{\mu_t - \mu_p}{SD_p}$, where μ_t is the mean of the active arm, μ_p is the mean of the placebo arm, and SD_p is the pooled standard deviation. The risk of publication bias was assessed using Begg's test.[25] Cochran's χ^2 test was used to examine heterogeneity among the included studies, and computed I^2, which is the proportion of the total variation due to heterogeneity between studies, was used to determine the degree of inconsistency across studies. Meta-regression analysis was conducted to explore covariates that might explain the heterogeneity among trials. For the meta-regression analyses, the effect sizes based on the random effect meta-analysis as a dependent variable were regressed on each or on a combination of study-level summary characteristics such as study duration; baseline and end-of-study levels of LDL, HDL, and total cholesterol and triglycerides; publication year; country; baseline health status of the participants/disease; treatment dose; sample size; percentage female; and mean age. The restricted maximum likelihood estimation method was used to estimate the between-study variances, and adjusted R^2 for the proportion of between-study variance explained by a covariate or covariates was reported. The statistical hypothesis of 0 SMD was tested using χ^2 and associated P value. A study with extreme effect size having 95%CIs not covered by the 95%CI of at least 2 other study was considered as an outlier. This was also confirmed if the effect size (SMD) was above the third quartile plus 1.5 times the interquartile range or below the first quartile minus 1.5 times the interquartile range, and such studies were excluded in the sensitivity analysis. All analyses were conducted using STATA statistical software (version 13, STATA Corp, College Station, TX, USA). All statistical tests were 2-sided, and a P value ≤ 0.05 was considered statistically significant.

RESULTS

Overall, 41 RCTs[12,14,16–19,26–58] consisting of 3434 participants with 1699 participants in the active arm and 1735 in the placebo arm were included in the meta-analysis. Fourteen of the trials for which sex information was reported were conducted among women only, with women constituting 63.4% of participants in trials for which sex was reported. The mean age of the participants was 55 years (SD = 11.6); the age range of the participants began at 19 years, but most of the participants were aged > 45 years. The study duration ranged from

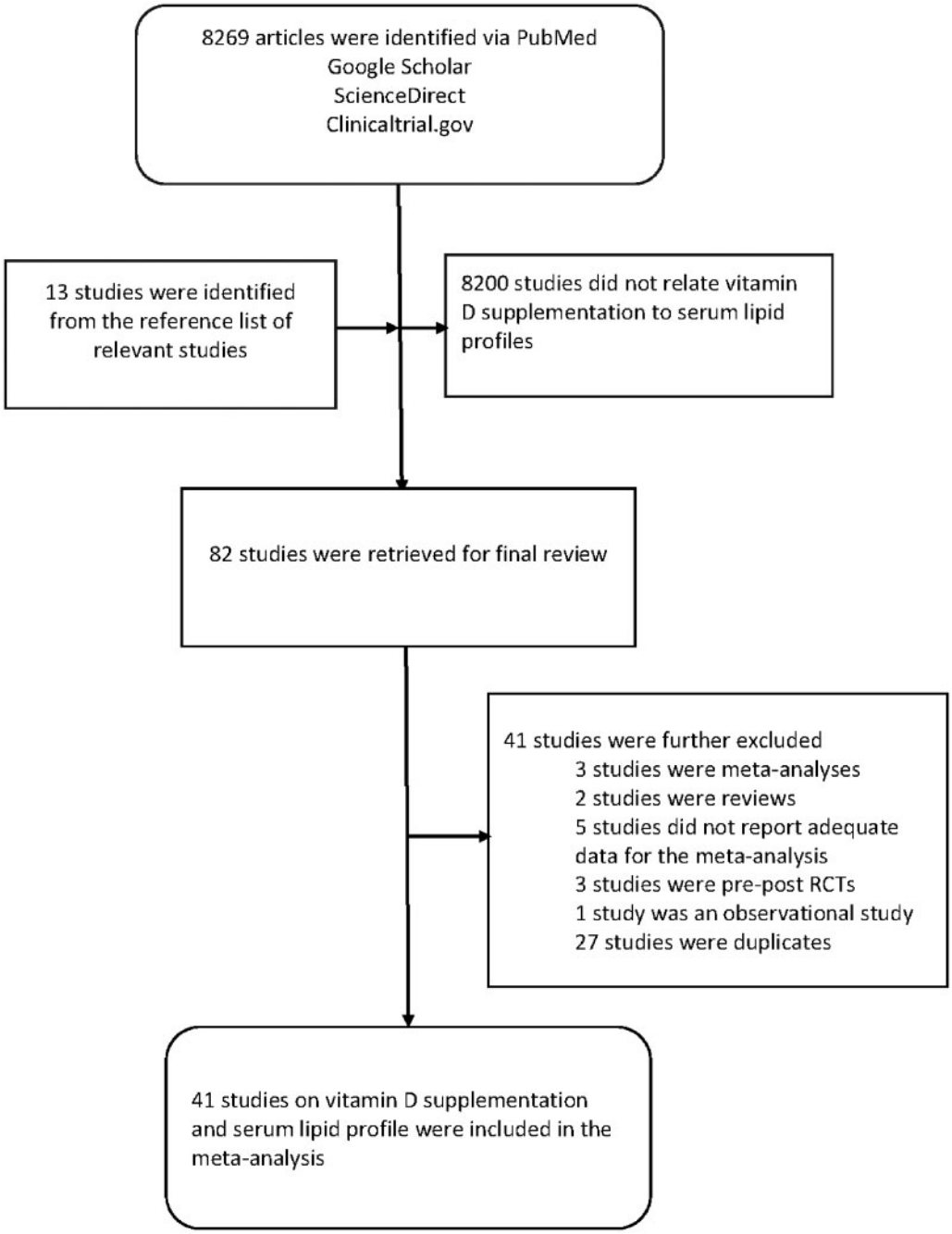

Figure 1 **Flow diagram of the literature search process.** *Abbreviation:* RCT, randomized controlled trial.

6 weeks to 3 years. The mean duration of the study was 6.9 (SD = 7.5) months (Table 2). Mean vitamin D supplement per day was 2795IU (range, 20–8570 IU). Twenty-one trials were conducted on participants with diabetes, 13 trials were conducted on apparently healthy participants, and 3 trials were conducted on those who were obese or overweight. In 24 (68.6%) trials for which vitamin D deficiency (≤20 ng/mL) at baseline was reported, participants were vitamin D sufficient at the end of the trial (see *Table S1 in the Supporting Information online*). In 4 (11.4%) trials, no improvement was seen in serum vitamin D after the trial. In 7 (20%) trials, participants had sufficient vitamin D (>20 ng/mL) both at baseline and at the end of the study. In 6 trials either both baseline and end-of-trial serum vitamin D or end-of-trial serum vitamin D was not reported (*see Table S1 in the Supporting Information online*).

Table 2 **Characteristics of the vitamin D intervention randomized controlled trials included in the meta-analysis**

Author	RxN/CN	%Female	Vitamin D Dose	Duration in months	Treatment				Placebo			
					Change in HDL (SD)	Change in LDL (SD)	Change in TAG (SD)	Change in Total cholesterol (SD)	Change in HDL (SD)	Change in LDL (SD)	Change in TAG (SD)	Change in Total cholesterol (SD)
Tamadon et al (2018)[26]	30/30	36.7	3571 IU/d	3	−0.7±11.9	−4.1±26.6	−9.0±37.5	−6.5±25.1	−0.7±8.3	2.1±31.7	7.3±42.1	2.7±34.7
Farrokhian et al (2017)[32]	30/30	50	3570 IU/d	6	0.4±3.2	2±34.0	2.3±32.9	2.9±32.7	−2.6±6.0	0.5±22.4	25.9±52.3	3.1±30.8
Ghaderi et al (2017)[31]	34/34	0	3570 IU/d	6	4.3±6.3	−11.1±17.9	−9.6±30.8	−8.7±20.9	2.0±3.4	5.9±27.5	15.6±30.2	11.0±27.4
Jamilian et al (2017)[30]	35/35	100	3570 IU/d	6	0.4±7.9	−2.5±39.3	7.6±76.3	−0.5±39.7	7.6±13.4	0.6±30.4	20.1±66.4	3.3±42.0
Liyanage et al (2017)[29]	41/41	–	1667 IU/d	6	5.4±7.2	−13.6±27.7	−4.6±37.7	−9.1±28.8	18.4±10.4	0.10±29.2	0.3±48.3	2.3±31.8
Riek et al (2018)[27]	11/15	50	4000 IU/d	4	5.0±9.8	0±36.5	−7.0±36.2	3.0±36.2	1.0±13.6	4±30.2	4±52.6	6.0±33.7
Mohammadi et al (2016)[33]	32/32	–	7143 IU/d	3				0 ±34.8			−9.0±48.0	3.0±53.7
Jafar et al (2016)[34]	30/29	100	2000 IU/d	3	3.0±10.5	−0.7±36.6	−4.5±54.4	−1.5±46.9	1.3±9.2	14.14±48.2	4.25±73.4	1.4±39.4
Munoz-Aguirre et al (2014)[13]	52/52	100	4000 IU/d	6	1.9±7.5	1.4±29.4	−11.2 ±111.1	0.8±37.2	2.1±7.6	4.0±39.4	−18.9±107.7	7.4±30.2
Shehab et al (2015)[35]	57/55	57.1	7143 IU/d	2	−3.9±10.2	3.9±34.8	8.9±79.7	3.9±44.6	−3.9±16.9	−3.9±63.7	0±79.7	−7.7±39.2
Qin et al (2015)[12]	28/28	44.5	2000 IU/d	6	7.4±12.31	−22.6±26.3	−32.5± 50.32	−26.0±36.7	−1.0±12.5	−3.6±31.1	−1.5±56.1	−3.4±42.3
Asemi et al (2015)[71]	26/26	100	7142 IU/d	8	0.1±4.5	4.1±18.8	−12.0±65.7	1.9±24.0	0.9±17.8	−2.2±31.7	19.4±45.7	2.5±35.3
Al-Zahrani et al (2014)[44]	100/100	51.4	4786 IU/d	3	0±7.7	0±30.8	0±84.8	0±36.2	0.3±8.4	0±29.9	−8.9±76.7	0±35.6
Dalbeni et al (2014)[42]	13/10	38.2	4000 IU/d	6				10.6±49.8				0.3±60.0
Eftekhari et al (2014)[41]	35/35	71.4	20 IU/d	3	−3.8±11.7	−31.1±32.0	−53.2±78.7	−45.5±37.0	−2.6±9.0	−26.7±38.5	−60.9±110.2	−41.5±43.8
Kampmann et al (2014)[40]	8/8	46.7	6520 IU/d	3	−1.9±3.9	0±3.9		0.4±3.9	−0.2±1.9	8.9±3.9		3.9±7.7
Kim et al (2014)[39]	13/11	100	1200 IU/d	3	4.5±9.4	−10.2±18.3	−25.1±50.9	−23.9±24.5	3.3±6.9	−8.5±22.0	−3±48.2	−13.3±33.2
Yousefi et al (2014)[37]	28/30	62.1	4000 IU/d	2	7.3±15.1	−0.6±37.5	−12.9±60.8	−12.8±39.7	7.8±14.8	1.3±40.7	10.8±83.2	16.3±43.3
Ramly et al (2014)[18]	93/99	100	2580 IU/d	12	2.7±18.5	13.9±31.0	18.6±53.5		3.5±15.7	11.21±56.2	58.45±42.2	
Ryu et al (2014)[38]	40/41	–	2000 IU/d	6	1.6±11.3	0.3±26.0	5.3±90.7	4.1±36.8	1.6±8.1	10.2±17.5	13.2±95.9	13.7±26.7
Moghassemi et al (2014)[17]	38/36	100	2000 IU/d	3	4.1±17.9	3.6±34.6	−0.7± 69.9	−9.2±47.7	4.4±13.5	0.8±31.2	−8.95±54.0	−25.7±46.2
Sadiya et al (2015)[36]	43/39	0	4500 IU/d	6	0±7.7	−3.9±33.0	0±87.2	0±38.7	0±10.2	3.9±35.4	8.9±139.1	7.7±44.6

(continued)

Table 2 **Continued**

Author	RxN/CN	%Female	Vitamin D Dose	Duration in months	Treatment				Placebo			
					Change in HDL (SD)	Change in LDL (SD)	Change in TAG (SD)	Change in Total cholesterol (SD)	Change in HDL (SD)	Change in LDL (SD)	Change in TAG (SD)	Change in Total cholesterol (SD)
Breslavsky et al (2013)[58]	24/23	53.2	1000 IU/d	12	0.8±11.5	16.5±38.0	−27.9±157.0	10.1±44.4	1.9±14.0	5.7±23.3	10.3±134.4	6.1±26.9
Chai et al (2013)[14]	22/21	30	800 IU /d	6			0.6±17.9	−8.1±9.7			0.8±17.9	−7.8±9.7
Witham et al (2013)[46]	25/25	100	1667 IU/d	2	0±7.73	−7.7±34.8	−8.9± 44.3	−11.6±38.7	0±7.7	3.867±34.8	0±35.4	0±19.3
Wood et al (2012)[47]	90/91	100	1000 IU/d	12	−2.3±5.9	−3.1±10.4	1.8±22.4	−5.0±16.1	−1.9±6.0	−1.2±11.9	1.8±18.2	−2.3±13.2
Muldowney et al (2012)[48]	51/56	54.3	6000 IU/d	5.5	−6.2±20.8	−6.8±59.2	−9.2±40.1	−6.2±55.5	0.4±16.6	−0.13±54.1	−2.4±43.3	−0.5±56.1
Wood et al (2012)[47]	83/83	100	1000 IU/d	12	−2.7±15.4	−12.1±34.8	2.7±44.3	−5.1±34.8	−1.2±19.3	−1.9±27.0	8.9±57.7	−2.7±30.9
Nikooyeh et al (2011)[51]	30/30	61.1	1000 IU/d	3	0.1±9.8	3.9±22.9	−0.2±61.2	5.3±42.5	1.0±9.0	4.9±25.4	20.8±96.6	9.8±45.9
Sai et al (2011)[50]	86/96	100	20 IU/d	36	−1.4±0.9	0.3±2.5	16.5±6	1.7±3	1.4±0.8	−0.03±2.3	9.3±6.6	2.3±4.7
Shab-Bidar et al (2011)[49]	50/50	57	1000 IU/d	3	24.0±83	−10.7±24.2	−30.3±81.3	−19.4±34.8	−0.6±6.7	−1.5±16.9	0.12±36.8	−1.8±31.7
Jorde et al (2010)[72]	114/112	64.2	5714 IU /d	12	−3.9±6.6	−13.9±19.7	8.9±8.9	−7.4±22.0	−3.5±7.0	−13.15±20.1	6.20±56.7	−7.7±22.0
Witham et al (2010)[52]	17/22	40.5	3333 IU/d	2				−5.0±34.3				6.6±53.7
Witham et al (2010)[52]	19/22	33.3	1667 IU/d	2				−8.1±40.5				6.6±53.7
Andersen et al (2009)[55]	31/27	0	800 IU/d	12	−2.6±6.0	−38.7±58.4	−14.8± 104.3	35.6±58.2	2.6±8.1	−3.9±33.5	0±107.1	9.0±52.14
Andersen et al (2009)[55]	30/29	100	800 IU/d	12	−2.6±10.9	−1.3±26.84	−11.8±53.9	1.3±38.1	5.2±10.9	14.18±35.6	8.9±48.9	18.0±38.7
Nagpal et al (2009)[53]	32/33	0	2000 IU/d	6	3.1±6.2	1.2±18.2	11.5±60.23	7.0±27.1	0.4±9.3	−5.80±26.7	−4.4±45.4	1.6±34.8
Zittermann et al (2009)[19]	82/83	67.3	3320 IU/d	12	−0.8±14.3	7.0±38.2	−17.7±52.9		−1.93±14.9	−3.09±32.8	15.1±58.6	
Pfeifer et al (2001)[56]	74/74	100	800 IU/d	2				−1.6±42.6				−9.2±41.4
Heikkinen et al (1997)[16]	83/95	100	300 IU/d	36	−3.1±1.6	6.2±3.5	14.2±5.4	6.2±3.9	−2.7±1.2	1.16±2.9	1.8±5.5	2.3±3.1
Ljunghall et al (1987)[57]	33/32	0	30 IU/d	12	0 ±11.8			−0.9±98.3	−0.4±7.5		5.3±129.9	−10.0±44.3

Presented values are mean changes (final − baseline) and standard deviation values. All included randomized controlled trials used parallel design.
Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; RCTs, randomized controlled trials; Rx, treatment; SD, standard deviation; TAG, triglyceride; VitD, vitamin D.

Total cholesterol

The random effect model pooled SMD in changes from baseline to the end of the trials between the supplementation arm and the placebo arm for total cholesterol was −0.17 (95%CI, −0.28 to −0.06; I^2=54.6%) (Figure 2). The nonstandardized mean total cholesterol difference was −3.69 (95%CI, −5.78 to −1.59). In meta-regression analysis, end-of-trial total cholesterol in the vitamin D arm explained 100% of the between-study heterogeneity; the adjusted R^2 was 100%. There was no evidence of publication bias (Begg's $P = 0.425$).

Low-density lipoprotein cholesterol

For LDL cholesterol, the SMD was −0.12 (95%CI, −0.23 to −0.01; I^2=52%) (Figure 3). The nonstandardized LDL cholesterol mean difference was −2.92 (95%CI, −5.27 to −0.58). There was no statistically significant publication bias for LDL cholesterol (Begg's $P = 0.06$). Removing the Kampmann[40] trial that appeared to be an outlier, the effect remained (SMD, −0.10; 95%CI, − 0.20 to −0.003) (*see Figure S1 in the Supporting Information online*). In meta-regression analysis, the mean changes in LDL cholesterol in each arm explained 100% of the between-study heterogeneity; the adjusted R^2 was 100%.

High-density lipoprotein cholesterol

For HDL cholesterol, the SMD was −0.19 (95%CI, −0.44 to 0.06; I^2 =91.1%) (Figure 4). The nonstandardized HDL cholesterol mean difference was −1.09 (95%CI, −2.46 to 0.28). In meta-regression analysis, baseline and end-of-trial HDL cholesterol in the placebo arm explained 100% of the between-study heterogeneity; the adjusted R^2 was 100%. There was no evidence of publication bias on the association of vitamin D with HDL cholesterol (Begg's $P = 0.478$). Removing the Sai[50] trial that appeared to be an outlier, there was no material change (SMD, −0.10; 95%CI, −0.28 to 0.09) (*see Figure S2 in the Supporting Information online*).

Triglycerides

The SMD for triglycerides was −0.12 (95%CI, −0.25 to 0.01; I^2=69.1%) (Figure 5). The nonstandardized triglyceride mean difference was −6.92 (95%CI, −11.97 to −1.86). Baseline and end-of-trial triglycerides in the treatment arm and mean change in triglycerides in the placebo arm explained 100% of the between-studies heterogeneity; the adjusted R^2 was 100%. Furthermore, removing the Sai[50] trial that appeared to be an outlier, vitamin D supplementation reduced serum triglycerides (SMD, −0.15; 95%CI, − 0.24 to −0.06; I^2 = 32.9%) (*see Figure S3 in the Supporting Information online*). Because there was an evidence of publication bias (Begg's $P = 0.003$) on the association of vitamin D supplementation with triglycerides, trim-and-fill analysis was conducted with the assumption that trials with direct association may have been suppressed. In the trim-and-fill analysis 12 data points in the positive direction were filled, and vitamin D no longer had a beneficial effect on serum triglycerides (SMD, 0.04; 95%CI, −0.09 to 0.17).

Stratified analysis

In a stratified analysis by trial duration (≤6 months vs >6 months), the effects for total cholesterol, LDL cholesterol, and triglycerides remained for the trials with duration ≤6 months and overall pooled results but disappeared for trials with a duration >6 months (data not shown). The difference might be attributed to the small number of trials (<10) with duration >6 months. There was no marked difference for HDL cholesterol by trial duration. In a stratified analysis by baseline serum vitamin D (≤20 ng/mL and >20 ng/mL) (*see Table S1 in the Supporting Information online*), the observed associations remained for total cholesterol and triglycerides in studies among participants with serum vitamin D deficiency at baseline, whereas in studies among participants with sufficient baseline serum vitamin D there was no beneficial effect; for LDL cholesterol the reverse was observed. Baseline serum vitamin D levels were not reported for 4 studies[14,16,41,50] and were not included in the baseline serum vitamin D stratified analysis. The pooled SMD for total cholesterol was −0.15 (95%CI, −0.24 to −0.05) for studies among participants with baseline serum vitamin D deficiency and –0.13 (95%CI, −0.28 to 0.03) for the studies among participants with sufficient baseline vitamin D; the overall SMD for total cholesterol was –0.14 (95%CI, −0.22 to −0.06). The SMD for triglycerides for studies among participants with serum vitamin D deficiency at baseline was −0.16 (95%CI, −0.29 to −0.02) and was −0.08 (95%CI, −0.24 to 0.08) for studies among participants with sufficient baseline serum vitamin D; the overall SMD was −0.13 (95%CI, −0.23 to −0.03). The SMD for LDL cholesterol was −0.13 (95%CI, −0.29 to 0.02) for studies among participants with baseline vitamin D deficiency, and −0.17 (95%CI, −0.33 to −0.02) for studies among participants with sufficient baseline vitamin D; the overall SMD for LDL cholesterol was −0.15 (95%CI, −0.24 to −0.05). The SMD for HDL cholesterol was not appreciably different based on baseline vitamin D levels. The SMD for HDL cholesterol for the

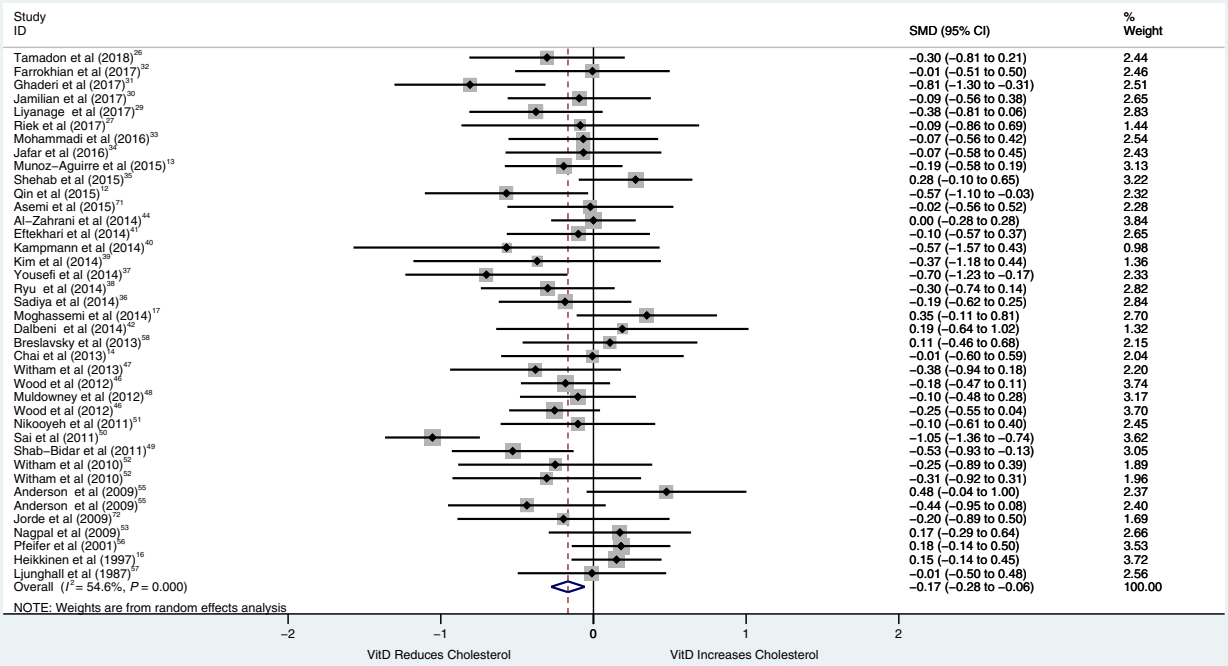

Figure 2 **Forest plot of the standardized mean difference (SMD) in changes from baseline of the total cholesterol in the vitamin D intervention studies.** The horizontal bar indicates the 95% confidence interval. The size of the rectangle at the center of the horizontal bar is proportional to the weight of the given study. The diamond at the bottom indicates the pooled SMD. *Abbreviations:* CI, confidence interval; SMD, standardized mean difference; VtD, vitamin D.

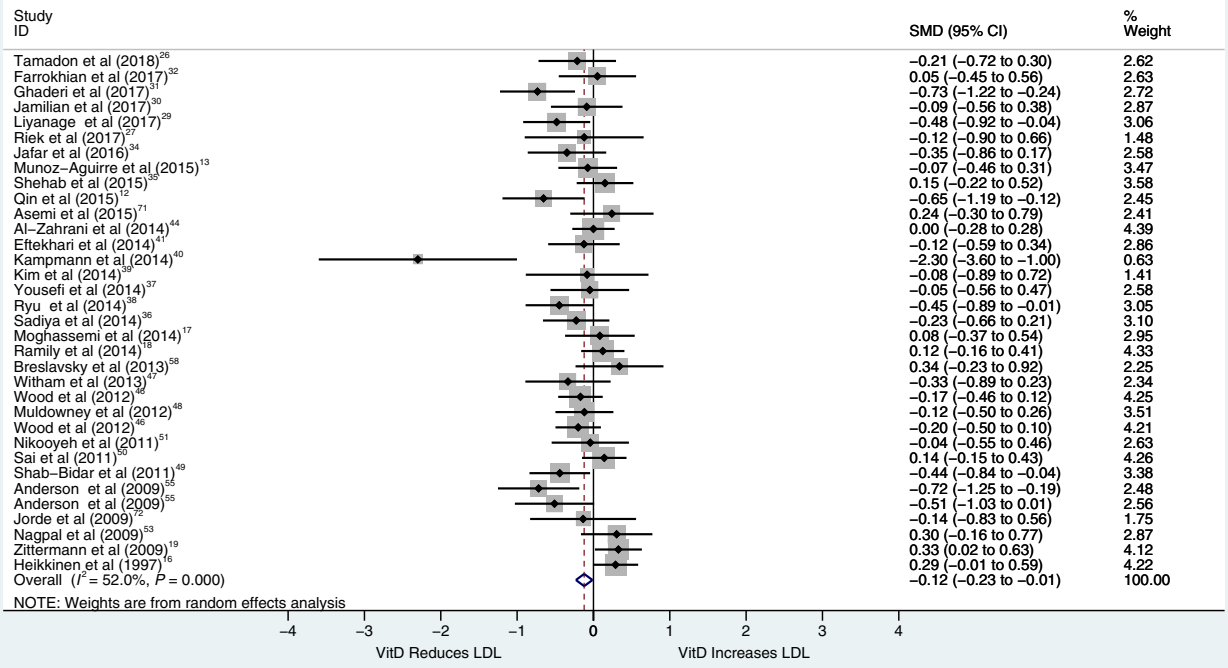

Figure 3 **Forest plot of the standardized mean difference (SMD) in changes from baseline of the low-density lipoprotein (LDL) cholesterol in the vitamin D intervention studies.** The horizontal bar indicates the 95% confidence interval. The size of the rectangle at the center of the horizontal bar is proportional to the weight of the given study. The diamond at the bottom indicates the pooled SMD. *Abbreviations:* CI, confidence interval; LDL, low-density lipoprotein; SMD, standardized mean difference; VtD, vitamin D.

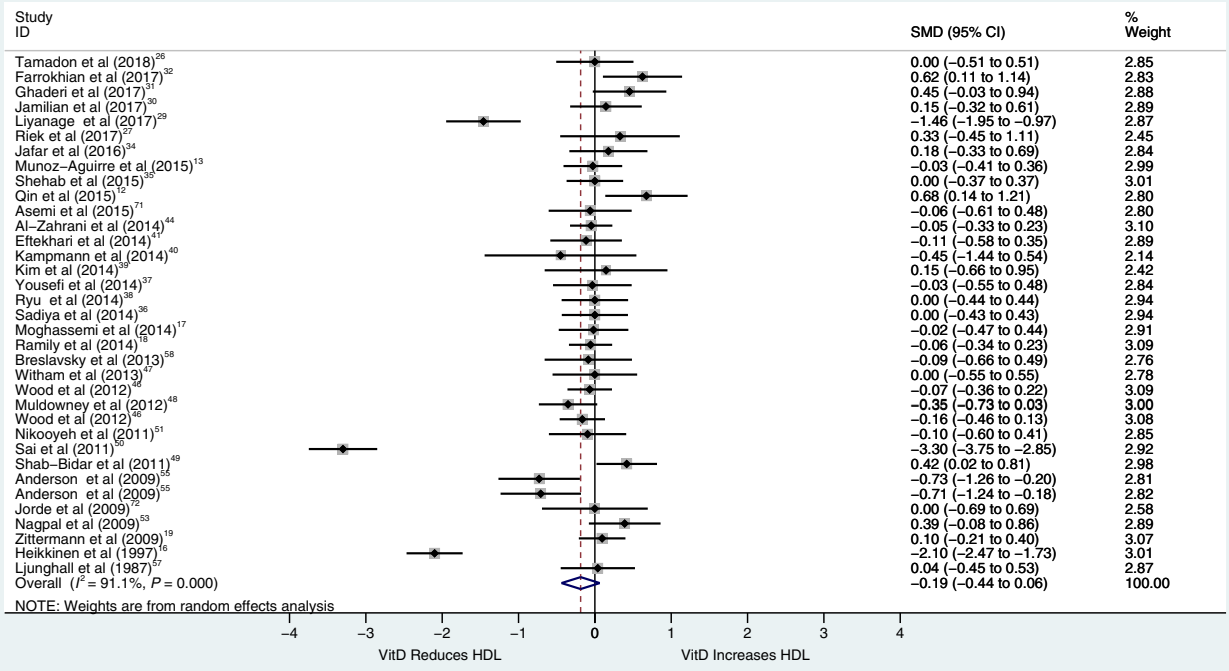

Figure 4 **Forest plot of the standardized mean difference (SMD) in changes from baseline of the high-density lipoprotein (HDL) cholesterol in the vitamin D intervention studies.** The horizontal bar indicates the 95% confidence interval. The size of the rectangle at the center of the horizontal bar is proportional to the weight of the given study. The diamond at the bottom indicates the pooled SMD. *Abbreviations:* CI, confidence interval; HDL, high-density lipoprotein; SMD, standardized mean difference; VtD, vitamin D.

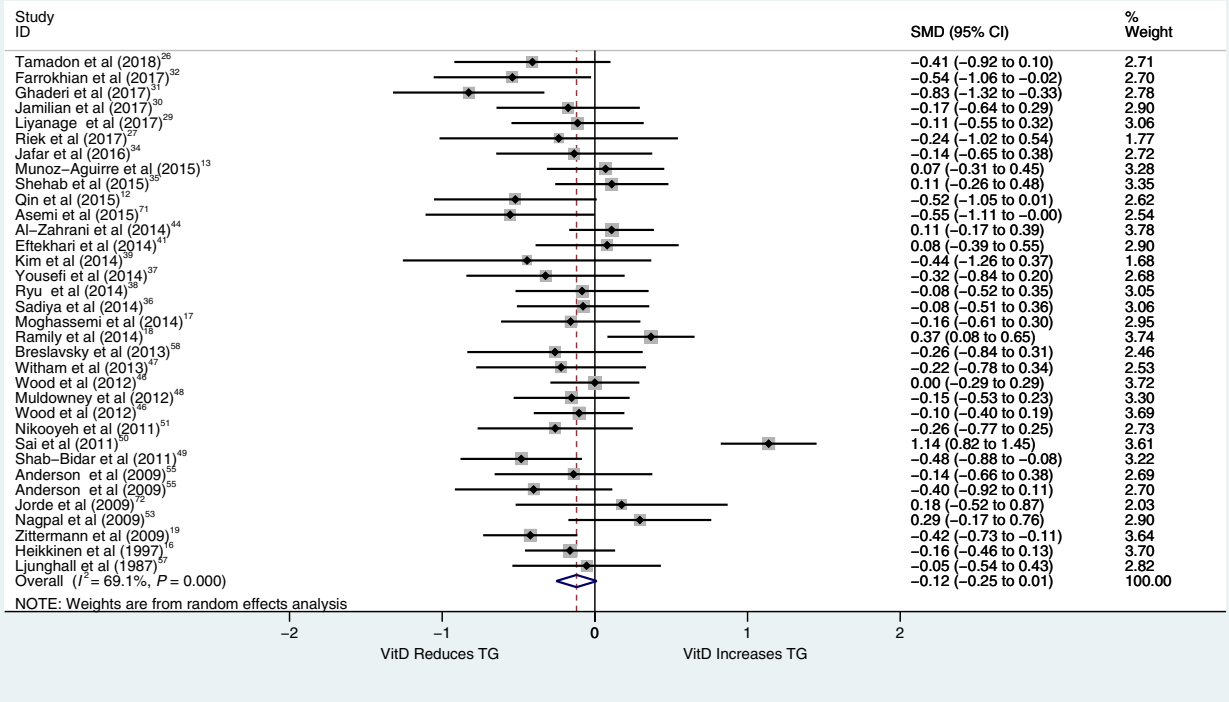

Figure 5 **Forest plot of the standardized mean difference (SMD) in changes from baseline of the triglyceride in the vitamin D intervention studies.** The horizontal bar indicates the 95% confidence interval. The size of the rectangle at the center of the horizontal bar is proportional to the weight of the given study. The diamond at the bottom indicates the pooled SMD. *Abbreviations:* CI, confidence interval; SMD, standardized mean difference; TG, triglyceride; VtD, vitamin D.

studies among participants with baseline serum vitamin D deficiency was −0.18 (95%CI, −0.41 to 0.05) and was −0.11 (95%CI, −0.51 to 0.29) for studies among participants with baseline serum vitamin D sufficiency; the overall SMD was −0.16 (95%CI, −0.36 to 0.03).

DISCUSSION

A meta-analysis of 41 RCTs evaluating the effect of vitamin D supplementation on lipids revealed that vitamin D supplementation has a beneficial effect on serum total cholesterol, LDL cholesterol, and triglycerides but not on HDL cholesterol. This is the largest meta-analysis to date evaluating this association; previous meta-analyses were based on ≤20 studies and focused on those with specific underlying health conditions, including type 2 diabetes[59] or gestational diabetes.[60] The present meta-analysis is the most comprehensive meta-analysis, including 41 vitamin D supplementation RCTs.

These results are similar to the findings of previous meta-analyses. For instance, a previous meta-analysis in 2012 reported that vitamin D has a beneficial effect on LDL cholesterol but not HDL cholesterol, triglyceride, or total cholesterol.[5] Another recent (2016) meta-analysis of 17 articles in participants with type 2 diabetes observed that vitamin supplementation lowered total cholesterol and LDL cholesterol but had no beneficial effect on triglycerides and HDL cholesterol.[59] Another meta-analysis in 2017 among women with gestational diabetes observed that vitamin D supplementation had a beneficial effect on serum LDL cholesterol, but in that meta-analysis, vitamin D was not beneficial on total cholesterol, HDL cholesterol, or triglycerides.[60] One study found vitamin D has a synergetic effect with cholesterol medications. In that study, vitamin D reduced LDL and total cholesterol compared with the arm that took only cholesterol medication.[61] One trial that was not included in this meta-analysis because the reported results are outliers found that vitamin D improved total cholesterol, LDL cholesterol, and HDL cholesterol but not triglycerides.[62] Three trials compared post–vitamin D supplementation serum lipid profiles to baseline serum lipid profiles and did not have a control arm. Among them, Al-Daghri et al reported vitamin D supplementation reduced total cholesterol, LDL cholesterol, and triglycerides,[63] whereas Manoy et al reported LDL cholesterol and HDL cholesterol improved after supplementation but total cholesterol and triglycerides were not different.[28] The Amarasekera et al pre/post trial did not find a beneficial effect of vitamin D supplementation among healthy adults in a trial that lasted 3 months.[64]

The magnitude of the baseline or end-of-trial lipid profiles or changes from baseline to the end of the trials in both arms explained almost all of the heterogeneity among the included studies. Among other trial-level covariates, including trial duration, publication year, country, the health status of the participants/disease, treatment dose, sample size, percentage female, and mean age, that were included in meta-regression analyses, only treatment duration appeared to explain some of the between-trial heterogeneity. In an analysis stratified by duration, the result remained consistent for trials of a short duration (≤6 months) but was no longer for trials of a long duration (>6 months). This difference by trial duration was no longer apparent when RCTs that appeared to be outliers, including the trials conducted by Sai et al[50] and Kampmann et al,[40] were removed. The Kampmann et al[40] and the Sai et al[50] trials appeared to be outliers in some of the analyses, and removal of the Kampmann et al trial from the analysis on LDL cholesterol and the Sai et al trial from the analysis on triglycerides resulted in stronger associations. The Sai et al study was designed to study the effect of estrogen and vitamin D supplementation in apparently healthy postmenopausal elderly women, and it was relatively large and had a long follow-up duration (3 y), but there was no mention of double blinding. However, at baseline, there was no evidence of differences in total cholesterol, HDL cholesterol, and triglycerides, but there was a difference in mean baseline LDL cholesterol. The Kampmann et al study was a double-blinded RCT among patients with type 2 diabetes with vitamin D insufficiency at baseline. It had a 3 month follow-up time but had a relatively small sample size (n =8 in each trial arm). Because none of the other covariates explained the heterogeneity among the trials, stratified analysis by those covariates was not conducted.

Because the meta-analysis indicated an evidence of publication bias for triglycerides, trim-and-fill analyses were conducted.[65] Trim-and-fill analysis tries to compensate for a publication bias by generating hypothetical missing studies with effects opposite to those likely favored and reported and pools those generated studies with studies included in a meta-analysis. The trim-and-fill analysis suggested 12 missing studies for triglycerides, and the augmented analysis suggested no beneficial effect for triglycerides. However, because there was no evidence of publication bias for total cholesterol in which 40 available trials were included, the augmented analysis that filled in 12 data points in the positive direction for potentially missing trials may have over-augmented. In meta-analyses of triglycerides, 35 trials were included, only 5 trials less than the analysis on total cholesterol and 1 trial less than the analysis on HDL cholesterol, both of which had no publication bias present.

The mechanism through which vitamin D affects circulating cholesterol levels may be through the action of vitamin D on the transcription activity of vitamin D receptor and insulin-induced gene-2 (Insig-2) expression. Insig-2 downregulates sterol regulatory-element binding protein-2 (SREBP-2) activation and inhibits 3-hydroxy-3-methyl glutaryl-coenzyme A reductase (HMGR) expression, an enzyme critical to cholesterol synthesis, thus reducing cholesterol synthesis.[66] Animal studies also support the role of vitamin D in cholesterol synthesis through inhibition of SREBP-2.[67] In a skeletal muscle cell, calcitriol altered lipid partitioning and lipid droplet packaging in a way that favored lipid turnover.[68] An animal study also indicated vitamin D regulates the level of lipogenic genes and controls lipid synthesis via the deactivation of SREBP.[69] In an experimental study, active vitamin D also resulted in the reduction of triglycerides in differentiated adipocytes, increased fatty acid ß-oxidation, and reduced de novo fatty acid synthesis.[70]

A strength of this review is that the inclusion of data from 41 RCTs provided enough power to detect the effect of vitamin D on serum lipid profiles. Generally, there was no evidence of major publication bias, especially for trials on total cholesterol. Most of the included studies were high-quality trials with randomization and double blinding minimizing the risks of residual confounding and bias. There were low dropout rates in the original trials, and per protocol analyses were used in most trials. One of the limitations of this review is that the follow-up period was short in most trials. Another limitation is that data on season was available in only 1 trial,[48] thus precluding examination of the role of vitamin D on serum lipid profile by season. Furthermore, none of the included studies evaluated potential differences in the effect of vitamin D supplementation by race.

CONCLUSION

In conclusion, this meta-analysis of RCTs indicates that vitamin D supplementation improved serum total cholesterol, LDL cholesterol, and triglycerides but not HDL cholesterol levels. It may be beneficial for patients at risk of cardiovascular diseases to be evaluated clinically for hypercholesterolemia and vitamin D deficiency, and clinicians may consider supplementing regular cholesterol treatments with vitamin D in vitamin D–deficient patients.

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Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Figure S1 **Forest plot of the standardized mean difference (SMD) in changes from baseline of the low-density lipoprotein (LDL) cholesterol in vitamin D intervention studies. The horizontal bar indicates the 95% confidence interval. The size of the rectangle at the center of the horizontal bar is proportional to the weight of the given study. The diamond at the bottom indicates the pooled SMD. The Kampmann et al[40] trial was omitted**

Figure S2 **Forest plot of the standardized mean difference (SMD) in changes from baseline of the high-density lipoprotein (HDL) cholesterol in vitamin D intervention studies. The horizontal bar indicates the 95% confidence interval. The size of the rectangle at the center of the horizontal bar is proportional to the weight of the given study. The diamond at the bottom indicates the pooled SMD. The Sai et al[50] trial was omitted**

Figure S3 **Forest plot of the standardized mean difference (SMD) in changes from baseline of the triglyceride in vitamin D intervention studies. The horizontal bar indicates the 95% confidence interval. The size of the rectangle at the center of the horizontal bar is proportional to the weight of the given study. The diamond at the bottom indicates the pooled SMD. The Sai et al[50] trial was omitted**

Table S1 **Characteristics of trials included in the meta-analysis**

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