Original Article

Effectiveness of vitamin D supplementation on lipid profile in polycystic ovary syndrome women: a meta-analysis of randomized controlled trials

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Background: Vitamin D deficiency (VDD) is prevalent in polycystic ovary syndrome (PCOS) and the relationship between dyslipidemia and vitamin D status is close. This meta-analysis was to evaluate the effect of vitamin D (alone or with co-supplementation) on lipid profile in PCOS patients.

Methods: Medline, the Cochrane Library, PubMed, and Web of Science were searched, and randomized controlled trials (RCTs) published prior to January, 2020 were identified. The pooled estimates of standardized mean deviation (SMD) with 95% confidence intervals (CI) were calculated using a fixed effect model or random effect model.

Results: A total of 954 identified studies were retrieved, and 11 RCTs involving 677 participants were ultimately included in the meta-analysis. The pooled results suggested an association between vitamin D supplementation and a reduction in total cholesterol (TC) concentrations (SMD: −0.36 mg/dL, 95% CI: −0.54 to −0.18 mg/dL, P<0.0001), triglycerides (TG) (SMD: −0.50 mg/dL, 95% CI: −0.68 to −0.32 mg/dL, P<0.00001), low-density lipoprotein cholesterol (LDL-C) (SMD: −0.28 mg/dL, 95% CI: −0.45 to −0.11 mg/dL, P=0.001), and very low-density lipoprotein cholesterol (VLDL-C) (SMD: −0.54 mg/dL, 95% CI: −0.74 to −0.35 mg/dL, P<0.00001), but no effect on high-density lipoprotein cholesterol (HDL-C) (SMD: 0.01 mg/dL, 95% CI: −0.16 to 0.18 mg/dL, P=0.89) was found. Subgroup analyses showed that the dosage of vitamin D used, the duration of intervention and the type of vitamin D supplementation (alone or with co-supplementation) might influence the effect of vitamin D on the lipid profile.

Conclusions: This meta-analysis demonstrated that PCOS patients with the therapy of vitamin D had a statistical improvement in TC, TG, LDL-C, and VLDL-C, but did not affect HDL-C concentrations.

Keywords: Meta-analysis; polycystic ovary syndrome (PCOS); lipid profile; vitamin D

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Introduction

Polycystic ovary syndrome (PCOS), accounting for the majority of cases of anovulatory infertility, is the most common endocrine disorder among women, with a prevalence of 5–20% among countries (1). Besides, PCOS is associated with obesity, insulin resistance (IR), hyperinsulinemia, dyslipidemia and vitamin D deficiency (VDD) (2-6). Among cardiovascular risk factors, dyslipidemia is certainly the most persistent and highly prevalent. Up to 70% of women with PCOS have dyslipidemia based on the NCEP guidelines (7), even thin women (8). PCOS can affect lipid metabolism through excess androgen and IR (2,9,10). In addition, dyslipidemia may increase the risk of cardiovascular disease in PCOS patients (11). However, the most common lipid-lowering drugs are statins and fibrates, both of which have some adverse reactions, such as hepatotoxicity and myopathy (12-14). With this in mind, the identification of new strategies should be taken into consideration.

In recent years, study have reported that vitamin D can regulate lipid metabolism (15). Moreover, VDD is common in PCOS patients and several studies have demonstrated that vitamin D status could affect lipid metabolism (16,17), The study of Maidana P *et al*. found that decreased serum vitamin D levels are associated with metabolic and hormonal disorders in patients with PCOS (18). Thus, many researchers have explored the effect of vitamin D on the lipid profile. Studies have showed that vitamin D may reduce triglycerides (TG) by affecting calcium intake (19-21). Many observational studies have reported that the serum 25-hydroxycholesterol [25(OH)D] concentration is closely related to the blood lipid concentration.However, the lipid-lowering effect of vitamin D varied with the study population, and may be more obvious in patients with metabolic disorders (22-24). Some randomized controlled trials (RCTs) (25-35) have evaluated the effect of vitamin D supplementation on blood lipid levels, but the results are controversial. Therefore, we designed this meta-analysis to try and resolve the current controversy.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/apm-20-2492).

Methods

Protocol and registration

This study was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (36).

Search strategy

This study was based on the Cochrane Handbook (37). Five databases were searched: Medline, the Cochrane Library, PubMed, and Web of Science, and all RCTs published before January 2020 were identified. Based on the PICOS (Participant, Intervention, Comparison, Outcome and Study design) principle (38), the search strategy was as follows: "vitamin D" OR "ergocalciferols" OR "cholecalciferol" OR "25-hydroxyvitamin D2" OR "hydroxycholecalciferols" OR "calcifediol" OR "calcitriol" OR "24,25-dihydroxyvitamin D3" OR "dihydrotachysterol" AND "polycystic ovary syndrome" OR "PCOS". We also searched The ClinicalTrials.gov registry for unpublished trials. If necessary, we contacted the authors for more information. Relevant references from the included studies were searched to retrieve additional eligible studies. There were no restrictions on language.

Study selection

All data were independently reviewed by two auditors (Jiaqian Luo and Jialing Yuan), according to the following inclusion and exclusion criteria.

Inclusion criteria: (I) participants: women with PCOS, aged >18 years; (II) intervention measure: vitamin D in any dose and dosage form; (III) control group: placebo, positive drug or blank control; (IV) outcome indicators: serum lipid profile [TC, TG, LDL-cholesterol (LDL-C), very LDL-C (VLDL-C), and high-density lipoprotein cholesterol (HDL-C)]; (V) study type: all RCTs.

Exclusion criteria: (I) not RCT; (II) no assessing primary data; (III) letters to the editor; and (IV) duplicate publication or secondary research paper.

A third reviewer (Tao Li) was consulted to resolve any disagreements.

Data extraction

Using a predesigned data extraction table, the following information was collected: study author(s); year of publication; study design; sample size; mean age, body mass index (BMI), mean serum 25(OH)D (ng/mL) of study subjects; follow-up duration; doses of vitamin D, and outcomes (TG, TC, LDL-C, VLDL-C, HDL-C). In cases

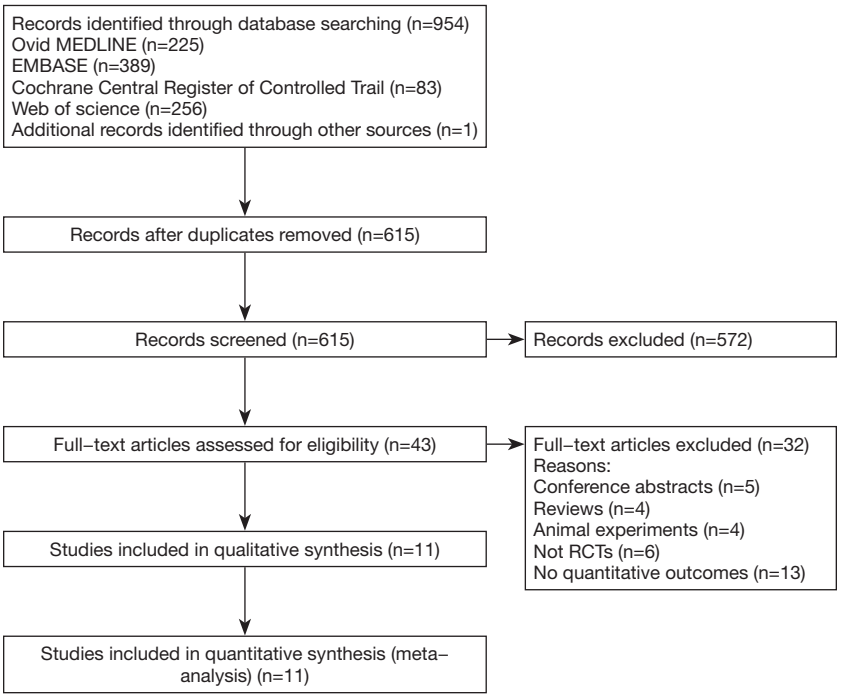

Figure 1 Flow diagram of study selection.

of disagreement, the differences were resolved through cross-checking, and discussion or consultation with the third researcher (Tao Li). If the original data were not provided directly in the text, reference was made to the tables or figures in the publication. If the relevant details were not fully reported in the study, the authors were contacted for further information.

Quality assessment

The quality of the included studies was evaluated according to the Cochrane Handbook for Systematic Reviews (version 5.3.0) (37). The two investigators (Jiaqian Luo and Jialing Yuan) independently evaluated and, if any, disagreements were resolved through discussion or consultation with a third investigator (Tao Li).

Data analysis

Using Revman 5.3 software for data analysis, we calculated the standardized mean difference (SMD) and 95% confidence interval (CI) of all outcomes (TG, TC, LDL-C, VLDL-C, HDL-C). The Q test and I^2 test were used to analyze heterogeneity. When the included studies had large heterogeneity ($P<0.10$ or $I^2>50\%$), the random-effects model was used to pool the estimations of SMD across studies. Otherwise, a fixed-effects model was used. Sensitivity analysis was used to find the source of heterogeneity and evaluate the stability and reliability of the meta-analysis results. Subgroup analyses were performed based on vitamin D doses, intervention duration, and type of supplementation. A funnel plot was constructed to determine publication bias. P values <0.05 were considered to be statistically significant.

Results

Search results and study characteristics

The flow diagram of our study selection process is shown in *Figure 1*. In total, we identified 954 citations with 339 duplicates. After the preliminary screening of the titles and abstracts, 43 studies were selected for full-text review and 32 studies were excluded because 6 were not RCTs, 13 included research providing no quantitative outcomes, and the remainder were either conference abstracts, reviews, or animal experiments. Finally, we enrolled 11 studies (25-35) in our meta-analysis.

As shown in *Table 1*, we summarized the characteristics

Table 1 Characteristics of the included studies

Study	Studied groups	Subjects (n)	Intervention	Supplemented dose of vitamin D	Duration (weeks)	Age (years), mean ± SD	BMI (kg/m^2), mean ± SD	Vitamin D (ng/mL), mean ± SD	
								Baseline	Final
Ardabili 2013	SG	24	Vitamin D	50,000 IU every 20 days	12	26.8±4.7	29.1±4.62	6.9±2.80	23.4±6.14***
	PG	26	Placebo	Placebo		27±3.7	28.28±3.51	7.28±2.93	8.57±3.98
Asemi 2015	SG [1]	26	Vitamin D	50,000 IU/week	8	25.6±4.4	29.3±3.9	11.6±4.7	23.4±7.1***
	SG [2]	26	Vitamin D + calcium			24.9±5.1	27.3±5.3	15.1±3.6	26.8±7.8***
	PG	26	Placebo	Placebo		24.3±5.2	27.5± 5.2	14.0±4.1	14.4±4.7
Dastorani 2018	SG	20	Vitamin D	50,000 IU every other week	8	29.9±4.4	27.7±3.9	10.5±2.5	21.7±5.9***
	PG	20	Placebo	Placebo		30.1±3.4	28.4±2.6	11.0±2.4	10.9±2.1
Foroozanfard 2017	SG	30	Low-dose vitamin D	1,000 IU/day	12	N/A	N/A	14.0±4.6	20.7± 6.2***
			High-dose vitamin D	4,000 IU/day				13.5±3.1	24.3±3.7***
	PG	30	Placebo	Placebo				14.0±3.5	14.1±3.6
Garg 2015	SG	15	Vitamin D + metformin	4,000 IU/day	24	22.0±4.61	26.8±4.56	7.7±6.05	31.5±13.88***
	PG	17	Placebo + metformin	Placebo		22.8±4.56	26.7±6.11	6.8±2.46	6.7±2.31
Irani 2015	SG	35	Vitamin D	50,000 IU/week	8	30.5±1.0	30 ±1	N/A	N/A
	PG	18	Placebo	Placebo		29.6±1.7	28±1.6		
Karamali 2017	SG	28	Vitamins D and K + calcium	200 IU twice daily	8	23.5±4.2	24.2±4.8	14.7±2.5	20.0±3.0***
	PG	27	Placebo	Placebo		23.3±3.4	24.3±3.9	14.8±3.9	14.5±5.0
Maktabi 2017	SG	35	Vitamin D	50,000 IU every 2 weeks	12	N/A	N/A	12.8±4.5	27.5±9.8***
	PG	35	Placebo	Placebo				14.5±5.1	14.4±5.2
Nasri 2017	SG	30	Vitamin D + EPO	1,000 IU/day	12	26.4±8.1	26.4±4.7	15.9±2.9	26.7±7.8***
	PG	30	Placebo	Placebo		25.4±4.7	26.9±4.9	14.6±2.1	14.1±1.9
Raja-Khan 2014	SG	13	Vitamin D	12,000 IU/day	12	28.2±5.2	37.20±4.53	19.9±9.47	67.3±28.62***
	PG	15	Placebo	Placebo		28.7±5.6	35.09±9.81	22.2± 6.86	22.45 ±7.02
Trummer 2018	SG	119	Vitamin D	20,000 IU/week	24	25.4±4.6	20.28±7.8	15.6±5.38	28.73±6.44***
	PG	61	Placebo	Placebo		27.2±5.5	19.9±7.32	15.6±5.60	18.21±9.46*

*P<0.05; ***P<0.001. EPO, evening primrose oil; N/A, not available; PG, placebo group; SG, supplemented group.

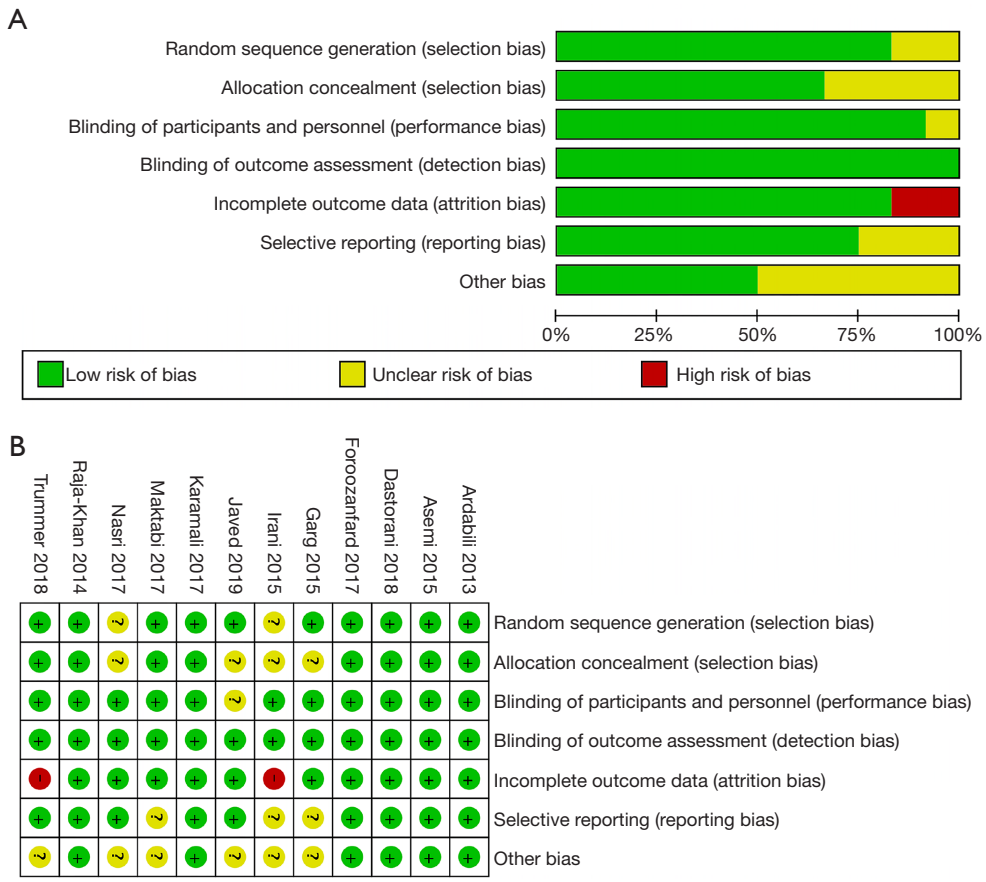

Figure 2 Quality evaluation of included studies by applying Cochrane risk of bias tool to assess the risk of bias. (A) Risk of bias summary. (B) Overall assessment of risk of bias.

of the 11 studies involving 677 subjects included in the meta-analysis, among which 391 patients were randomly distributed into a vitamin D group and the rest were the control group. The sample size ranged from 28 to 180. The doses of vitamin D varied from 400 to 12,000 IU/day with duration from 8 to 24 weeks.

Quality assessment

The results of quality assessment of the RCTs included in our meta-analysis are shown in *Figure 2*. Randomization was performed according to a computer-generated random list or by means of a randomly generated number pattern in nine trials (25-29,31,32,34,35); two RCTs did not provide details about the method of randomization (30,33). With respect to allocation, eight trials were categorized as low risk (25-28,31,32,34,35) with the appropriate use of allocation concealment, and three trials were unclear (29,30,33). Regarding to blinding of participants and personnel and outcome assessment, all RCTs were low risk (25-35). Nine of the RCTs included in our study were characterized by a low risk of blinding of incomplete outcome data (25-29,31-34), and two trials were categorized as high risk (30,35). Selective reporting was evaluated: three RCTs were categorized as high risk (29,30,32), and the rest were classified as low risk (25-28,31,33-35). Moreover, six trials (25-28,31,34) were classified as low risk and the remaining five were classified as unclear (29,30,32,33,35) for other bias.

Pooled analysis

Effect of vitamin D on serum TC

All 677 subjects had data on the effect of vitamin D on serum TC (25-35). Results demonstrated that vitamin D statistically reduced TC in patients with PCOS (*Figure 3A*:

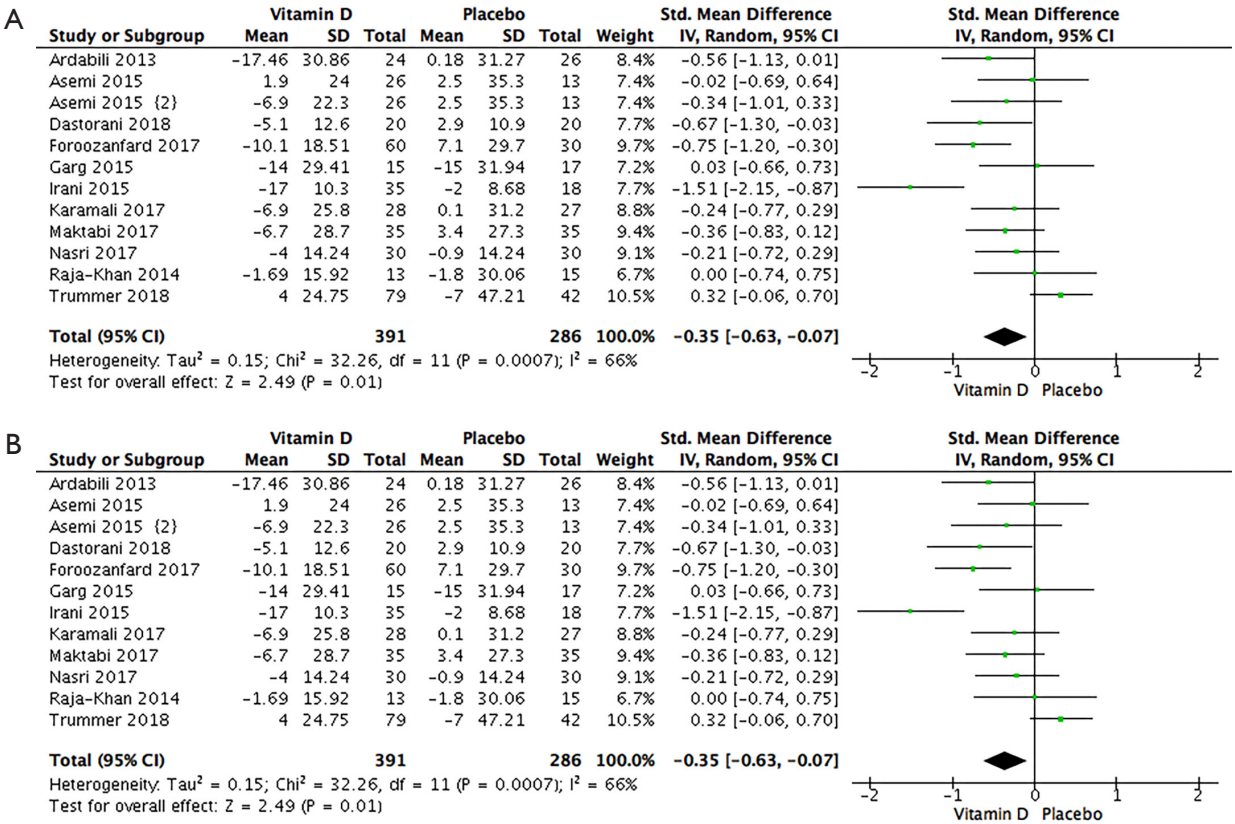

Figure 3 Effect of vitamin D on total cholesterol. (A) Results of the effect of vitamin D on total cholesterol. (B) Re-analysed data of the effect of vitamin D on total cholesterol after eliminating two studies.

–0.35 mg/dL, 95% CI: –0.63 to –0.07 mg/dL, P=0.01, I^2 =66%).

Sensitivity analysis was performed to find the sources of heterogeneity and most of the heterogeneity belonged to the studies by Trummer *et al.* (35), and Irani *et al.* (30). We therefore re-analysed the data after excluding those studies. The heterogeneity among the studies was clearly reduced (I^2 =0%, P=0.55) and the results demonstrated that vitamin D statistically reduced serum TC (*Figure 3B*: –0.36 mg/dL, 95% CI: –0.54 to –0.18 mg/dL, P<0.0001).

Subgroup analyses were also performed based on vitamin D dosage, intervention duration and type of supplementation (*Table 2*). Regarding the dose of intervention, vitamin D in doses ≤5,000 IU/day statistically reduced serum TC in patients with PCOS (–0.29 mg/dL, 95% CI: –0.58 to –0.01 mg/dL, P=0.04). Regarding the duration of intervention, in the duration of ≤12 weeks statistically reduced serum TC in patients with PCOS (–0.39 mg/dL, 95% CI: –0.57 to –0.20 mg/dL, P<0.0001). For the type of supplementation, vitamin D alone statistically reduced serum TC (–0.39 mg/dL, 95% CI: –0.76 to –0.01 mg/dL, P=0.04).

Effect of vitamin D on serum TG

Results for the 677 participants (25-35) showed that vitamin D statistically reduced TG in patients with PCOS (*Figure 4A*: –0.35 mg/dL, 95% CI: –0.59 to –0.12 mg/dL, P=0.003, I^2 =52%). Sensitivity analysis demonstrated that most of the heterogeneity belonged to the studies by Trummer *et al.* (35), and Raja-Khan *et al.* (34). The re-analysed data demonstrated that vitamin D statistically reduced serum TG as well after excluding those studies (*Figure 4B*: –0.50 mg/dL, 95% CI: –0.68 to –0.32 mg/dL, P<0.00001, I^2 =0%).

Subgroup analyses indicated that vitamin D in doses ≤5,000 IU/day statistically reduced serum TG (–0.37 mg/dL, 95% CI: –0.63 to –0.11 mg/dL, P=0.005). For a duration ≤12 weeks, vitamin D statistically reduced

Table 2 Subgroup meta-analysis of the included studies

Variable	Model for meta-analysis	No. of trials	Effect size (95% CI) mg/dL	P value	I^2 (%)	Q-statistics (P)
TC						
Vitamin D dosage						
≤5,000 IU/day	Random-effects model	8	−0.29 (−0.58, −0.01)	0.04	59	0.02
>5,000 IU/day		4	−0.48 (−1.20, 0.24)	0.19	78	0.004
Intervention duration						
≤12 weeks	Fixed-effects model	10	−0.39 (−0.57, −0.20)	<0.0001	0	0.59
>12 weeks		2	0.25 (−0.08, 0.59)	0.13	0	0.47
Type of supplementation						
Vitamin D alone	Random-effects model	9	−0.39 (−0.76, −0.01)	0.04	75	<0.0001
Co-supplement		3	−0.25 (−0.57, 0.07)	0.12	0	0.96
TG						
Vitamin D dosage						
≤5,000 IU/day	Random-effects model	8	−0.37 (−0.63, −0.11)	0.005	50	0.05
>5,000 IU/day		4	−0.29 (−0.88, 0.29)	0.33	67	0.03
Intervention duration						
≤12 weeks	Fixed-effects model	10	−0.45 (−0.63, −0.27)	<0.00001	37	0.11
>12 weeks		2	0.06 (−0.27, 0.39)	0.72	38	0.20
Type of supplementation						
Vitamin D alone	Random-effects model	9	−0.25 (−0.53, 0.02)	0.07	55	0.02
Co-supplement		3	−0.64 (−0.97, −0.32)	0.0001	0	0.65
LDL-C						
Vitamin D dosage						
≤5,000 IU/day	Fixed-effects model	8	−0.33 (−0.53, −0.13)	0.001	18	0.29
>5,000 IU/day		4	−0.15 (−0.48, 0.18)	0.36	28	0.24
Intervention duration						
≤12 weeks	Fixed-effects model	10	−0.30 (−0.48, −0.13)	0.0008	22	0.24
>12 weeks		1	0.04 (−0.66, 0.73)	0.91	–	–
Type of supplementation						
Vitamin D alone	Fixed-effects model	8	−0.37 (−0.58, −0.17)	0.0003	26	0.23
Co-supplement		3	−0.06 (−0.38, 0.26)	0.73	0	0.88
HDL						
Vitamin D dosage						
≤5,000 IU/day	Fixed-effects model	7	0.08 (−0.12, 0.28)	0.43	0	0.85
>5,000 IU/day		4	−0.17 (−0.50, 0.16)	0.30	0	0.76

Table 2 (*continued*)

Table 2 (*continued*)

Variable	Model for meta-analysis	No. of trials	Effect size (95% CI) mg/dL	P value	I^2 (%)	Q-statistics (P)
Intervention duration						
≤12 weeks	Fixed-effects model	10	0.02 (–0.15, 0.20)	0.79	0	0.81
>12 weeks		1	–0.16 (–0.86, 0.54)	0.65	–	–
Type of supplementation						
Vitamin D alone	Fixed-effects model	8	–0.02 (–0.22, 0.18)	0.84	0	0.84
Co-supplement		3	0.10 (–0.22, 0.42)	0.55	0	0.44
VLDL-C						
Vitamin D dosage						
≤5,000 IU/day	Fixed-effects model	6	–0.51 (–0.72, –0.30)	<0.00001	0	0.54
>5,000 IU/day		2	–0.71 (–1.20, –0.23)	0.004	0	0.40
Type of supplementation						
Vitamin D alone	Fixed-effects model	5	–0.48 (–0.72, –0.24)	<0.0001	0	0.42
Co-supplement		3	–0.54 (–0.74, –0.35)	0.0001	0	0.68

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol.

serum TG (–0.45 mg/dL, 95% CI: –0.63 to –0.27 mg/dL, P<0.00001). Regarding the type of supplementation, co-supplement statistically reduced serum TG (–0.64 mg/dL, 95% CI: –0.97 to –0.32 mg/dL, P=0.0001).

Effect of vitamin D on serum LDL-C

Meta-analysis of 10 studies with 556 participants demonstrated that vitamin D statistically reduced LDL-C (*Figure 5*: –0.28 mg/dL, 95% CI: –0.45 to –0.11 mg/dL, P=0.001, I^2 =19).

The results of subgroup analyses are shown in *Table 2*. Subgroup analyses showed that vitamin D in doses ≤5,000 IU/day statistically reduced serum LDL-C in patients with PCOS (–0.33 mg/dL, 95% CI: –0.53 to –0.13 mg/dL, P=0.001). Administration of vitamin D for at ≤12 weeks statistically reduced the serum LDL-C in the patients (–0.30, 95% CI: –0.48 to –0.13, P=0.0008). Regarding the type of supplementation, vitamin D alone statistically reduced serum LDL-C (–0.37 mg/dL, 95% CI: –0.58 to –0.17 mg/dL, P=0.0003).

Effect of vitamin D on serum HDL-C

The meta-analysis of 10 RCTs with 556 patients showed that vitamin D did not statistically change serum HDL in patients with PCOS (*Figure 6*: 0.01 mg/dL, 95% CI: –0.16 to –0.18 mg/dL, P=0.89, I^2 =0%).

Subgroup analyses showed that the effect of vitamin D on TG did not depend on vitamin D dosage, intervention duration, or type of supplementation (*Table 2*).

Effect of vitamin D on serum VLDL-C

Meta-analysis of 7 RCTs with 443 patients showed that vitamin D statistically changed serum VLDL-C in patients with PCOS (*Figure 7*: –0.54 mg/dL, 95% CI: –0.74 to –0.35 mg/dL, P<0.00001, I^2 =0%).

According to subgroup analyses (*Table 2*), any vitamin D dosage and type of supplementation could statistically reduce serum VLDL-C in patients with PCOS (≤5,000 IU/day: –0.51 mg/dL, 95% CI: –0.72 to –0.30 mg/dL, P<0.00001; >5,000 IU/day: –0.71 mg/dL, 95% CI: –1.20 to –0.23 mg/dL, P=0.004; vitamin D alone: –0.48 mg/dL, 95% CI: –0.72 to –0.24 mg/dL, P<0.0001; co-supplement: –0.54 mg/dL, 95% CI: –0.74 to –0.35 mg/dL, P=0.0001).

Publication bias

According to the funnel plots, there was no obvious publication bias on TG, TC, LDL-C, VLDL-C, HDL-C. (*Figure 8A,B,C,D,E*).

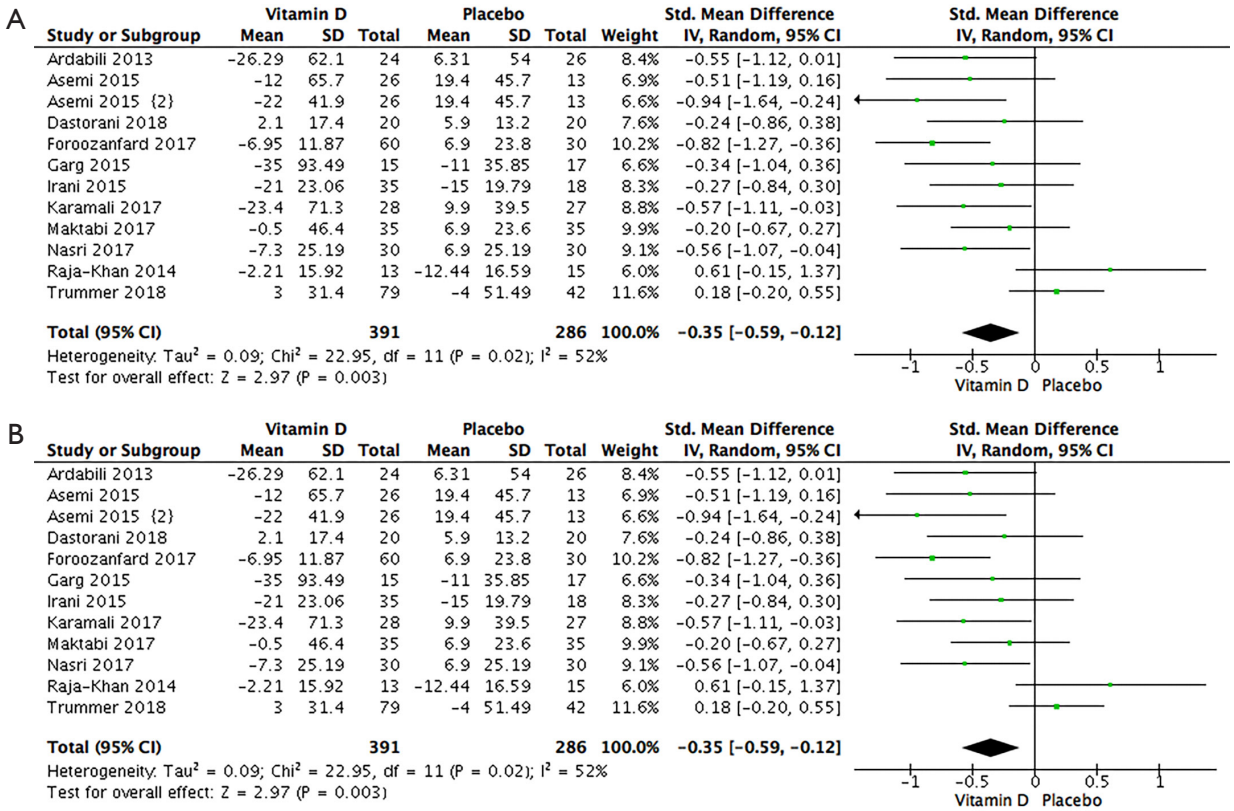

Figure 4 Effect of vitamin D on triglycerides. (A) Results of the effect of vitamin D on triglycerides. (B) Re-analysed data of the effect of vitamin D on total cholesterol after eliminating two studies.

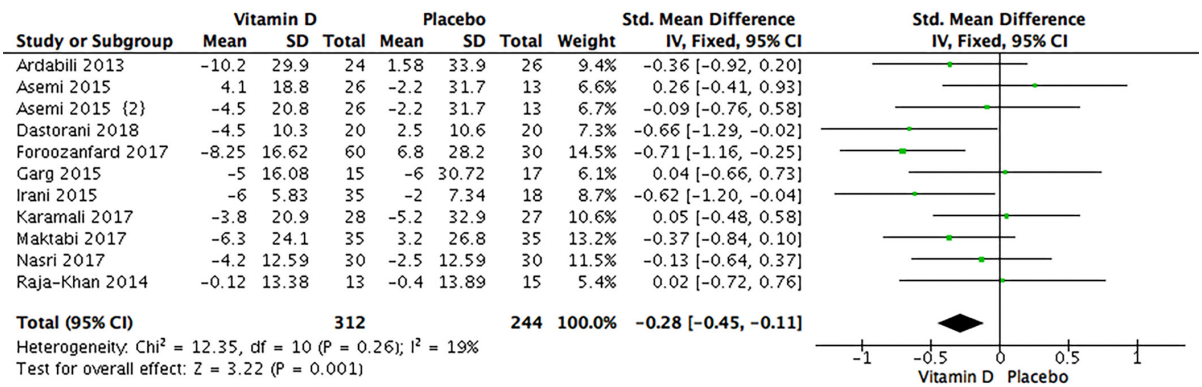

Figure 5 Results of the effect of vitamin D on LDL cholesterol. LDL, low-density lipoprotein.

Discussion

The present meta-analysis of 11 RCTs with 677 participants assessed the effectiveness of vitamin D supplementation on the serum lipid profiles of women with PCOS. The pooled results from the current study revealed that vitamin D supplementation had statistical effects on TC, TG, LDL-C, and VLDL-C, but the changes in serum HDL-C were not satisfactory. Sensitivity analysis further verified the conclusions. It must be kept in mind that following vitamin D supplementation alone, TC and LDL-C concentrations

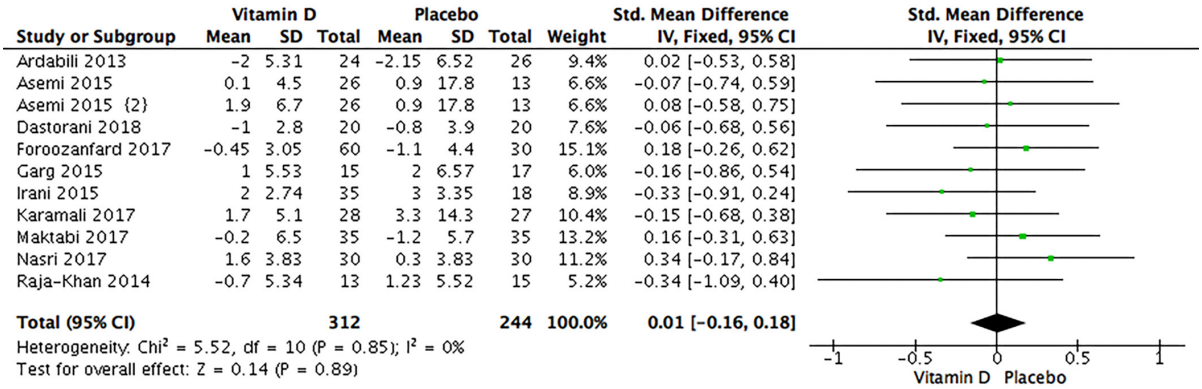

Figure 6 Results of the effect of vitamin D on HDL cholesterol. HDL, high-density lipoprotein.

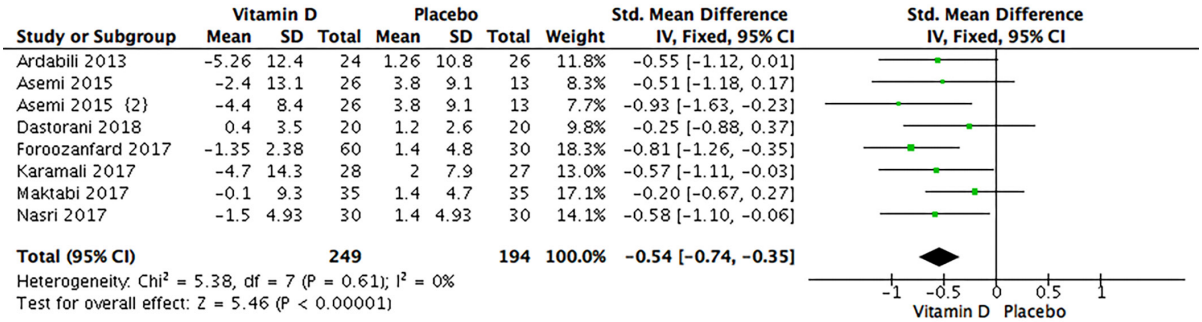

Figure 7 Results of the effect of vitamin D on VLDL cholesterol. VLDL, very low-density lipoprotein.

statistically decreased compared with co-supplementation of vitamin D, while the result for TG concentrations was contrary. TC, TG and LDL-C concentrations were statistically reduced only at the lower dosage (≤5,000 IU/day) of vitamin D and duration ≤12 weeks. Circulating concentrations of VLDL-C were not affected by the type of intervention or the dosage of vitamin D used for supplementation.

VDD is a worldwide problem affecting half of the general adult population, but especially in women with PCOS (39). About 67–85% of women with PCOS have serum concentrations of 25(OH)D <20 ng/mL (40). What's more, there is a close relationship between vitamin D status and metabolic dysfunction in women with PCOS (16-18,41,42). Many studies have explored the effect of vitamin D supplementation on metabolic disorders in patients with PCOS, but the results have been controversial. The study of Ardabili *et al.* indicated that vitamin D supplements could decrease serum total cholesterol, triglyceride, and VLDL levels significantly, but it did not affect serum HDL-cholesterol and LDL-cholesterol. Asami *et al.* showed that calcium plus vitamin D supplementation for eight weeks among vitamin D deficient women with PCOS had beneficial effects on serum triglycerides and VLDL-cholesterol levels, but it did not affect other lipid profiles. Dastorani *et al.* found that 50,000 IU vitamin D supplementation every other week for 8 weeks had beneficial effects on lipid profile in women with PCOS. Karamali *et al.* found calcium, vitamins D and K co-supplementation for 8 weeks among vitamin D-deficient women with PCOS had beneficial effects on serum triglycerides and VLDL cholesterol levels. Nasri *et al.* showed that vitamin D and EP co-supplementation for 12 weeks among vitamin D-deficient women with PCOS significantly improved triglycerides, VLDL cholesterol. However, vitamin D supplementation had no significant effect on serum lipid profile in PCOS in the studies of Garg*et al.*, Irani *et al.*, Raja-Khan *et al.*, and Trummer *et al.* (25-35). Recently, a meta-analysis by Łagowska *et al.* suggested that vitamin D supplementation

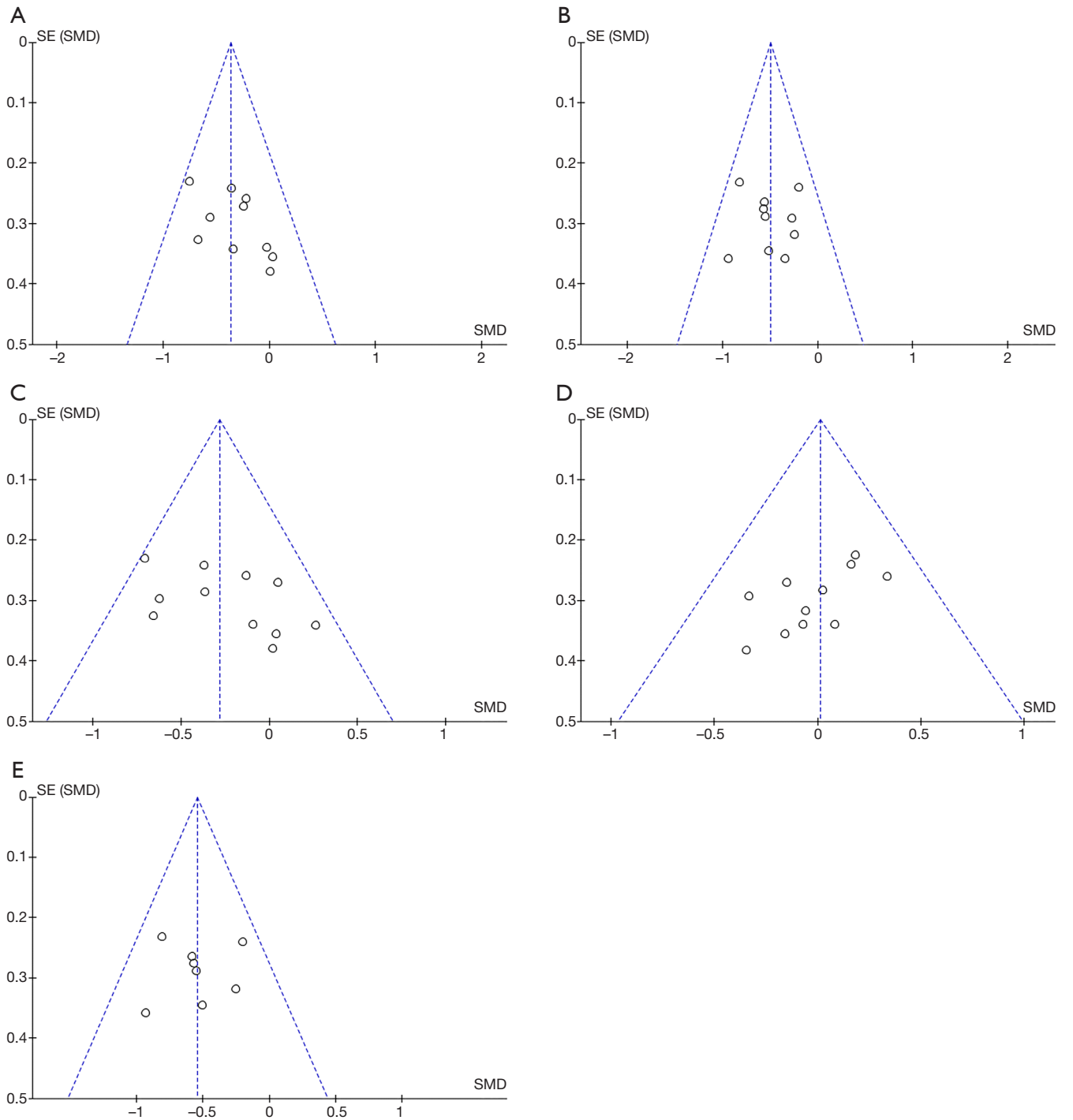

Figure 8 Funnel plot of SE by standardized mean difference for (A) TC, (B) TG, (C) LDL-C, (D) HDL-C, (E) VLDL-C, detailing publication bias in the studies selected for analyses. Closed circles represent observed published studies. TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol.

had a positive effect on IR in women with PCOS (43). In our meta-analysis, we investigated the effects of vitamin D supplementation on blood lipid levels in patients with PCOS. Our results showed that PCOS patients treated with vitamin D had associated improvements in TC, TG, LDL and VLDL-C levels, but no effect on HDL was observed. This finding is in line with the results of a meta-analysis by Akbari *et al.*, which underlined that vitamin D supplementation statistically decreased LDL-C concentrations in gestational diabetes patients, though other lipid profile parameters did not change (44). In addition, a meta-analysis by Tina *et al.* also demonstrated that vitamin D supplementation improved serum concentrations of TC, TG, and LDL-C, but negligible changes in serum HDL-C, in patients with T2DM (45). However, in 2012, a meta-analysis conducted by Wang *et al.* concluded that vitamin D supplementation could increase LDL-C and suggested that the lipid-lowering effects of vitamin D supplementation might be seen more apparently in patients with metabolic disorders such as T2DM or PCOS (46).

The exact mechanism by which vitamin D affects lipid markers has not been elucidated. It has been demonstrated that vitamin D increases LPL gene expression in muscles and adipose tissue, and activation of *LPL* increases the clearance of circulating lipoprotein particles (20). Cho *et al.* indicated that vitamin D may decrease hepatic TG production or secretion by its effects on calcium intake (19). And other researchers attribute it to the effects of vitamin D in reducing parathyroid hormone and improving insulin sensitivity (40,46,47). Moreover, the serum TC concentration is affected by cholesterol absorption from the gut and endogenous biosynthesis of cells. Kane *et al.* suggested that vitamin D might reduce intestinal cholesterol absorption (48).

Based on our subgroup results, the administration of vitamin D ≤5,000 IU/day statistically reduced the serum concentrations of TC, TG, LDL-C, and VLDL-C, which according with the results of the meta-analysis by Xue *et al.* (49), who suggested that supplementation with a low dose of vitamin D was enough to reduce TG concentration, whereas supplementation with high doses was not beneficial. Besides, Sanders *et al.* pointed out that bolus doses of vitamin D_3 >500,000 IU might increase the risk of fracture, altered biochemical markers, and cause issues with tolerability (50). Thus, we concluded that supplying vitamin D could improve the serum lipid profile, and supplementation of vitamin D ≤5,000 IU/day seemed to have a statistical effect compared with higher doses.

In the subgroup analysis performed according to the type of supplementation, statistical reductions of serum TC, LDL-C, and VLDL-C concentrations were observed in the vitamin D alone group, and statistical reductions of serum TG and VLDL-C concentrations were observed in the co-supplementation group. It is worth noting that vitamin D supplementation alone had a tendency to reduce serum TG concentration, but had no statistical significance (P=0.07). By contrast, previous studies observed a statistical reduction in TG affected by 4,500 IU/day of vitamin D supplementation for 2 months in females with T2DM (51), and by 50,000 IU/day of vitamin D supplementation for 16 weeks in subjects with metabolic syndrome (52). In our study, we also found a tendency to improved TG levels with vitamin D alone supplementation among these women with PCOS. Therefore, we speculate that vitamin D supplementation alone is likely to have TG-lowering effect, but larger samples and high-quality studies are needed to definitely identify this effect. Moreover, all three studies included in co-supplementation group showed a statistical reduction in serum TG concentration after vitamin D plus other nutrient supplementation (26,31,33). Two of the studies were combined with calcium (26,31) and one with evening primrose oil (EPO) (33). Previous studies have shown that calcium intake may lead to reduced absorption of fatty acids and increased fecal fatty acid content by forming insoluble calcium-fatty soaps in the gut, thereby reducing the serum TG concentration (53). In addition, increased intracellular calcium in the liver results in stimulating microsomal TG transfer protein, and thus reduced serum TG concentration (19). EPO is rich in gamma-linolenic acid, which would have a TG-lowering effect by inhibiting synthesis of hepatic TG (54). As mentioned before, it is possible that co-supplementation with vitamin D and calcium or EPO may be more effective than single supplementation in reducing the serum TG concentration.

We also demonstrated that serum TC, TG, LDL-C, and VLDL-C concentrations were statistically reduced after ≤12 weeks. This result, however, needs to be interpreted with caution because there was little literature for the >12 weeks subgroup, in which at most two RCTs were included. Larger prospective studies are needed to further validate our results.

The Endocrine Society guidelines (55) recommend that people should maintain blood levels of 25(OH)D >20 ng/mL to prevent rickets and osteomalacia. Moreover, to maximize the effects of vitamin D on calcium, bone and

muscle metabolism, the blood level of 25(OH)D should >30 ng/mL, and 25(OH)D at this concentration may have additional health benefits in reducing the risk of common cancers, autoimmune diseases, T2DM and Cardiovascular Disease (CVD). Considering that VDD is very common and that few foods contain vitamin D, the guidelines also suggest that increased dietary intake of vitamin D for patients at risk of VDD is necessary. As stated earlier, a relatively high prevalence of VDD is observed in women with PCOS (40). Additionally, there is an association between vitamin D status and metabolic dysfunction in women with PCOS, and there are positive associations of VDD with some comorbidities of PCOS, including T2D and CVD (41,42). All of the studies included in this meta-analysis showed that vitamin D supplementation helped restore physiological serum levels of 25(OH)D in PCOS women with VDD (25-35), and a beneficial effect of vitamin D supplementation on glucose metabolism was reported as well (43). Our study also indicated that vitamin D supplementation (alone or combined with other nutrients) may help improve the lipid profile. Although our study found that vitamin D supplementation showed a statistical reduction effect on lipid metabolism in PCOS patients, we can not directly prove the clinical significance of vitamin D supplementation in improving lipid metabolism because only a slight lipid-lowering effect was seen in this meta-analysis. But considering the high-prevalence of VDD and dyslipidemia in PCOS patients, and the recommendation for vitamin D supplementation in populations at high-risk for VDD, vitamin D supplementation may be a simple and low-risk add-on therapy for PCOS patients with VDD and dyslipidemia.

Several strengths of the current study are as follows. Firstly, this meta-analysis used an up-to-date literature search representing the most available data on this topic. Secondly, all included studies were placebo-controlled RCTs with acceptable methodological quality and the least probable chance of bias. Thirdly, the design of the study was analyses of a specific population (PCOS patients) instead of pooling populations with different health conditions. There are also some limitations. Firstly, we found few eligible studies and none of them were sufficiently powered because they had relatively small numbers of participants. Secondly, the results of subgroup analyses of duration of therapy and type of vitamin D supplementation need to be interpreted with caution as there was little literature included, especially in the >12-week' duration subgroup, in which only two RCTs were included. Thirdly, patients might have had different status of PCOS. Finally, the history of using antidyslipidemic drugs (e.g., statins) was not clear.

Conclusions

To date, the evidence from RCTs indicated that vitamin D supplementation (alone or with co-supplementation) could statistically improve lipid metabolism, but the effect is small. However, considering the high-prevalence of VDD and dyslipidemia in PCOS patients, and the recommendation of vitamin D supplementation in populations at high-risk for VDD, vitamin D supplementation may be a simple and low-risk add-on therapy for PCOS patients with VDD and dyslipidemia. Vitamin D dosage, the duration of intervention and type of vitamin D supplementation (alone or with co-supplementation) may influence the effects of vitamin D supplementation on the lipid profile. The lipid-modulating effects of vitamin D supplement should be further investigated through large-scale, randomized trials with adequate doses, duration, and types of supplementation.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-2492). The authors have no conflicts of interest to declare.

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