BMC Endocrine Disorders

RESEARCH

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The impact of vitamin D supplementation on glycemic control and lipid metabolism in polycystic ovary syndrome: a systematic review of randomized controlled trials

Miao Yu[1], Shuai Chen[1], Xia Liu[1], Hui Dong[2] and Deng-Chao Wang[2*]

Abstract

Background Polycystic ovary syndrome (PCOS) is a prevalent endocrine condition affecting both metabolic and reproductive health in women. The impact of vitamin D on metabolic regulation has attracted growing interest. The purpose of this study is to investigate the impact of vitamin D supplementation on key metabolic parameters-namely blood glucose, insulin, and lipid levels-in individuals with PCOS.

Methods A systematic review was conducted to identify relevant studies in PubMed, Embase, Cochrane Library, Web of Science, and ClinicalTrials.gov. The search focused on randomized controlled trials (RCTs) evaluating the impact of vitamin D supplementation in patients with PCOS. Meta-analysis was performed using RevMan 5.3 software, and study quality was evaluated with the Cochrane Risk of Bias Tool. In addition, outcome-related evidence was graded using the GRADE system, and TSA was performed to determine if the number of participants met the required threshold.

Results A total of 691 individuals with PCOS from 13 RCTs were evaluated. The meta-analysis indicated that the supplementation of vitamin D led to a notable reduction in the subsequent metabolic parameters: fasting blood glucose[MD=-2.91 mg/dL, 95% CI (-4.78, -1.04) mg/dL, $P=0.002$], insulin levels[MD=-1.98 μIU/mL, 95% CI (-3.32, -0.64) μIU/mL, $P=0.004$], triglycerides[MD=-11.01 mg/dL, 95% CI (-16.42, -5.61) mg/dL, $P<0.0001$], total cholesterol [MD=-11.69 mg/dL, 95% CI (-15.56, -7.82) mg/dL, $P<0.00001$], very low-density lipoprotein cholesterol (VLDL-cholesterol) [MD=-2.64 mg/dL, 95% CI (-4.50, -0.79) mg/dL, $P=0.005$], and low-density lipoprotein cholesterol (LDL-cholesterol) [MD=-5.85 mg/dL, 95% CI (-10.28, -1.42) mg/dL, $P=0.010$]. Nevertheless, the supplementation of vitamin D did not exert a significant impact on high - density lipoprotein cholesterol (HDL - cholesterol) [MD=-0.21 mg/dL, 95% CI (-0.81, 1.22) mg/dL, $P=0.69$]. Begg's and Egger's tests suggested a minimal probability of publication bias, and the TSA confirmed that the optimal sample size for major outcomes had been reached, supporting the robustness of the meta-analysis results.

*Correspondence:
Deng-Chao Wang
wangdengchaopwk@163.com

Full list of author information is available at the end of the article

Conclusion Vitamin D supplementation shows significant benefits in improving metabolic parameters in PCOS patients, particularly in reducing fasting blood glucose, insulin, and lipid levels, suggesting a potential role of vitamin D in PCOS management. The long-term outcomes and most effective dose of vitamin D warrant further investigation in future research.

Clinical trial number Not applicable.

Keywords Polycystic ovary syndrome, Vitamin D, Meta-analysis

Introduction

Affecting nearly 10% of women globally, polycystic ovary syndrome (PCOS) is one of the most widespread endocrine disorders. It is manifested through irregular menstrual cycles, elevated androgen levels (hyperandrogenism), and aberrant ovarian morphology [1, 2]. PCOS often shows a strong association with insulin resistance as well as metabolic syndrome. This connection elevates the likelihood of developing both cardiovascular disease and diabetes [3, 4]. The vitally important fat-soluble nutrient, vitamin D, exerts a decisive influence in the links of calcium and phosphorus metabolism. Moreover, it has a key part in modulating insulin secretion and lipid metabolism, which has drawn increasing interest in recent research [5, 6].

Recent studies indicate a close association between vitamin D deficiency and the occurrence and development of PCOS. Vitamin D intake may contribute to better metabolic health in PCOS patients by enhancing insulin sensitivity and regulating lipid metabolism [7, 8]. Although several RCTs have explored the impacts of vitamin D supplementation in the context of PCOS, they frequently encounter the issue of having small sample sizes. This constraint has the potential to restrict the broad applicability of the results obtained from these investigations. Moreover, there are disparities among different studies. In certain research, vitamin D supplementation has led to remarkable enhancements in glycemic regulation and lipid metabolism. However, other investigations have indicated that there are no substantial effects [9–21]. These differences may arise from variations in study design, intervention doses, and baseline characteristics of participants. Consequently, a systematic review to integrate existing data in this field is essential.

To ensure the rigor and reliability of the findings, this study conducts an extensive data collection from multiple databases and applies the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system. It conducts a thorough appraisal of the evidence quality within the incorporated studies, thereby elucidating the dependability of the outcomes. Additionally, Trial Sequential Analysis (TSA) is utilized to evaluate whether the sample size of included studies is sufficient and to confirm if the Required Information Size (RIS) is reached, thereby reducing the impact of random errors on the outcomes. Through a comprehensive approach combining meta-analysis, GRADE evaluation, and TSA analysis, this research conducts a systematic assessment of how vitamin D supplementation influences the regulation of blood glucose and lipid metabolism among individuals with PCOS, providing robust support and guidance for clinical practice.

Materials and methods

The conduct and reporting of this systematic review were in line with the Preferred Reporting Items for Systematic Reviews and Meta- Analyses Protocols (PRISMA- P) guidelines [22]. The registration number assigned to this particular review is INPLASY2024110109.

Inclusion and exclusion criteria

Inclusion criteria

(1) Participants: Women aged 18 years and older who meet the diagnostic criteria for PCOS. (2) Interventions: The intervention group is provided with vitamin D supplementation, while the control group receives a placebo. (3) Outcome Measures: ① changes in fasting blood glucose; ② changes in insulin; ③ changes in triglycerides; ④ changes in total cholesterol; ⑤ changes in VLDL-cholesterol; ⑥ changes in HDL-cholesterol; ⑦ changes in LDL-cholesterol. (4) Study Design: RCTs with no restrictions on language or publication date.

Exclusion criteria

(1) Duplicate publications. (2) Studies not focused on vitamin D supplementation or combined with other interventions without separate reporting of vitamin D outcomes. (3) Studies lacking primary outcome measures. (4) Non-RCTs, retrospective studies, meta-analyses, reviews, letters, case reports, conference abstracts, and commentaries.

Search strategy

This study adopted a comprehensive literature retrieval strategy to ensure comprehensive coverage of relevant studies. Multiple databases were searched, including: (1) PubMed, (2) Embase, (3) Cochrane Library, (4) Web of Science, and (5) ClinicalTrials.gov. Relevant keywords were used during the search process, such as "PCOS", "Polycystic Ovary Syndrome", "Polycystic Ovarian

Syndrome", "25-hydroxyvitamin D", "Vitamin D", "Cholecalciferol", "Calcitriol", "Hydroxyvitamin D", "Randomized Controlled Trial" and "RCT". The last search was conducted on October 27, 2024. For instance, the detailed search approach in PubMed was formulated like this: (((Polycystic Ovary Syndrome) OR (Polycystic Ovarian Syndrome) OR (PCOS)) AND ((Vitamin D) OR (Cholecalciferol) OR (25-hydroxyvitamin D) OR (Calcitriol) OR (Hydroxyvitamin D))) AND ((Randomized Controlled Trial) OR (RCT)). Furthermore, the reference lists of the included studies were thoroughly examined to identify additional studies meeting the predefined inclusion criteria.

Data extraction

During the data extraction stage, we adhered to predefined inclusion and exclusion criteria to extract relevant information from the selected studies. The data we extracted covered both the basic information about the study (e.g., author, the publication year), the traits of the participants (e.g., number of samples, age, body mass index), intervention details (e.g., dosage and duration of vitamin D), control group information, and primary outcome measures. All the data were separately retrieved by two authors through the utilization of a standardized data collection form, aiming to guarantee consistency and comprehensiveness. When discrepancies arose, a consensus was achieved via discussion. If the units of measurement for the same outcome differed across studies, conversions were performed to ensure uniformity of units for each outcome.

Quality assessment

The Cochrane Risk of Bias Tool (RoB2) was used to assess the methodological quality of the included studies. This tool covers five key dimensions: Firstly, the randomization process; secondly, the deviations from the prespecified interventions; thirdly, the handling of missing data; then, the accuracy of outcome measurement; and finally, the selectivity of the reported results [23]. The studies were categorized into three categories: (1) low risk, (2) high risk, and (3) some concerns regarding the risk of bias. The evaluation procedure was executed by two independent authors. In the event of discrepancies, a third author rendered the final judgment.

Statistical methods

Statistical analyses were performed using RevMan version 5.3. For each outcome in the included studies, a combined effect size was calculated. To represent changes in glycemic control and lipid metabolism, the mean difference (MD) was adopted, and all combined effect sizes were shown along with a 95% confidence interval (CI). In cases where the magnitude of change cannot be retrieved from the original study, the standard deviation (SD) of the change is computed by taking the difference between the end - of - trial value and the baseline value.

$$SD_{\{\{change\}\}} = \sqrt{\left\{ \begin{array}{l} SD^2_{\{\{before\}\}} + SD^2_{\{\{after\}\}} \\ -\ 2 \cdot r \cdot SD_{\{\{before\}\}} \cdot SD_{\{\{after\}\}} \end{array} \right\}}$$

Heterogeneity among study results was evaluated using the I^2 statistic. Specifically, an I^2 value below 25% implies no heterogeneity, a value ranging from 25 to 50% indicates low heterogeneity, an I^2 between 50% and 75% shows moderate heterogeneity, and a value within 75 – 100% represents high heterogeneity. For data synthesis, a random-effects model was used under circumstances of heterogeneity, whereas a fixed-effects model was applied when heterogeneity was not detected [24]. Subgroup analyses were performed in accordance with the dose of vitamin D and the duration of treatment. Publication bias was evaluated by employing Egger's and Begg's tests in the STATA software. For all statistical analyses, a two - sided test was employed, with the significance criterion set at $P < 0.05$.

GRADE evidence quality assessment

In this study, the internationally recognized GRADE system was systematically and comprehensively applied to rigorously assess the quality of evidence provided by the included studies. This system categorizes evidence quality into four distinct levels: (1) very low, indicating numerous limitations and a high degree of uncertainty; (2) low, suggesting relatively poor quality with limited credibility; (3) moderate, implying a reasonable level of reliability and persuasiveness; and (4) high, representing strong evidence capable of providing robust support for research conclusions. The evaluation process is based on five key dimensions: (1) risk of bias, (2) precision of outcomes, (3) consistency across studies, (4) directness of evidence, and (5) potential risk of publication bias [25].

TSA analysis

TSA was performed using predetermined parameters, including statistical power ($1\text{-}\beta = 0.80$), significance level ($\alpha = 0.05$), and effect size. If the TSA boundaries are crossed, it suggests that the existing evidence is adequate to support a reliable conclusion. Conversely, if boundaries are not crossed, further research may be necessary to confirm the findings of the current meta-analysis. According to the meta-analysis results, parameters including MD, variance, and heterogeneity adjustment were defined for constructing and analyzing the TSA model [26].

Results

General characteristics of the selected literature

Through a comprehensive search of multiple databases, 148 relevant studies were initially identified. After eliminating duplicates, 67 studies remained. Screening the abstracts of these 67 studies resulted in the exclusion of 46 studies that failed to meet the inclusion criteria, with primary reasons being irrelevance to the study objectives (38 studies) and articles classified as experience summaries or conference abstracts (8 studies). The full texts of the remaining 21 studies were then assessed, resulting in the exclusion of 8 articles: 4 lacked relevant outcome data, 2 involved non-placebo control groups, and 2 utilized combination therapy in the intervention arm. Ultimately, 13 RCTs that conformed to the inclusion criteria were included (Fig. 1). These RCTs involved a total of 691 PCOS patients, of whom 371 were allocated to the vitamin D intervention and 320 to the control group [9–21] (Table 1).

Risk of Bias assessment results

As depicted in Fig. 2, it presents the outcomes of the bias assessment carried out using the ROB 2 tool for various studies.

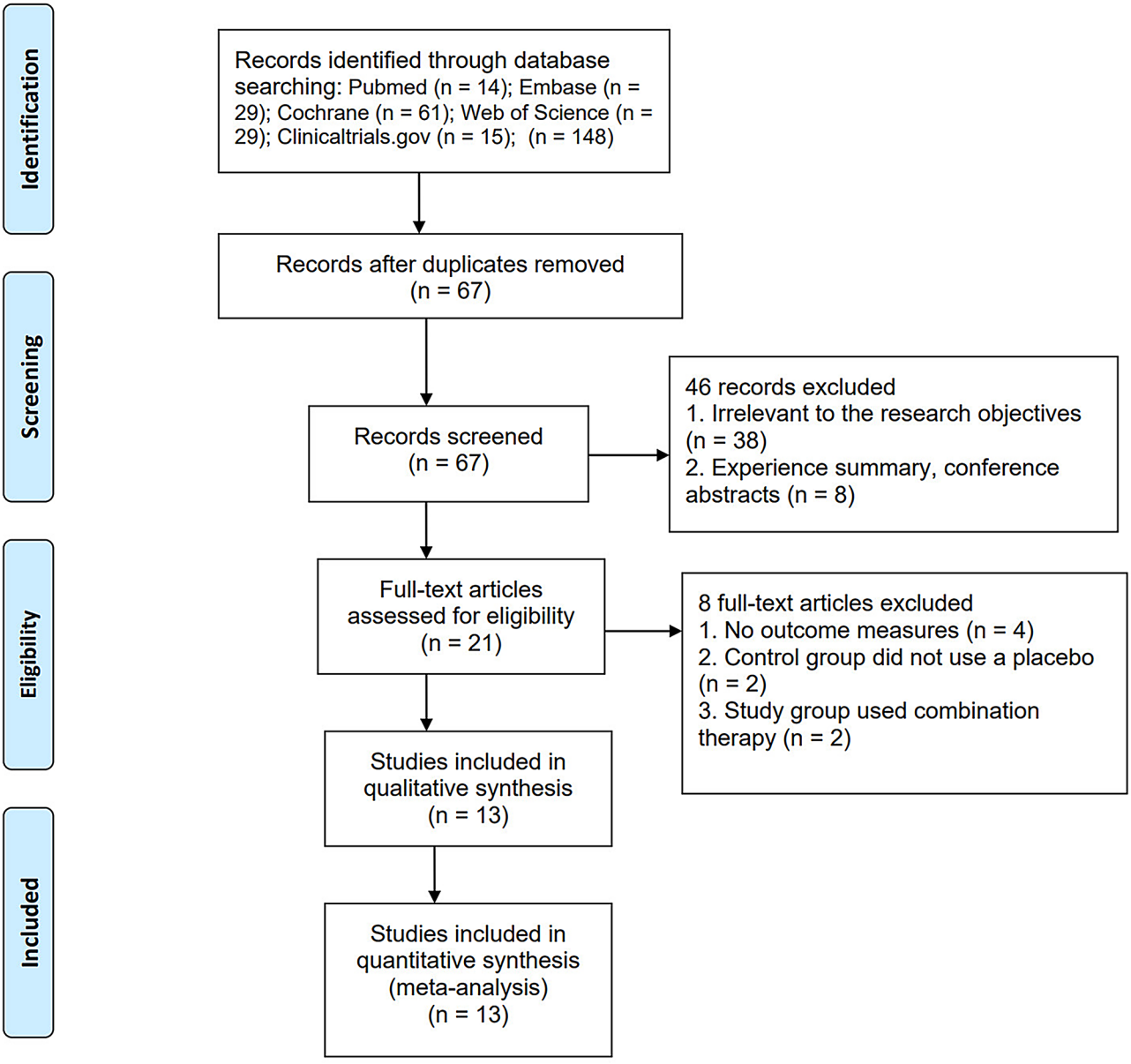

Fig. 1 PRISMA flow diagram

Table 1 Basic characteristics of included studies

Study	Country	Group	Sample size	Age (years)	BMI (kg/m²)	Intervention	Duration (weeks)	Outcome measures
Al-Bayyari 2021 [9]	Jordan	Vitamin D group	29	23.6 ± 4.3	27.3 ± 1.9	50,000 IU/week of vitamin D3	12	①②
		Placebo group	29	23.9 ± 6.0	26.9 ± 1.6	Placebo	12	
Ardabili 2012 [10]	Iran	Vitamin D group	24	26.8 ± 4.7	29.1 ± 4.6	5,000 IU/daily of vitamin D3	8	①②
		Placebo group	26	27.0 ± 3.7	28.3 ± 3.5	Placebo	8	
Asemi 2015 [11]	Iran	Vitamin D group	26	25.6 ± 4.4	29.3 ± 3.9	50,000 IU/week of vitamin D3	8	①②③④⑤⑥⑦
		Placebo group	26	24.3 ± 5.2	27.5 ± 5.2	Placebo	8	
Dastorani 2018 [12]	Iran	Vitamin D group	20	29.9 ± 4.4	27.7 ± 3.9	50,000 IU/week of vitamin D3	8	①②③④⑤⑥⑦
		Placebo group	20	30.1 ± 3.4	28.4 ± 2.6	Placebo	8	
Foroozanfard 2017 [13]	Iran	Vitamin D group	30	18 ~ 40	Na	4,000 IU/day of vitamin D3	12	①②③④⑤⑥⑦
		Placebo group	30	18 ~ 40	Na	Placebo	12	
Garg 2015 [14]	India	Vitamin D group	15	22.0 ± 4.6	26.8 ± 4.6	4,000 IU/day of vitamin D3	24	①③④⑤⑥⑦
		Placebo group	17	22.8 ± 4.6	26.7 ± 6.1	Placebo	24	
Irani 2015 [15]	USA	Vitamin D group	35	30.5 ± 1.0	30.0 ± 1.0	50,000 IU/week of vitamin D3	8	②③④⑥⑦
		Placebo group	18	29.6 ± 1.7	28.0 ± 1.6	Placebo	8	
Javed 2019 [16]	United Kingdom	Vitamin D group	18	28.6 ± 5.5	35.4 ± 10.6	3,200 IU/day of vitamin D3	12	①②③④⑥⑦
		Placebo group	19	29.1 ± 7.5	33.8 ± 7.2	Placebo	12	
Maktabi 2017 [17]	Iran	Vitamin D group	35	22.0 ± 1.6	22.7 ± 3.4	50,000 IU/2 weeks of vitamin D3	12	①③④⑥⑦
		Placebo group	35	23.1 ± 3.3	24.1 ± 3.8	Placebo	12	
Rahimi-Ardabili 2013 [18]	Iran	Vitamin D group	24	26.8 ± 4.7	29.1 ± 4.6	50,000 IU/2 weeks of vitamin D3	12	②③④⑥⑦
		Placebo group	26	27.0 ± 3.7	28.3 ± 3.5	Placebo	12	
Raja-Khan 2014 [19]	USA	Vitamin D group	13	28.2 ± 5.2	37.2 ± 4.5	12,000 IU/day of vitamin D3	12	①②③④⑤⑥⑦
		Placebo group	15	28.7 ± 5.6	35.1 ± 9.8	Placebo	12	
Seyyed Abootorabi 2018 [20]	Iran	Vitamin D group	21	26.2 ± 4.6	Na	50,000 IU/week of vitamin D3	8	①②
		Placebo group	17	22.7 ± 4.4	Na	Placebo	8	
Trummer 2019 [21]	Austria	Vitamin D group	81	25.4 ± 4.6	27.3 ± 7.4	20,000 IU/week of vitamin D3	24	①
		Placebo group	42	27.2 ± 5.5	28.3 ± 7.8	Placebo	24	

Abbreviations: Na: Not Available

① Changes in fasting blood glucose; ② Changes in insulin; ③ Changes in triglycerides; ④ Changes in total cholesterol; ⑤ Changes in VLDL-cholesterol; ⑥ Changes in HDL-cholesterol; ⑦ Changes in LDL-cholesterol

Meta-Analysis results

Change in fasting blood glucose

Eleven studies [9–14, 16, 17, 19–21] involving 584 patients with PCOS compared changes in fasting blood glucose. Due to the observed low heterogeneity among the studies ($P = 0.19$, $I^2 = 27\%$), the overall results were synthesized using a random-effects approach. The findings revealed that the change in fasting blood glucose was more favorable in the vitamin D group, implying that the supplementation of vitamin D was more efficient in bringing down fasting blood glucose. This difference was statistically significant [MD=-2.91 mg/dL, 95% CI (-4.78, -1.04) mg/dL, $P = 0.002$]. Detailed results are shown in Fig. 3.

Change in insulin

Ten studies [9–14, 16, 17, 19, 20] involving 463 patients with PCOS compared the change in insulin. Given the relatively low statistical heterogeneity across the studies ($P = 0.11$, $I^2 = 38\%$), the combined results were analyzed using a random-effects model. The findings revealed that change in insulin were more favorable in the vitamin D group than in the placebo group, suggesting that vitamin D supplementation was more effective in reducing insulin, with a statistically significant difference[MD=-1.98 μIU/mL, 95% CI (-3.32, -0.64) μIU/mL, $P = 0.004$]. Detailed results are shown in Fig. 4.

Change in triglyceride

Nine studies [11–19] involving 422 patients with PCOS compared the change in triglyceride. Given the absence of significant statistical heterogeneity across the studies ($P = 0.34$, $I^2 = 12\%$), the combined results were analyzed using a fixed-effects model. Findings indicated that vitamin D supplementation was more effective in reducing triglyceride, with a statistically significant

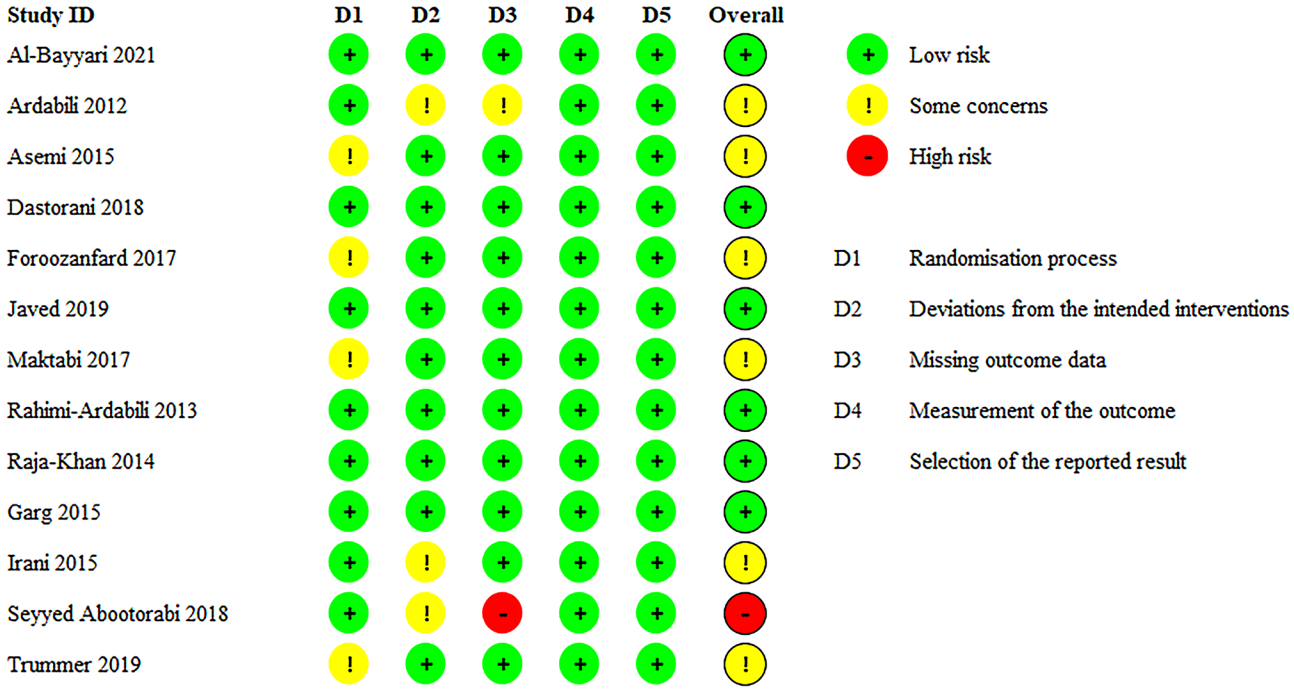

Fig. 2 Quality assessment results of the included studies

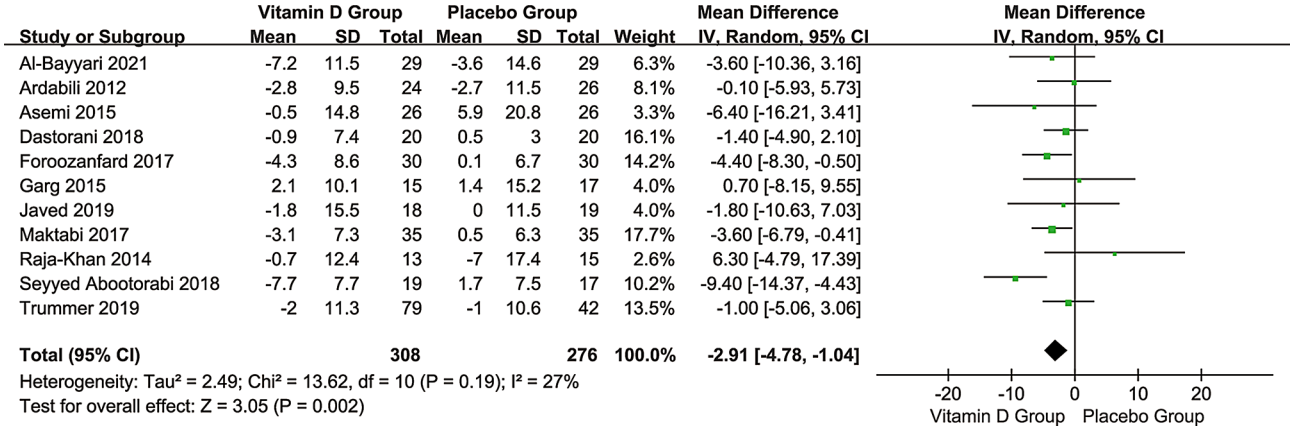

Fig. 3 Comparison of change in fasting blood glucose between the two groups

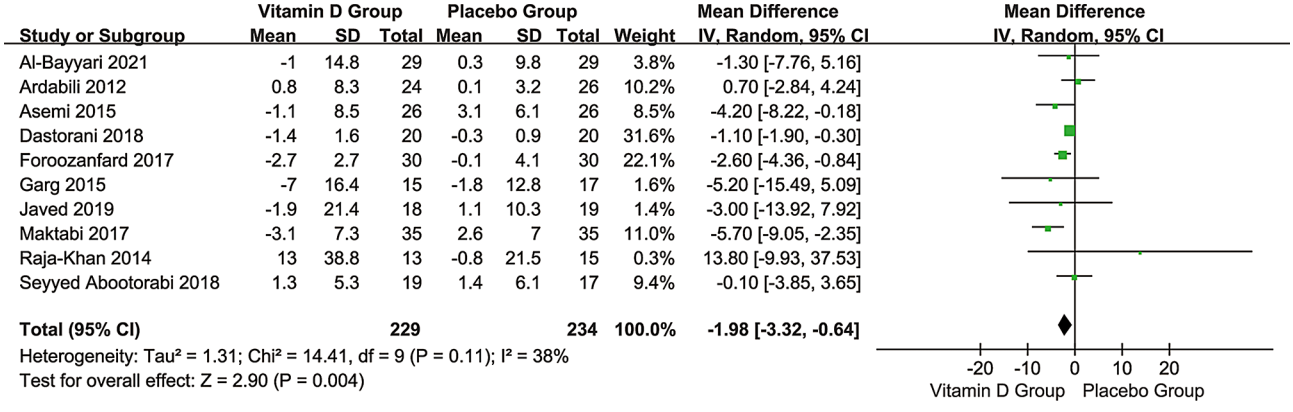

Fig. 4 Comparison of change in insulin between the two groups

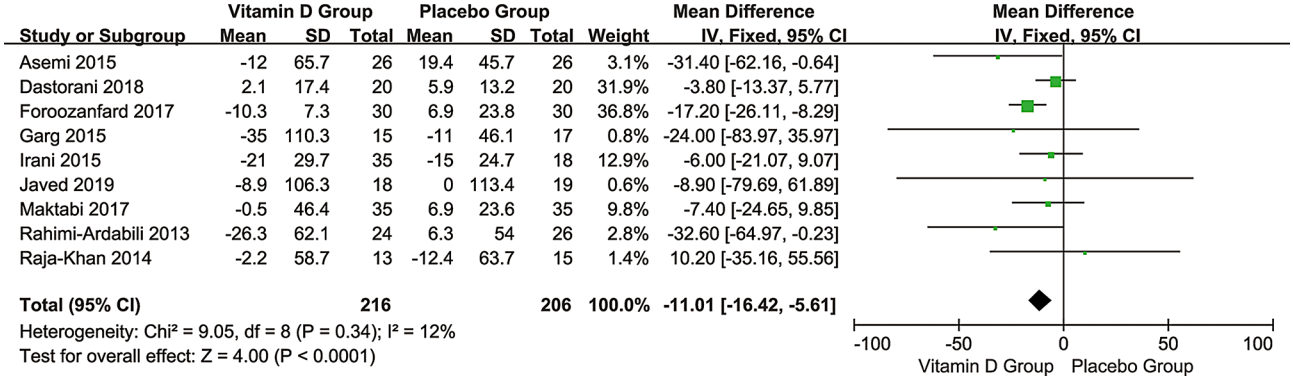

Fig. 5 Comparison of change in triglycerides between the two groups

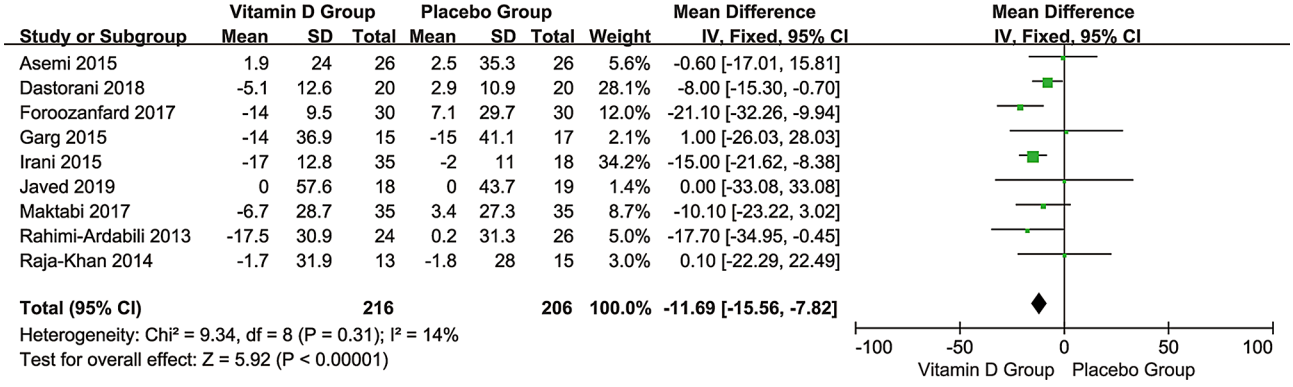

Fig. 6 Comparison of change in total cholesterol between the two groups

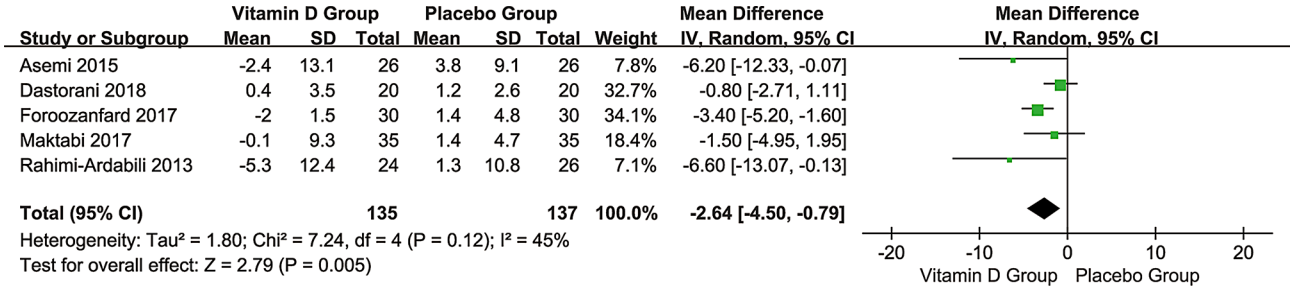

Fig. 7 Comparison of change in VLDL-cholesterol between the two groups

difference[MD=-11.01 mg/dL, 95% CI (-16.42, -5.61) mg/dL, $P<0.0001$]. Detailed results are shown in Fig. 5.

Change in total cholesterol

Nine studies [11–19] involving 422 patients with PCOS compared the change in total cholesterol. Given the absence of statistical heterogeneity across the studies ($P=0.31$, I^2 = 14%), the combined results were analyzed using a fixed-effects model. The findings showed that vitamin D supplementation was more effective in reducing total cholesterol, with a statistically significant difference[MD=-11.69 mg/dL, 95% CI (-15.56, -7.82) mg/dL, $P<0.00001$]. Detailed results are shown in Fig. 6.

Change in VLDL-Cholesterol

Five studies [11–13, 17, 18] involving 272 patients with PCOS compared the change in VLDL-cholesterol. Given the low level of statistical heterogeneity ($P=0.12$, I^2 = 45%), the combined analysis was performed using a random-effects model. The findings suggested that vitamin D supplementation was more effective in reducing VLDL-cholesterol, with a statistically significant difference[MD=-2.64 mg/dL, 95% CI (-4.50, -0.79) mg/dL, $P=0.005$]. Detailed results are shown in Fig. 7.

Change in LDL-Cholesterol

Nine studies [11–19] involving 422 patients with PCOS compared the change in LDL-cholesterol. Given the

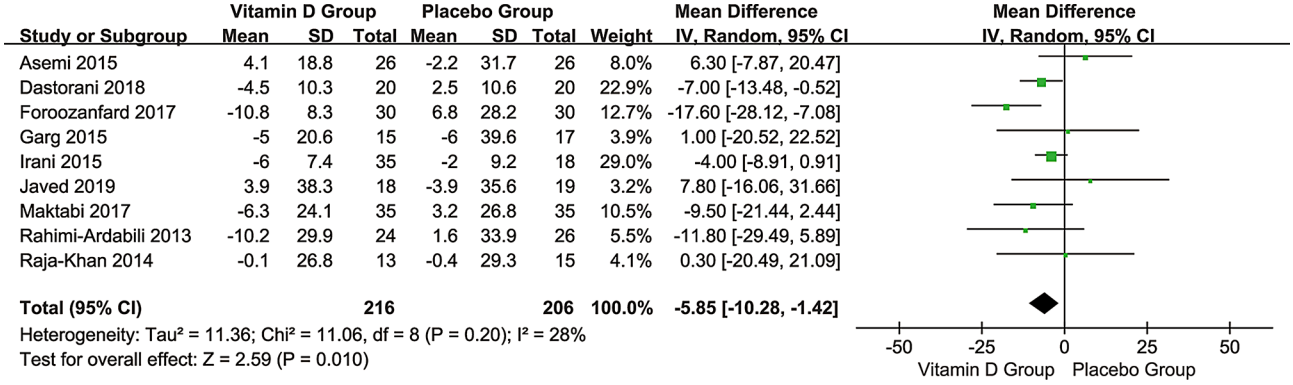

Fig. 8 Comparison of change in HDL-cholesterol between the two groups

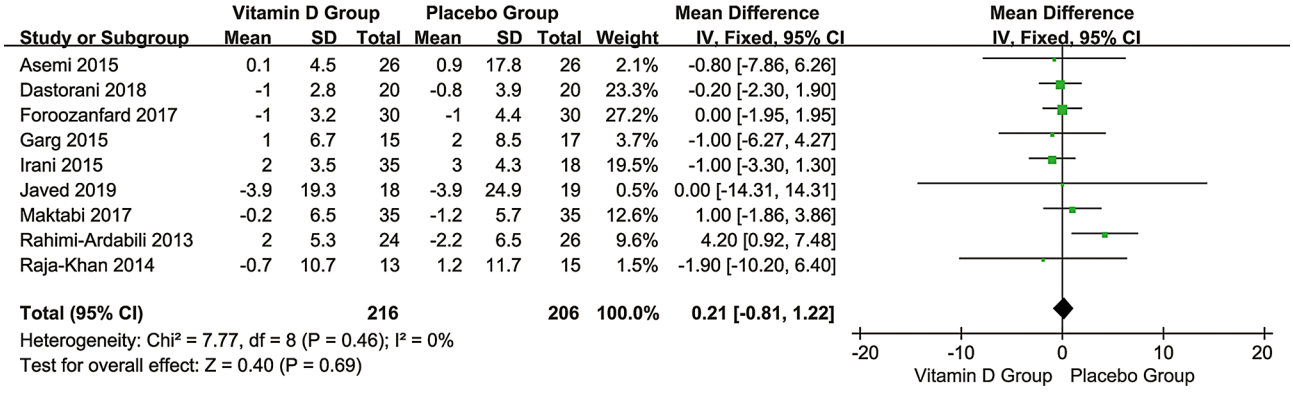

Fig. 9 Comparison of change in LDL-cholesterol between the two groups

low statistical heterogeneity observed across the studies ($P = 0.20$, $I^2 = 28\%$), the combined results were analyzed using a fixed-effects model. The findings showed that vitamin D supplementation was more effective in reducing LDL-cholesterol, with a statistically significant difference [MD=-5.85 mg/dL, 95% CI (-10.28, -1.42) mg/dL, $P = 0.010$]. Detailed results are shown in Fig. 8.

Change in HDL-Cholesterol

Nine studies [11–19] involving 422 patients with PCOS compared the change in HDL-cholesterol. Given the absence of heterogeneity across the studies ($P = 0.46$, $I^2 = 0\%$), the pooled results were analyzed using a fixed-effects model. Findings indicated that the effect difference in HDL-cholesterol between the vitamin D and placebo groups did not reach statistical significance [MD=-0.21 mg/dL, 95% CI (-0.81, 1.22) mg/dL, $P = 0.69$]. Detailed results are shown in Fig. 9.

Publication Bias analysis

Potential publication bias for different outcome measures was evaluated through the implementation of Egger's and Begg's tests. The results of Egger's test for publication bias were as follows: changes in fasting blood glucose ($P = 0.934$), changes in insulin ($P = 0.179$), changes in triglycerides ($P = 0.258$), changes in total cholesterol ($P = 0.229$), changes in VLDL-cholesterol ($P = 0.767$), changes in LDL-cholesterol ($P = 0.331$), and changes in HDL-cholesterol ($P = 0.457$). Correspondingly, Begg's test yielded the following p-values: changes in fasting blood glucose ($P = 0.436$), changes in insulin ($P = 0.107$), changes in triglycerides ($P = 0.175$), changes in total cholesterol ($P = 0.858$), changes in VLDL-cholesterol ($P = 1.000$), changes in LDL-cholesterol ($P = 0.602$), and changes in HDL-cholesterol ($P = 0.251$). Overall, the statistical evidence points to a low risk of publication bias.

Subgroup analysis results

Subgroup analyses were carried out according to the Vitamin D3 dosage, which was classified into two categories: less than 50,000 IU/week and 50,000 IU/week or more. Additionally, subgroup analyses were also done in terms of treatment duration, divided into less than 12 weeks and 12 weeks or longer (Table 2).

GRADE evidence quality assessment

The evidence quality for changes in fasting blood glucose, changes in insulin, changes in triglycerides, changes in VLDL-cholesterol, and changes in HDL-cholesterol was considered low, whereas the evidence for changes in total

Table 2 Results of subgroup analysis based on different doses of vitamin D3 and treatment durations

			Number of	Sample	Heterogeneity test results			
Outcome	**Method of grouping**	**Subgroup**	**studies**	**size**	**P-value**	**I^2 Value**	**Effect model**	**Meta-analysis results**
Changes in fasting	Dose of Vitamin D3	< 50,000 IU/week	6	370	0.69	0	Fixed	MD=-2.58, 95% CI (-4.47,- 0.68), *P* = 0.008
blood glucose		≥ 50,000 IU/week	5	214	0.04	60	Random	MD=-3.65, 95% CI (-8.19,0.89), *P* = 0.12
	Treatment duration	< 12 weeks	4	178	0.04	64	Random	MD=-4.02, 95% CI (-8.63, 0.60), *P* = 0.09
		≥ 12 weeks	7	406	0.56	0	Fixed	MD=-2.66, 95% CI (-4.55, -0.77), *P* = 0.006
Changes in insulin	Dose of Vitamin D3	< 50,000 IU/week	5	249	0.14	42	Random	MD=-2.74, 95% CI (-5.09, -0.39), *P* = 0.02
		≥ 50,000 IU/week	5	214	0.40	1	Fixed	MD=-1.16, 95% CI (-1.92, -0.39), *P* = 0.003
	Treatment duration	< 12 weeks	4	178	0.31	15	Fixed	MD=-1.09, 95% CI (-1.84, -0.33), *P* = 0.005
		≥ 12 weeks	6	285	0.41	1	Fixed	MD=-3.13, 95% CI (-4.61, -1.65), *P* < 0.0001
Changes in	Dose of Vitamin D3	< 50,000 IU/week	5	249	0.71	0	Fixed	MD=-16.16, 95% CI (-23.75,-8.58), *P* < 0.0001
triglycerides		≥ 50,000 IU/week	4	173	0.35	9	Fixed	MD=-5.70, 95% CI (-13.40, 2.00), *P* = 0.15
	Treatment duration	< 12 weeks	3	145	0.24	29	Random	MD=-7.43, 95% CI (-17.93, 3.07), *P* = 0.29
		≥ 12 weeks	6	277	0.64	0	Fixed	MD=-15.45, 95% CI (-22.93, -7.97), *P* < 0.0001
Changes in total	Dose of Vitamin D3	< 50,000 IU/week	5	249	0.42	0	Fixed	MD=-14.69, 95% CI (-21.86, -7.53), *P* < 0.0001
cholesterol		≥ 50,000 IU/week	4	173	0.21	33	Random	MD=-9.42, 95% CI (-15.77, -3.07), *P* = 0.004
	Treatment duration	< 12 weeks	3	145	0.17	44	Random	MD=-10.07, 95% CI (-16.95, -3.20), *P* = 0.004
		≥ 12 weeks	6	277	0.37	8	Fixed	MD=-13.32, 95% CI (-20.14, -6.49), *P* = 0.0001
Changes in	Dose of Vitamin D3	< 50,000 IU/week	3	180	0.36	2	Fixed	MD=-3.20, 95% CI (-4.75, -1.65), *P* < 0.0001
VLDL-cholesterol		≥ 50,000 IU/week	2	92	0.10	63	Random	MD=-2.68, 95% CI (-7.73, 2.36), *P* = 0.30
	Treatment duration	< 12 weeks	2	92	0.10	63	Random	MD=-2.68, 95% CI (-7.73, 2.36), *P* = 0.30
		≥ 12 weeks	3	180	0.36	2	Fixed	MD=-3.20, 95% CI (-4.75, -1.65), *P* < 0.0001
Changes in	Dose of Vitamin D3	< 50,000 IU/week	5	249	0.27	22	Fixed	MD=-10.69, 95% CI (-17.26, -4.12), *P* = 0.001
HDL-cholesterol		≥ 50,000 IU/week	4	173	0.39	0	Fixed	MD=-4.14, 95% CI (-7.85, -0.43), *P* = 0.03
	Treatment duration	< 12 weeks	3	145	0.24	29	Random	MD=-4.01, 95% CI (-8.91, 0.89), *P* = 0.11
		≥ 12 weeks	6	277	0.29	18	Fixed	MD=-9.69, 95% CI (-15.95, -3.42), *P* = 0.002
Changes in	Dose of Vitamin D3	< 50,000 IU/week	5	249	0.26	24	Fixed	MD=-0.92, 95% CI (-0.47, 2.31), *P* = 0.19
LDL-cholesterol		≥ 50,000 IU/week	4	173	0.95	0	Fixed	MD=-0.62, 95% CI (-2.11, 0.87), *P* = 0.42
	Treatment duration	< 12 weeks	3	145	0.88	0	Fixed	MD=-0.58, 95% CI (-2.09, 0.94), *P* = 0.46
		≥ 12 weeks	6	277	0.34	12	Fixed	MD = 0.84, 95% CI (-0.53, 2.21), *P* = 0.23

cholesterol and changes in LDL-cholesterol was assessed as moderate, as presented in Table 3.

TSA results

A sequential analysis of 11 studies assessing changes in fasting blood glucose was carried out, using a significance level of $\alpha = 0.05$ and a power of 80% ($\beta = 0.20$). The cumulative Z-value traversed both the conventional boundary and the TSA boundary before arriving at the RIS, showing that the meta-analysis results are stable and statistically valid. The actual included sample size was 584, exceeding the required sample size (RIS = 423), allowing for a conclusive and robust result. Detailed results are shown in Fig. 10.

Discussion

PCOS, which is a common endocrine disorder, notably impacts the metabolic and reproductive aspects of women's health [27, 28]. For this research, a meta-analysis involving 13 RCTs was carried out to assess how vitamin D supplementation influenced metabolic parameters in 691 PCOS patients. The findings indicated that vitamin D resulted in a notable decrease in the levels of fasting blood glucose, insulin, triglycerides, total cholesterol, VLDL-cholesterol, and LDL-cholesterol, while demonstrating no marked influence on HDL-cholesterol. Considering that insulin resistance and dyslipidemia are core metabolic abnormalities in PCOS, the findings of this study suggest that vitamin D supplementation may offer specific metabolic benefits for women with PCOS by improving insulin sensitivity and regulating lipid metabolism [29, 30]. These results highlight the potential of vitamin D to enhance metabolic health in individuals with PCOS, laying the groundwork for future targeted interventions.

The mechanisms of vitamin D's effects primarily involve enhancement of pancreatic β-cell function and increased insulin sensitivity. First, vitamin D enhances the function of pancreatic β-cells, promoting insulin secretion. This process is closely related to vitamin D's regulation of intracellular calcium ions, which play a crucial role in insulin synthesis and release. A deficiency in vitamin D may lead to β-cell dysfunction, thereby impairing insulin synthesis [31–33]. Second, vitamin D reduces blood glucose levels by enhancing cellular insulin sensitivity; it regulates the expression of genes involved in insulin signaling, thereby improving cellular responsiveness to insulin. Increased insulin sensitivity means that lower levels of insulin are needed to achieve effective blood glucose reduction, thereby reducing the overall demand for insulin [34, 35]. Additionally, vitamin D has anti-inflammatory effects, which may alleviate the negative impact of chronic inflammation on insulin function, an effect particularly beneficial in reducing insulin resistance [36, 37].

Vitamin D supplementation significantly improves lipid metabolism, suggesting that it may enhance lipid metabolism in patients with PCOS through multiple mechanisms. First, vitamin D is believed to regulate lipid synthesis and breakdown in the liver. Research shows that vitamin D affects the expression of genes involved in hepatic lipid metabolism through activation of the vitamin D receptor, thereby inhibiting pathways associated with fatty acid synthesis in the liver [6, 38]. Additionally, vitamin D may promote fatty acid oxidation, further reducing lipid accumulation in the liver [39, 40]. Second, there is a strong association between vitamin D and insulin resistance. Improved insulin sensitivity supports enhanced lipid metabolism, which lowers serum triglyceride and LDL cholesterol levels. Vitamin D deficiency is closely linked to insulin resistance, so supplementation may influence lipid metabolism by enhancing insulin sensitivity [41–43]. Finally, vitamin D may impact lipid metabolism by modulating inflammatory responses. PCOS is often marked by chronic low-grade inflammation, while vitamin D contributes significantly to immune regulation and the suppression of inflammatory markers. By alleviating inflammatory responses, vitamin D may make a further contribution to the enhancement of lipid metabolism [44–46]. The lack of significant change in HDL cholesterol levels could be due to several factors. HDL cholesterol synthesis and metabolism are influenced by multiple factors such as genetic predisposition, nutritional intake, and levels of physical activity [47–49], which may be less affected by vitamin D supplementation. Yang et al. carried out a comprehensive investigation involving 601 participants to evaluate whether vitamin D supplementation could enhance lipid profiles in individuals with prediabetes. The results showed that vitamin D did not produce a significant change in HDL cholesterol levels [50]. Similarly, in a comprehensive analysis of 3,434 participants, Dibaba and colleagues assessed the effects of vitamin D on lipid profiles and reported no significant change in HDL cholesterol levels following supplementation [51]. Although our study included 691 patients, the intervention durations in most of the included trials were relatively short, typically ranging from 8 to 12 weeks. HDL cholesterol, as a biomarker that responds slowly to lifestyle and long-term metabolic changes, may require a longer intervention period to show significant improvements. Therefore, future research should include extended follow-up and expanded cohorts to better evaluate vitamin D's impact on HDL cholesterol.

While vitamin D is widely regarded as safe, excessive intake can lead to adverse effects like hypercalcemia and kidney stone formation [14, 52]. The included studies provided limited reporting on adverse events, making it

Table 3 GRADE assessment of outcome measures

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	New Comparison	Control	Relative (95% CI)	Absolute		
Changes in fasting blood glucose (Better indicated by lower values)												
11	randomised trials	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	308	276	-	MD 2.91 lower (4.78 to 1.04 lower)	⊕⊕OO LOW	IMPORTANT
Changes in insulin (Better indicated by lower values)												
10	randomised trials	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	229	234	-	MD 1.98 lower (3.32 to 0.64 lower)	⊕⊕OO LOW	IMPORTANT
Changes in triglycerides (Better indicated by lower values)												
9	randomised trials	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	216	206	-	MD 11.01 lower (16.42 to 5.61 lower)	⊕⊕OO LOW	IMPORTANT
Changes in total cholesterol (Better indicated by lower values)												
9	randomised trials	serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	216	206	-	MD 11.69 lower (15.56 to 7.82 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Changes in VLDL-cholesterol (Better indicated by lower values)												
5	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	135	137	-	MD 2.64 lower (4.5 to 0.79 lower)	⊕⊕OO LOW	IMPORTANT
Changes in HDL-cholesterol (Better indicated by lower values)												
9	randomised trials	serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	216	206	-	MD 5.85 lower (10.28 to 1.42 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Changes in LDL-cholesterol (Better indicated by lower values)												
9	randomised trials	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	216	206	-	MD 0.21 lower (0.81 lower to 1.22 higher)	⊕⊕OO LOW	IMPORTANT

Abbreviations:CI: Confdence interval; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; MD: Mean diference

[1] Lack of allocation concealment

[2] Lack of blinding

[3] Wide confdence interval

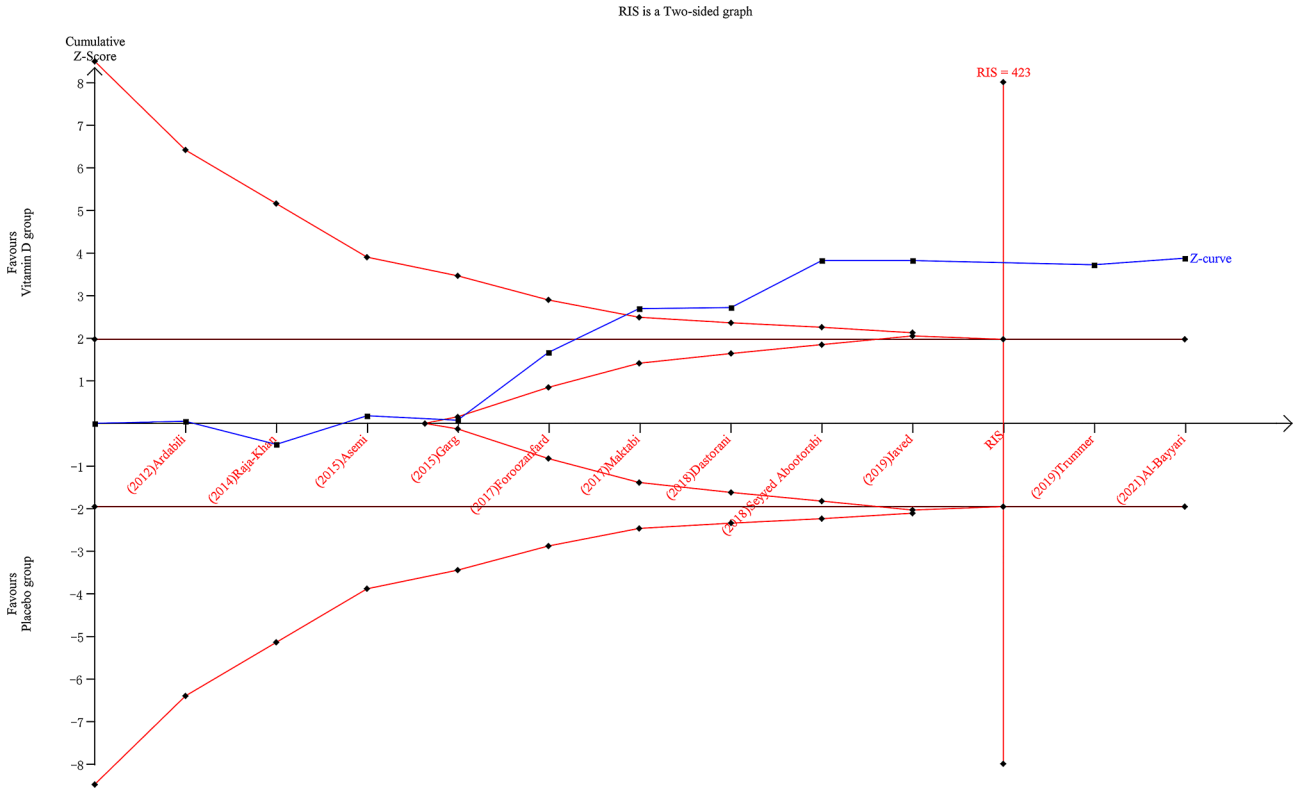

Fig. 10 Trial sequential analysis (TSA) for change in fasting blood glucose

insufficient to fully assess its safety. Additionally, individual differences in vitamin D absorption and metabolism may influence both the effectiveness and risks of supplementation, which should be further explored in future research. Vitamin D can improve insulin resistance and is beneficial for patients with PCOS [41–43], but recent research suggests that insulin resistance itself may reduce the bioavailability of vitamin D, leading to decreased vitamin D levels [53]. Therefore, monitoring serum vitamin D levels during treatment is recommended. Due to differences in sun exposure, genetic factors, and dietary habits, the metabolism of vitamin D varies significantly across different races and ethnic groups. In future research as well as clinical practice, these factors ought to be taken into account and analyzed [54–56].

In this study, the GRADE system and TSA were employed to evaluate the robustness and credibility of the findings. The GRADE system provides a transparent framework for evaluation. According to the findings, the certainty of evidence was rated as low for outcomes such as changes in fasting blood glucose, changes in insulin, changes in triglycerides, changes in VLDL cholesterol, and changes in HDL cholesterol, while moderate-quality evidence was observed for changes in total cholesterol and changes in LDL cholesterol. The reasons for the lower quality of evidence mainly include: first, certain studies exhibited elevated risk of bias, primarily resulting from inadequate implementation of blinding protocols; second, due to the limited sample sizes in certain studies, the resulting effect estimates showed wide confidence intervals and insufficient statistical precision. Although Begg's and Egger's tests revealed no evidence of significant publication bias ($P > 0.05$), the reliability of these methods diminishes when fewer than 10 studies are included, potentially limiting their ability to identify true bias. TSA further validated the adequacy of the sample size, ensuring the robustness of the study conclusions. TSA results indicated that the RIS for the primary outcomes had been achieved, signifying that our results are not only reliable but also statistically well-powered. The combination of these two methods not only enhances the credibility of the study but also provides guidance for future research, recommending careful consideration of sample size design and evidence quality assessment in similar studies.

Despite offering valuable insights into the impact of vitamin D on metabolic markers in PCOS patients, some limitations must be noted. First, the total number of eligible studies remains relatively low. Although the TSA analysis indicated that the sample size meets statistical requirements and this study analyzed 13 RCTs, the limited number of studies may still be insufficient to fully represent the effects of vitamin D supplementation on PCOS patients, potentially limiting the generalizability

of the results. Second, the intervention durations were generally short, which may affect the ability to observe changes in certain metabolic markers, such as HDL cholesterol. Longer intervention periods may help better elucidate the effects of vitamin D on lipid metabolism. Third, variations in vitamin D dosage, administration routes, and follow-up times across studies may have contributed to decreased consistency in the results. Fourth, although some metabolic indicators (such as fasting blood glucose) showed statistically significant improvements, the actual magnitude of change was relatively small and may not be sufficient to produce meaningful clinical benefits on their own. Therefore, the clinical relevance of these findings should be interpreted with caution. Fifth, variations in measurement methods for metabolic indicators, particularly insulin, may have influenced the results. Differences in assay techniques or kits used across studies could contribute to heterogeneity and affect the accuracy of the pooled estimates. Finally, the inability to fully control for potential confounding factors related to PCOS, such as lifestyle, dietary habits, and other underlying conditions, may further impact the accuracy of the results. Future studies should overcome these limitations by implementing larger and longer-duration RCTs to confirm the impact of vitamin D on metabolic indicators in PCOS patients.

Findings from this study demonstrate that vitamin D supplementation markedly improves metabolic markers, including reductions in fasting blood glucose, insulin, triglycerides, total cholesterol, VLDL-C, and LDL-C, though its effect on HDL cholesterol levels was not significant. Although the findings suggest a potential benefit of vitamin D in enhancing metabolic markers in PCOS patients, further validation through larger and longer-term RCTs is required due to current study limitations.

Acknowledgements
Not applicable.

Author contributions
Miao Yu: Participated in the conceptual design of the study, supervised the research process, and provided critical input during manuscript revision. Shuai Chen: Performed data analysis and made substantial contributions to manuscript refinement. Xia Liu: Was responsible for data collection and statistical processing, and assisted in drafting and revising the manuscript. Hui Dong: Supported data analysis and interpretation, and contributed to manuscript preparation and final proofreading. Deng-Chao Wang: Served as the corresponding author; coordinated the overall execution of the study, ensured data accuracy and research integrity, and managed communication and revisions with the journal.

Funding
None.

Data availability
All data generated or analyzed during this study were included in this published article.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Sichuan Vocational College of Health and Rehabilitation, Zigong, Sichuan 643000, China
[2]Department of General Surgery, Zigong Fourth People's Hospital, 19 Tanmulin Road, Zigong, Sichuan 643000, P.R. China

Received: 19 January 2025 / Accepted: 1 April 2025
Published online: 21 April 2025

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