Kazeminia *et al.*
Middle East Fertility Society Journal (2024) 29:45
https://doi.org/10.1186/s43043-024-00201-w

Middle East Fertility Society Journal

REVIEW

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The effect of vitamin D on the hormonal profile of women with polycystic ovarian syndrome: a systematic review and meta-analysis

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Abstract

Background Polycystic ovarian syndrome (PCOS) is recognized as the most common endocrine disorder among women of reproductive age and the most common cause of infertility. Given the importance of the subject and the inconsistency of the results of the primary studies, the present study aimed at estimating the pooled effect of vitamin D on the hormonal profile of women with PCOS using systematic review and meta-analysis.

Main body A systematic literature review was performed in PubMed, Scopus, Embase, Web of Science (WoS), Cochrane, ClinicalTrials.gov databases, and Google Scholar motor engine using related Medical Subject Headings (MeSH) and Free Text words with no time limit to April 2022. Heterogeneity among studies was quantified using I^2 index. After eliminating duplicates and irrelevant studies, ultimately, 19 articles with a sample size of 450 in the intervention group and 450 in the control group were included in the meta-analysis. As a result of the combination of studies, mean the standardized difference (SMD) before and after the intervention was obtained 0.241 ± 0.098 for dehydroepiandrosterone sulfate (DHEAS), 0.330 ± 0.092 for sex hormone-binding globulin (SHBG), 0.707 ± 0.171 for testosterone, 0.614 ± 0.199 for luteinizing hormone (LH), 0.220 ± 0.119 for follicle-stimulating hormone (FSH), 0.655 ± 0.505 for anti-Müllerian hormone (AMH), and 0.369 ± 0.109 for Free Androgen Index (FAI) in the intervention group compared to the control group. The results indicated that 8-week interventions had a greater positive effect than 12-week interventions.

Conclusion The results of the current meta-analysis revealed a significant positive effect of vitamin D on the hormonal profile of women with PCOS, which should be considered by obstetricians and midwives.

Keywords Meta-analysis, Polycystic ovary syndrome, Systematic review, Vitamin D

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Introduction

Polycystic ovarian syndrome (PCOS) is a common endocrine and metabolic disorder among women of childbearing age [1, 2]. PCOS is characterized by a set of disorders, including androgen elevation (clinical and biochemical symptoms), lack of ovulation or oligo-anovulation, and the appearance of small and abundant cysts on ultrasound scans of ovaries [3]. Several underlying factors, such as diet, environmental factors, physical activity, genetic factors, and neuroendocrine factors, are determinants in the development of PCOS at different periods of life [4]. Compared to healthy individuals, people with PCOS typically exhibit lower levels of follicle-stimulating hormone (FSH), sex hormone-binding globulin (SHBG), and high-density lipoprotein (HDL), as well as higher levels of luteinizing hormone (LH), testosterone, insulin, cholesterol, and triglycerides in serum tests [5–7].

The prevalence of PCOS varies between 2.2 and 26% across different countries [8]. PCOS is associated with adverse complications, including infertility, gestational hypertension, preeclampsia, gestational diabetes, cardiovascular complications, diabetes, cancer, hypertension, and psychological complications [9]. The incidence of these symptoms and complications can lead to disorders in various aspects of the quality of life [10–13].

Lifestyle modification interventions are considered the first-line treatment for women with PCOS. Additionally, medications such as metformin, oral contraceptive pills, and anti-androgens are prescribed by specialists [14]. Various non-pharmacological therapies (NPT), including exercise and physical activity, diet, acupressure, and dietary supplements have been studied and have reported improving effects on hormone levels, metabolic indices, and anthropometric measures [15].

Serum vitamin D status is one of the factors associated with PCOS [16]. Vitamin D deficiency is more common among people with PCOS and obesity since the accumulation of vitamin D in adipose tissue reduces its availability [17, 18]. The relationship between inadequate serum vitamin D levels and endocrine disorders has been reported in many studies [18, 19]. Vitamin D receptors are expressed in skeletal tissue, parathyroid glands, and ovaries, mediating the biological function of vitamin D [20, 21].

Several primary studies have been conducted on the effect of vitamin D on the hormonal profile of women with PCOS with conflicting results [7, 22, 23]. The only relevant meta-analysis study, conducted by Pergialiotis et al. [24], had several limitations, including the search for articles being limited to 2016, the lack of searching some important databases (Embase and Web of Science (WoS)), the lack of investigating some items of the hormonal profile, the limited number of studies included, the lack of examining publication bias, and the lack of evaluating the impact of potential factors, such as the year of publication, sample size, total dose of vitamin D, mean age, Body Mass Index (BMI), baseline vitamin D level, score of Joanna Briggs Institute (JBI), number of weeks of intervention, and frequency of taking vitamin D. Given the importance of the subject, inconsistencies of the results of primary studies, and limitations of the aforementioned meta-analysis, the present study aimed to estimate the pooled effect of vitamin D on the hormonal profile of women with PCOS using systematic review and meta-analysis.

Materials and method

The present systematic review and meta-analysis were carried out according to the PRISMA 2020 protocol (http://www.prisma-statement.org/), including identification, screening, eligibility, and included [25]. No time limit to April 2022. All steps of identification, selection, and study quality assessment, as well as data extraction were independently done by two researchers (M.K. and F.R.). Any disagreement between the two researchers was resolved through consultation with a third researcher (M.R.).

Identification of studies

A systematic literature review was conducted in the international databases of PubMed, Scopus, Embase, Web of Science (WoS), Cochrane, and ClinicalTrials.gov to identify relevant publications. The searches included the combinations of the Medical Subject Headings (MeSH) for PubMed/Emtree (Elsevier's authoritative life science thesaurus) for Embase and Free Text words. No time and language limitations were regarded for the search to retrieve as comprehensive as possible relevant studies. Finally, the Google Scholar motor engine and references of all eligible articles were manually reviewed to maximize the comprehensiveness of the search. For instance, the PubMed search strategy was defined as follows:

((((((((((((((((((((((((((((((("Vitamin D"[MeSH Terms]) OR (Ergocalciferols[MeSH Terms])) OR ("Vitamin D"[Title/Abstract])) OR (Ergocalciferol*[Title/Abstract])) OR (Calciferols[Title/Abstract])) OR ("Vitamin D 2"[Title/Abstract])) OR ("Vitamin D2"[Title/Abstract])) OR ("D2, Vitamin"[Title/Abstract])) OR (Cholecalciferols[Title/Abstract])) OR ("Vitamin D3"[Title/Abstract])) OR ("Vitamin D 3"[Title/Abstract])) OR ("(3 Beta,5Z,7E)-9,10-Secocholesta-5,7,10(19)-trien-3-ol"[Title/Abstract])) OR (Calciol[Title/Abstract])) OR ("Hydroxyvitamins D"[Title/Abstract])) OR (Hydroxycholecalciferol[Title/Abstract])) OR ("25-Hydroxyvitamin D 3"[Title/Abstract])) OR ("25 Hydroxyvitamin D 3"[Title/Abstract])) OR ("25-Hydroxycholecalciferol Monohydrate"[Title/Abstract])) OR ("25 Hydroxycholecalciferol Monohydrate"[Title/Abstract])) OR

("Monohydrate, 25-Hydroxycholecalciferol"[Title/Abstract])) OR ("25-Hydroxyvitamin D3"[Title/Abstract])) OR ("25 Hydroxyvitamin D3"[Title/Abstract])) OR (Calcidiol [Title/Abstract])) OR ("25-Hydroxycholecalciferol"[Title/Abstract])) OR ("25 Hydroxycholecalciferol"[Title/Abstract])) OR ("Calcifediol, (3 beta,5E,7E)-Isomer"[Title/Abstract])) OR ("Calcifediol Anhydrous"[Title/Abstract])) OR ("Anhydrous, Calcifediol"[Title/Abstract])) OR (Dedrogyl[Title/Abstract])) OR (Hidroferol[Title/Abstract])) OR ("Calcifediol, (3 alpha,5Z,7E)-Isomer"[Title/Abstract])) OR (Calderol[Title/Abstract])) AND ((((((((((((((("Polycystic Ovary Syndrome"[MeSH Terms]) OR ("Polycystic Ovary Syndrome"[Title/Abstract])) OR (PCOS[Title/Abstract])) OR (PCO[Title/Abstract])) OR ("Ovary Syndrome, Polycystic"[Title/Abstract])) OR ("Syndrome, Polycystic Ovary"[Title/Abstract])) OR ("Stein-Leventhal Syndrome"[Title/Abstract])) OR ("Stein Leventhal Syndrome"[Title/Abstract])) OR ("Syndrome, Stein-Leventhal"[Title/Abstract])) OR ("Sclerocystic Ovarian Degeneration"[Title/Abstract])) OR ("Ovarian Degeneration, Sclerocystic"[Title/Abstract])) OR ("Sclerocystic Ovary Syndrome"[Title/Abstract])) OR ("Polycystic Ovarian Syndrome"[Title/Abstract])) OR ("Ovarian Syndrome, Polycystic"[Title/Abstract])) OR ("Sclerocystic Ovaries"[Title/Abstract])) OR ("Ovary, Sclerocystic"[Title/Abstract])) OR ("Sclerocystic Ovary"[Title/Abstract])).

Inclusion criteria

The inclusion criteria were original articles, interventional studies, and studies that investigated the effect of vitamin D on the hormonal profile of women with PCOS.

Exclusion criteria

The exclusion criteria encompassed a range of study types, including irrelevant studies, cross-sectional studies, qualitative studies, case series, case reports, letters to the editor, papers presented at conferences, secondary studies, dissertations, animal studies, studies with overlapping data, and those that lacked sufficient data, specifically the failure to report the mean and standard deviation before and after the intervention in both the placebo and intervention groups.

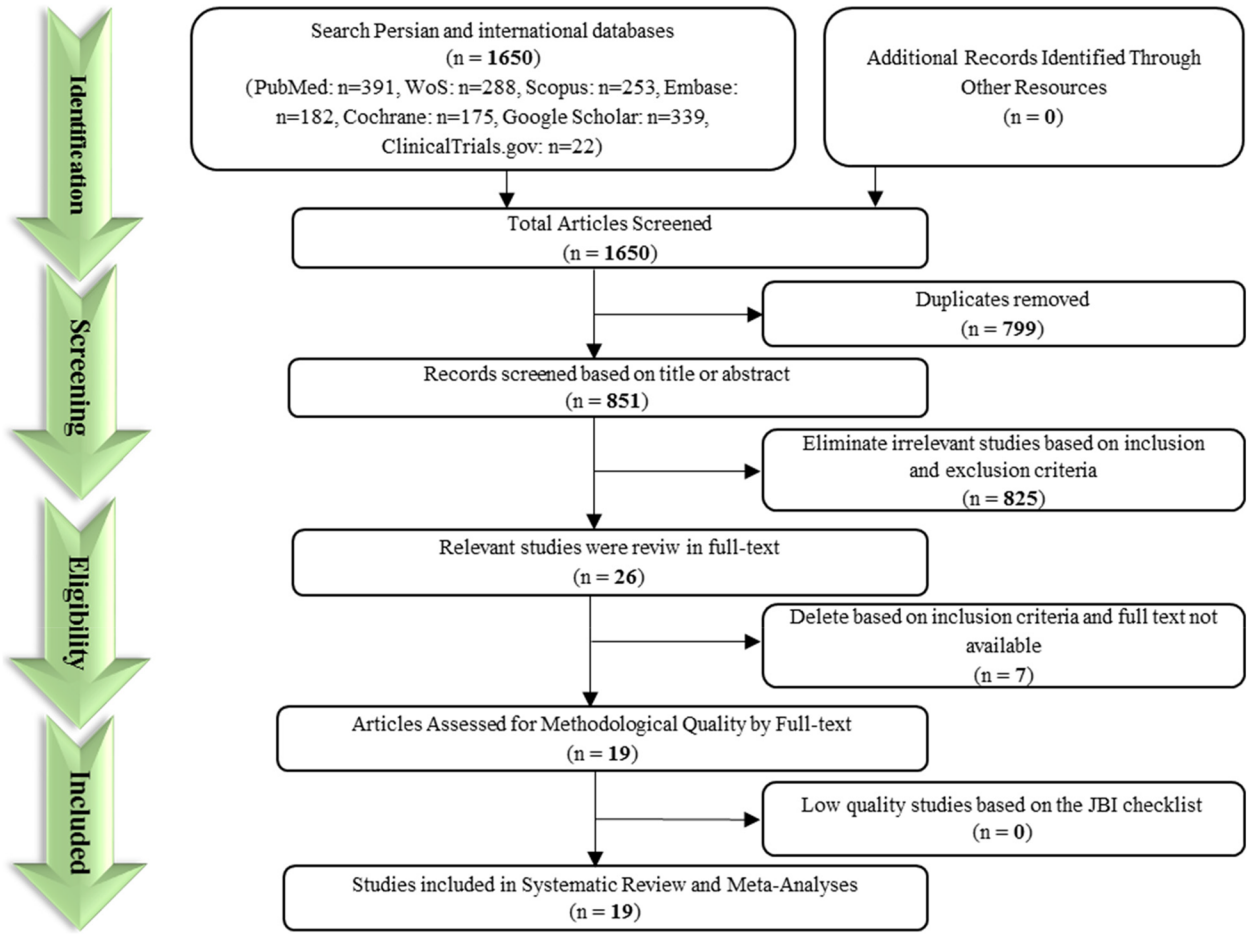


Fig. 1 The preferred items for systematic reviews and meta-analyses (PRISMA 2020) flow diagram of study inclusion

Table 1 The characteristics of studies included in the systematic review and meta-analysis

Author, year (reference)	Country	Sample size (intervention/placebo)	Total dose	Study design	Age (intervention/placebo)	Baseline BMI (kg/m^2) (intervention/placebo)	Baseline vitamin D (intervention/placebo)	Intervention duration	JBI score
Maktabi, 2018 [29]	Iran	30/30	33,600 IU vitamin D supplements	A randomized, double-blind, placebo-controlled trial	23.8 ± 5.7/24.8 ± 4.8	24.2 ± 3.8/25.6 ± 4.8	–	Twice a day for 12 weeks	12, High
Razavi, 2016 [23]	Iran	27/27	33,600 IU vitamin D supplements	A randomized, double-blind, placebo-controlled trial	18–40	–	14.4 ± 2.9/14.6 ± 5.5	Thrice a day for 8 weeks	10, High
Maktabi, 2017 [7]	Iran	35/35	50,000 IU vitamin D supplements	A randomized, double-blind, placebo-controlled trial	–	–	12.8 ± 4.5/14.5 ± 5.1	Twice a day for 12 weeks	10, High
Jamilian, 2017 [22]	Iran	30/30	33,600 IU vitamin D supplements	A randomized, double-blind, placebo-controlled trial	28 ± 5/25 ± 5	31 ± 6/30 ± 6	–	Daily for 12 weeks	11, High
Ostadmohammadi, 2019 [30]	Iran	30/30	50,000 IU vitamin D supplements	A randomized, double-blind, placebo-controlled trial	24.4 ± 4.7/25.4 ± 5.1	24.3 ± 4.2/25.1 ± 4.9	–	Twice a day for 12 weeks	10, High
Dravecká, 2016 [31]	Slovakia	09-Nov	50,000 IU vitamin D supplements	A randomized, double-blind, placebo-controlled trial	29.33 ± 4.89/27.6 ± 4.96	–	–	Daily for 12 weeks	8, Medium
Gupta, 2017 [32]	India	25/25	72,000 IU vitamin D supplements	A randomized, double-blind, placebo-controlled trial	26.04 ± 2.73/6.64 ± 3.73	24.93 ± 2.81/25.55 ± 1.98	–	Daily for 12 weeks	8, Medium
Dastorani, 2018 [16]	Iran	20/20	50,000 IU vitamin D supplements	A randomized, double-blind, placebo-controlled trial	29.9 ± 4.4/ 30.1 ± 3.4	27.7 ± 3.9/28.4 ± 2.6	10.5 ± 2.5/11.0 ± 2.4	Thrice a day for 8 weeks	13, High
Javed, 2019 [6]	UK	18/19	28,800 IU vitamin D supplements	A randomized, double-blind, placebo-controlled trial	28.6 ± 5.5/29.1 ± 7.5	–	–	Twice a day for 12 weeks	10, High
Kadoura, 2019 [33]	Syria	18/16	336,000 IU vitamin D supplements	A randomized, placebo-controlled clinical trial	23.06 ± 3.32/23.38 ± 3.54	25.48 ± 4.97/28.01 ± 4.41	20.42 ± 6.10/19.88 ± 3.92	Daily for 8 weeks	10, High
Jafari-Sfidvajani, 2018 [5]	Iran	26/28	60,000 IU vitamin D supplements	A randomized, double-blind, placebo-controlled trial	28.43 ± 6.27/27.83 ± 5.71	31.13 ± 4.99/31.61 ± 4.91	–	Once a week for 12 weeks	12, High

Table 1 (continued)

Author, year (reference)	Country	Sample size (intervention/placebo)	Total dose	Study design	Age (intervention/placebo)	Baseline BMI (kg/m^2) (intervention/placebo)	Baseline vitamin D (intervention/placebo)	Intervention duration	JBI score
Yahya, 2019 [34]	Iraq	24/17	56,000 IU vitamin D	A prospective interventional randomized-controlled, open-label study	24.71 ± 4.07/22.76 ± 3.8	26.46 ± 4.09/ 27.59 ± 4.63	–	Once a week for 8 weeks	8, Medium
Sert, 2022 [35]	Turkey	35/35	40,000 IU vitamin D supplements	A randomized, double-blind, placebo-controlled trial	21.7 ± 3.5	–	8.6 ± 3.2/8.9 ± 2.6	Once a week for 8 weeks	11, High
Rashidi, 2009 [36]	Iran	30/30	33,600 IU vitamin D supplements	A pilot study	24.95 ± 3.56/25.805 ± 4.61	25.75 ± 3.94/27.81 ± 3.78	-	Daily for 12 weeks	9, High
Bonakdaran, 2012 [37]	Iran	15/16	33,600 IU vitamin D supplements	A randomized placebo-controlled clinical trial	24.7 ± 3.3/25.2 ± 7.9	24.8 ± 5.3/25.3 ± 5.1	-	Daily for 12 weeks	10, High
Garg, 2015 [38]	India	15/18	336,000 IU vitamin D supplements	A prospective double-blind randomized control trial	22.0 ± 4.61/22.8 ± 4.56	26.8 ± 4.56/26.7 ± 6.11	-	Daily for 12 weeks	11, High
Irani, 2015 [39]	Iran	35/18	40,000 IU vitamin D supplements	A randomized placebo-controlled trial	30.5 ± 1/29.6 ± 1.7	30 ± 1/28 ± 1.6	-	Once a week for 8 weeks	8, Medium
Raja-Khan, 2014 [40]	USA	13/15	336,000 IU vitamin D supplements	A randomized, placebo-controlled trial	28.2 ± 5.2/28.7 ± 5.6	37.2 ± 4.53/37.6 ± 10.0	-	Daily for 12 weeks	10, High
Hosseini, 2019 [41]	Iran	15/15	11,200 IU vitamin D supplements	A randomized, placebo-controlled trial	28.56 ± 1.55/29.23 ± 2.11	26.71 ± 0.91/26.49 ± 0.90	-	Daily for 8 weeks	8, Medium

Table 2 The hormonal profile of studies included in the systematic review and meta-analysis

Author, year (reference)	Group	DHEAS (μg/ml) (before/after)	SHBG (nmol/L) (before/after)	Testosterone (ng/mL) (before/after)	LH (mIU/ml) (before / after)	FSH (mIU/ml) (before/after)	AMH (ng/mL) (before/after)	FAI (before/after)
Maktabi, 2018 [29]	Intervention	–	43.2 ± 28.2/52.2 ± 34.8	1.6 ± 0.6/1.4 ± 0.5	–	–	–	0.20 ± 0.15/0.16 ± 0.16
	Placebo	–	41.6 ± 17.3/45.4 ± 16.9	1.4 ± 0.9/1.5 ± 0.9	–	–	–	0.15 ± 0.17/0.12 ± 0.07
Razavi, 2016 [23]	Intervention	1.9 ± 1.2/1.1 ± 1.4	–	3.7 ± 1.6/1.6 ± 1.0	14.7 ± 8.8/7.7 ± 4.8	7.8 ± 2.9/7.6 ± 3.9	–	–
	Placebo	1.8 ± 0.8/1.7 ± 0.8	–	3.5 ± 2.3/3.6 ± 2.6	14.0 ± 14.3/12.8 ± 7.1	7.8 ± 1.8/8.3 ± 2.3	–	–
Maktabi, 2017 [7]	Intervention	2.8 ± 1.1/2.3 ± 1.0	42.4 ± 13.3/47.9 ± 17.0	1.3 ± 0.6/1.3 ± 0.7	–	–	–	0.12 ± 0.07/0.11 ± 0.09
	Placebo	3.4 ± 2.2/2.9 ± 1.8	42.4 ± 38.3/46.4 ± 20.0	1.5 ± 0.7/1.6 ± 0.6	–	–	–	0.20 ± 0.22/0.14 ± 0.10
Jamilian, 2017 [22]	Intervention	1.0 ± 0.5/0.9 ± 0.4	40.2 ± 10.8/59.3 ± 25.3	1.6 ± 0.7/1.4 ± 0.6	–	–	–	0.16 ± 0.17/0.10 ± 0.07
	Placebo	1.0 ± 0.3/1.0 ± 0.3	42.9 ± 18.0/43.6 ± 16.5	1.8 ± 0.6/1.9 ± 0.6	–	–	–	0.17 ± 0.12/0.17 ± 0.12
Ostadmohammadi, 2019 [30]	Intervention	–	38.4 ± 5.9/39.6 ± 5.7	1.0 ± 0.3/0.9 ± 0.2	–	–	–	–
	Placebo	–	40.2 ± 5.0/40.3 ± 5.3	1.1 ± 0.4/1.1 ± 0.3	–	–	–	–
Dravecká, 2016 [31]	Intervention	3.4 ± 1.55/4.3 ± 2.0	48.9 ± 29/56.3 ± 49.7	–	7.09 ± 4.91/8.33 ± 6.42	–	–	8.6 ± 5.4/12.39 ± 8.06
	Placebo	3.8 ± 1.9/4.0 ± 2.0	48.9 ± 30.67/44.33 ± 28	-	7.06 ± 4.28/11.91 ± 20.41	–	–	10.78 ± 5.2/10.72 ± 9.38
Gupta, 2017 [32]	Intervention	1.28 ± 0.82/1.36 ± 0.39	–	1.65 ± 2.40/0.96 ± 0.24	9.59 ± 2.40/9.73 ± 1.80	5.55 ± 1.22/5.51 ± 1.14	–	–
	Placebo	1.3 ± 0.9/1.28 ± 0.5	–	1.7 ± 1.40/1.8 ± 0.3	9.2 ± 2.1/9.0 ± 1.1	5.8 ± 1.0/5.6 ± 1.0	–	–
Dastorani, 2018 [16]	Intervention	–	–	–	–	–	7.7 ± 3.4/7.0 ± 3.1	–
	Placebo	–	–	–	–	–	8.7 ± 2.7/8.6 ± 2.5	–
Javed, 2019 [6]	Intervention	–	24.0 ± 24.8/24.5 ± 19.8	1.1 ± 0.9/1.1 ± 0.8	–	–	–	5.3 ± 5.8/4.9 ± 5.5
	Placebo	–	19.0 ± 17.0/20.0 ± 13.0	1.1 ± 0.4/1.2 ± 0.4	–	–	–	5.5 ± 3.1 /5.9 ± 3.4
Kadoura, 2019 [33]	Intervention	–	–	–	7.73 ± 5.17/ 6.10 ± 3.23	5.45 ± 1.73/ 6.17 ± 1.67	–	–
	Placebo	–	–	–	10.03 ± 5.55/6.86 ± 3.76	6.33 ± 2.10/6.89 ± 1.91	–	–
Jafari-Sfidvajani, 2018 [5]	Intervention	2.14 ± 1.51/2.27 ± 1.11	27.17 ± 24.22/27.83 ± 18.94	0.70 ± 0.37/0.54 ± 0.16	–	–	–	5.91 ± 7.81/3.77 ± 4.06
	Placebo	2.17 ± 1.32/2.59 ± 1.29	31.61 ± 38.13/26.55 ± 22.64	0.66 ± 0.34/0.57 ± 0.29	–	–	–	5.85 ± 7.25/5.29 ± 6.43
Yahya, 2019 [34]	Intervention	–	–	2.87 ± 2.41/1.89 ± 0.64	5.33 ± 2.53/4.09 ± 1.24	5.07 ± 1.69/5.21 ± 1.38	4.47 ± 2.46/3.42 ± 1.43	–
	Placebo	–	–	1.37 ± 0.81/1.31 ± 0.96	7.44 ± 3.86/4.78 ± 2.08	5.69 ± 1.17/5.93 ± 1.84	4.08 ± 3.10/2.96 ± 1.88	–
Sert, 2022 [35]	Intervention	–	25.1 ± 13.3/30.6 ± 8.9	–	–	–	–	–
	Placebo	–	24.5 ± 3.8/25.6 ± 8.6	–	–	–	–	–
Rashidi, 2009 [36]	Intervention	–	–	–	10.24 ± 6.38/9.90 ± 3.58	4.95 ± 1.66/5.20 ± 1.98	–	–
	Placebo	–	–	–	9.65 ± 4.91/8.81 ± 4.51	5.67 ± 1.70/5.28 ± 1.78		-
Bonakdaran, 2012 [37]	Intervention	2.65 ± 1.34/2.64 ± 1.07	–	0.94 ± 0.45/1.06 ± 0.31	–	–	–	–
	Placebo	3.16 ± 1.64/3.33 ± 1.54	–	0.88 ± 0.43/1.22 ± 0.65	–	–	–	–
Garg, 2015 [38]	Intervention	2.36 ± 0.65/2.38 ± 0.12	–	0.47 ± 0.19/0.35 ± 0.12	–	–	–	–
	Placebo	2.69 ± 0.1/3.08 ± 0.98	–	0.55 ± 0.1/0.52 ± 0.11	–	–	–	–
Irani, 2015 [39]	Intervention	1.17 ± 1.6/1.21 ± 1.3	32.9 ± 2.9/33.9 ± 3.6	3.04 ± 0.29/3.84 ± 0.43	9 ± 2.7/8.3 ± 1.2	5.9 ± 0.6/4.5 ± 0.5	–	–
	Placebo	1.4 ± 2.0/1.43 ± 1.8	39 ± 4.9/43 ± 9.4	3.23 ± 0.34/3.6 ± 0.4	12 ± 2.8/9.2 ± 1.6	6.8 ± 0.7/5.2 ± 0.6	–	–
Raja-Khan, 2014 [40]	Intervention	–	–	5.4 ± 2.8/5.5 ± 3.7	–	–	–	–
	Placebo	–	–	4.1 ± 1.7/5.06 ± 2.9	–	–	–	–
Hosseini, 2019 [41]	Intervention	–	–	–	–	–	11.85 ± 1.52/9.71 ± 1.12	–
	Placebo	–	–	–	–	–	12.65 ± 1.23/12.41 ± 0.94	–

Selection process of studies

All studies obtained from different databases were imported into EndNote X8 software. After excluding the duplicates, the title and abstract of the articles were thoroughly screened to eliminate irrelevant studies. In the following, the full text of the remaining articles was carefully inspected for eligibility. Researchers extracted the articles without knowing the names of authors, institutes, and journals. The quality assessment of all studies included in the systematic review and meta-analysis was done.

Quality assessment of the studies

The quality assessment of the studies was done using the Joanna Briggs Institute (JBI) checklist, known as a standard checklist for the quality assessment of studies [26]. This checklist consists of 13 different items, including randomization, allocation, the similarity of treatment groups in the beginning, the blindness of the participants, the blindness of doers, the blindness of the evaluators of the results, similar treatment in groups except intervention, follow up, participant analysis, outcomes, reliability of the method of measuring results, appropriate statistical analysis, and trial design appropriate. Each item is answered as "yes" for pointed, "no" for not pointed, and "not applicable" for not reported. The total score range based on the JBI items is between 0 and 13. Studies with a score of 1–4 were considered as "low quality", 5–8 as "medium quality", and 9–13 as "high quality" [27].

Data extraction

The data were manually collected from all articles included in the systematic review and meta-analysis using a pre-prepared checklist. The items of this checklist consisted of the name of the first author, country, year of publication, sample size, intervention duration, study design, total dose, baseline BMI, baseline vitamin D, and JBI score.

Statistical analysis

The present study estimated the effect of vitamin D on the hormonal profile of women with PCOS. In this regard, the mean and SD of placebo and intervention groups in each study were used to combine the results of different studies. Heterogeneity among studies was quantified using I^2 index and $I^2 < 50\%$ was considered for "low heterogeneity" and $I^2 > 50\%$ for "high heterogeneity". The fixed effects model was used in low heterogeneity conditions and the random effects model was applied in high heterogeneity conditions [28]. Egger's regression intercept was employed to investigate publication bias. Further, the meta-regression was used to investigate the relationship between SMD before and after the intervention in the intervention and placebo

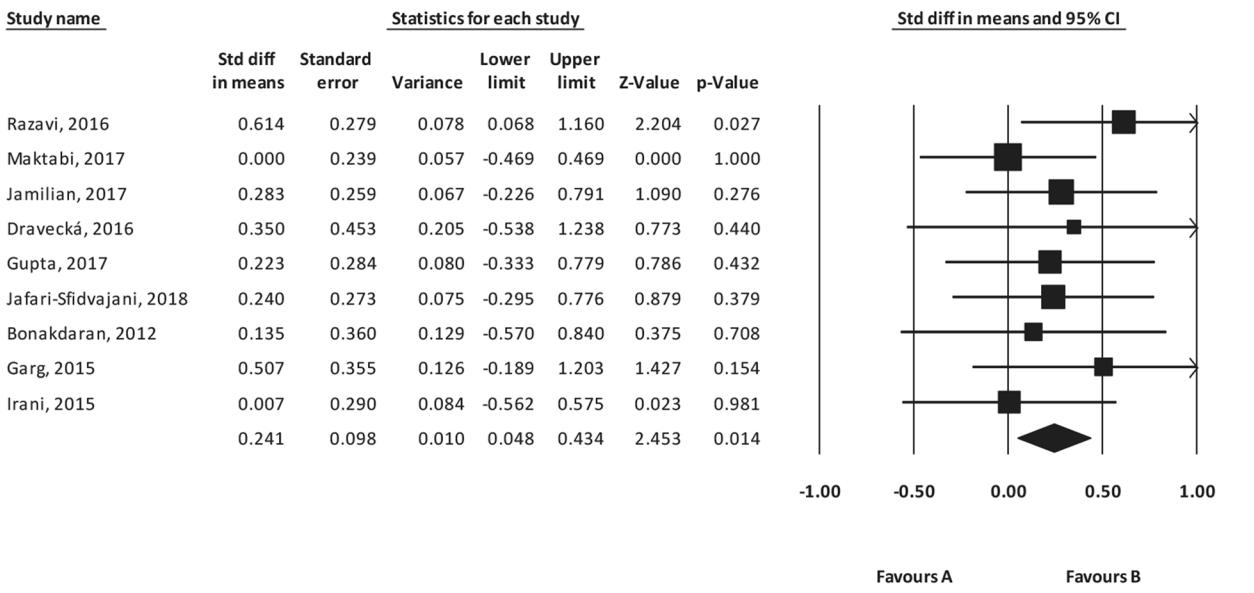


Fig. 2 The forest plot of studies included in the meta-analysis for DHEAS based on the fixed effects model

groups and the year of publication, sample size, total dose of vitamin D, mean age, BMI, baseline vitamin D level, and JBI score. The data were analyzed using Comprehensive Meta-Analysis (Version 2) software and *P*-value less than 0.05 was considered statistically meaningf.ull.

Results

The summary of how articles included in the meta-analysis

The initial systematic literature search retrieved 1650 articles using defined search strategies. After excluding 799 duplicates in different databases, 825 irrelevant studies were eliminated by screening the title and abstract. Then, the full text of the remaining 26 studies was inspected carefully and 7 studies were removed, due to not meeting the eligibility criteria. After quality assessment, 19 eligible studies were finally included in the meta-analysis. Figure 1 displays the PRISMA 2020 flow diagram.

General characteristics of the eligible studies

The total sample size was 450 in the intervention group and 450 in the placebo group. The oldest study was carried out in 2009 and the most recent study in 2022. In this regard, a large number of studies were conducted in Iran with 11 articles. The highest quality assessment score based on the JBI checklist was related to the study of Dastorani et al. (2018) with a score of 13 [16]. In addition, all the articles included in the study were of medium or high quality based on the JBI checklist. The study design of the majority of the studies ($n=13$) were randomized, double-blind, and placebo-controlled trials. Table 1 indicates the characteristics of articles included in the study.

Generally, 9 studies examined the effect of vitamin D on the level of DHEAS, 9 studies investigated the effect of intervention on the level of SHBG, 13 studies considered the effect of intervention on the level of testosterone, 7 studies evaluated the effect of intervention on the level of LH, 6 studies assessed the effect of intervention on the FSH level, 3 studies examined the effect of intervention on AMH level, and 6 studies investigated the effect of intervention on Free Androgen Index (FAI). We reported vitamin D dosage in the included studies weekly. The total dose intake ranged from 11,200 to 72,000 IU weekly. Table 2 displays the data on the effect of the intervention on the hormonal profile.

Meta-analysis

Since the result of I^2 test demonstrated a high significant heterogeneity among studies for Testosterone, LH, and anti-Müllerian hormone (AMH) (I^2 testosterone = 75.57, I^2 LH = 63.31, and I^2 AMH = 83.77), the random effects model was employed to combine the effect size of the studies. However, given that the results indicated low heterogeneity ($I^2=0.00$) among studies for DHEAS, SHBG, FSH, and FAI, the fixed effects model was used.

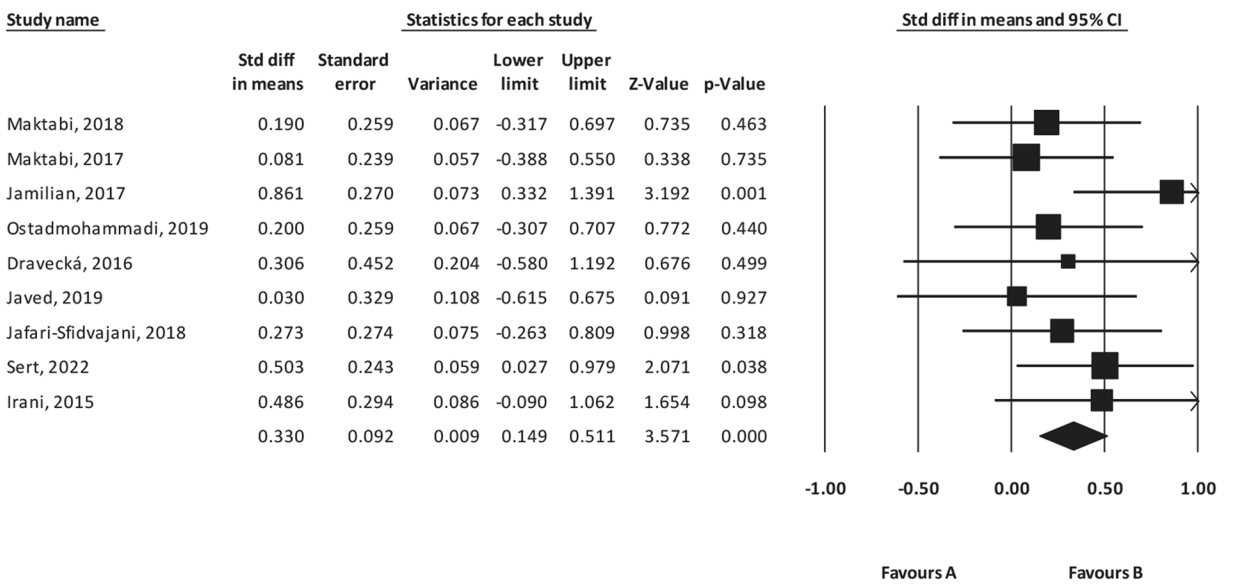


Fig. 3 The forest plot of studies included in the meta-analysis for SHBG based on the fixed effects model

As a result of the combination of studies, SMD before and after the intervention was obtained 0.241 ± 0.098 for DHEAS (Fig. 2), 0.330 ± 0.092 for SHBG (Fig. 3), 0.707 ± 0.171 for testosterone (Fig. 4), 0.614 ± 0.199 for LH (Fig. 5), 0.220 ± 0.119 for FSH (Fig. 6), 0.655 ± 0.505 for AMH (Fig. 7), and 0.369 ± 0.109 for FAI (Fig. 8) in the intervention group compared to the placebo group. The forest plot demonstrates the estimated SMD ± 95% CI of each study and the pooled SMD ± 95% CI of all included studies before and after the intervention in the intervention group compared to the placebo group. The 95% CI is indicated by the horizontal line of each square (Fig. 8).

According to Egger's regression intercept, there was no publication bias at the 0.05 level in the studies (*P* DHEAS = 0.445, *P* SHBG = 0.928, *P* testosterone = 0.050, *P* LH = 0.735, *P* FSH = 0.146, *P* AMH = 90 and *P* FAI = 0.405).

Meta-regression

As shown in Table 3, the effect of potential factors, such as year of publication, sample size, total dose of vitamin D, mean age, baseline BMI, baseline vitamin D level, and JBI score on the hormonal profile of women with PCOS was investigated using meta-regression. The results revealed that the effect of the intervention on AMH level decreases with increasing sample size and the total dose of consumption ($P < 0.05$). Further, the impact of the intervention on testosterone levels is enhanced by increasing the total dose of consumption ($P < 0.05$). The effect of the intervention on the level of DHEAS and LH decreases by increasing the level of baseline vitamin D ($P < 0.05$). Furthermore, the effect of the intervention on LH level increases with age ($P < 0.05$). The effect of the year of publication, BMI, and JBI score on the hormonal profile was not significant ($P > 0.05$).

Sub-group analysis

The subgroup analysis was reported in terms of the number of weeks of intervention (8-week and 12-week) and the frequency of consumption (once a day, twice a day, three times a day, and once a week) (Table 4). Based on the results, 8-week interventions had a more positive effect on the hormonal profile of women with PCOS compared to 12-week interventions. The consumption

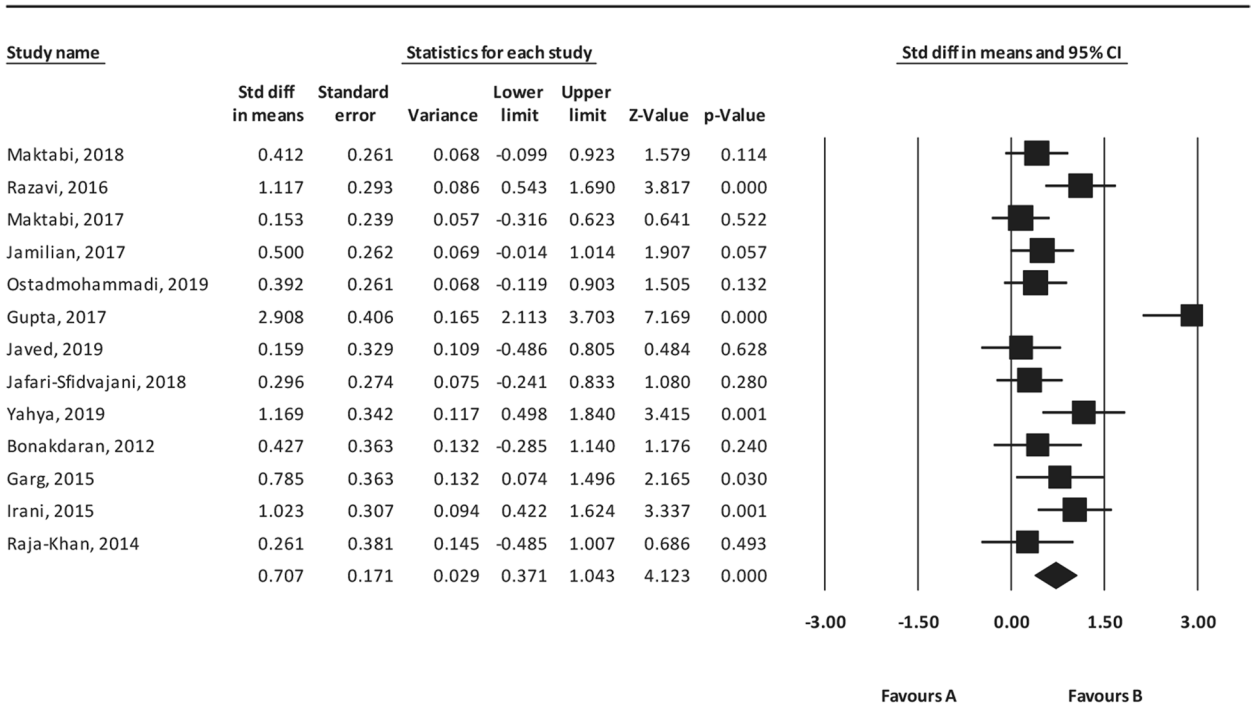


Fig. 4 The forest plot of studies included in the meta-analysis for testosterone based on the random effects model

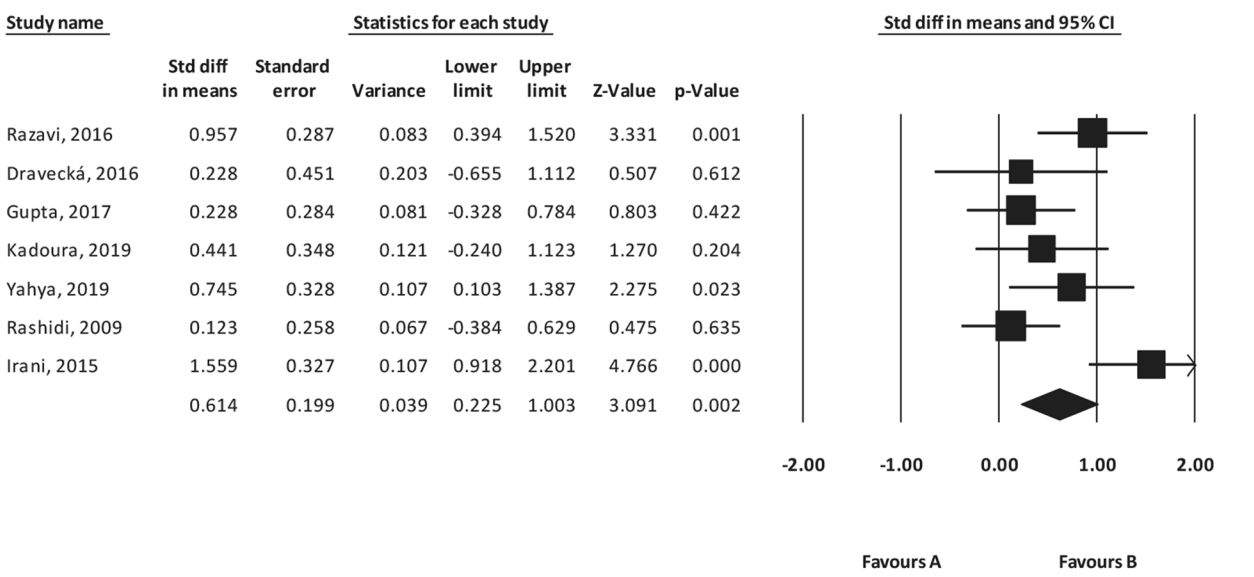


Fig. 5 The forest plot of studies included in the meta-analysis for LH based on the random effects model

of vitamin D three times a day had the greatest effect on DHEAS, Testosterone, LH, FSH, and FAI, twice a day on SHBG, and once a day on AMH.

Discussion

The present study aimed to estimate the effect of vitamin D intake on the hormonal profile of women with PCOS using systematic review and meta-analysis. After combining the data collected from 19 articles, the standardized mean difference before and after the intervention was obtained for DHEAS, SHBG, testosterone, LH, FSH, AMH, and FAI in the intervention group compared to the control group, indicating a positive effect of vitamin D intake on the hormonal profile of women with PCOS.

Insulin resistance seems to be one of the predominant features of PCOS, along with the dysfunction of the hypothalamic-pituitary axis, leading to hormonal changes, including an increase in the LH/FSH ratio and circulating androgens [42]. Further, hyperinsulinemia influences the production of SHBG and its circulating level, resulting in the enhancement of serum testosterone levels [43]. The most common clinical manifestations of hormonal changes among women with PCOS include menstrual disorders, such as amenorrhea and oligomenorrhea, hirsutism, type II diabetes, obesity, cardiovascular disease (CVDs), persistent acne, hyperhidrosis, dysfunctional uterine bleeding (DUB), and development of metabolic syndrome [44, 45]. Vitamin D plays an important role in bone homeostasis and may increase insulin receptor expression by increasing insulin production and glucose metabolism, thereby reducing insulin resistance, which is a predominant feature of PCOS, and improving the hormonal profile [46].

SHGB is a glycoprotein that binds to the sex hormones, androgens, and estrogen. Other steroid hormones, including progesterone, cortisol, and other corticosteroids, also bind to it by transcortin. SHGB regulates the access of target cells to sex steroids by binding to and carrying them in the blood [47]. SHBG often elevates in patients with hypogonadism, hyperthyroidism, liver cirrhosis, anorexia nervosa, and those taking oral contraceptive pills and antiepileptic drugs. Decreased SHBG concentrations are associated with hypothyroidism, PCOS, obesity, hirsutism, high androgens, hair loss, acne, Cushing's disease, and acromegaly [48]. Based on the results of the present study, vitamin D supplementation increases SHGB levels, and 8-week interventions with taking vitamin D twice daily are more effective.

DHEAS is a steroid hormone found in both men and women. DHEAS plays an important role in the

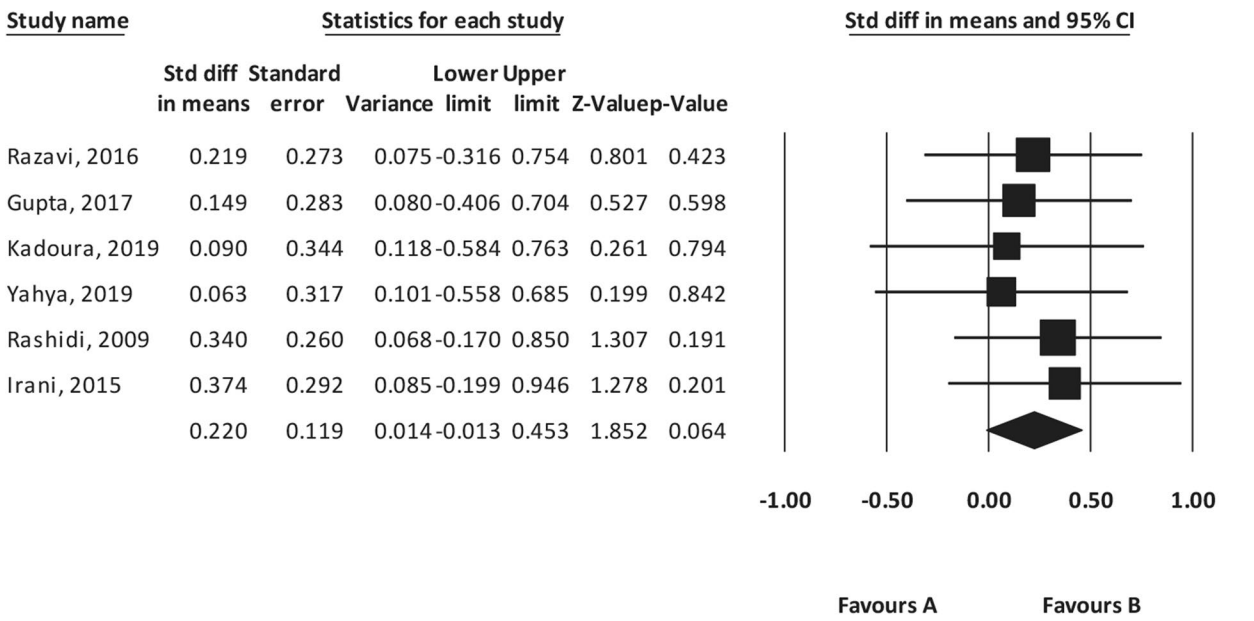


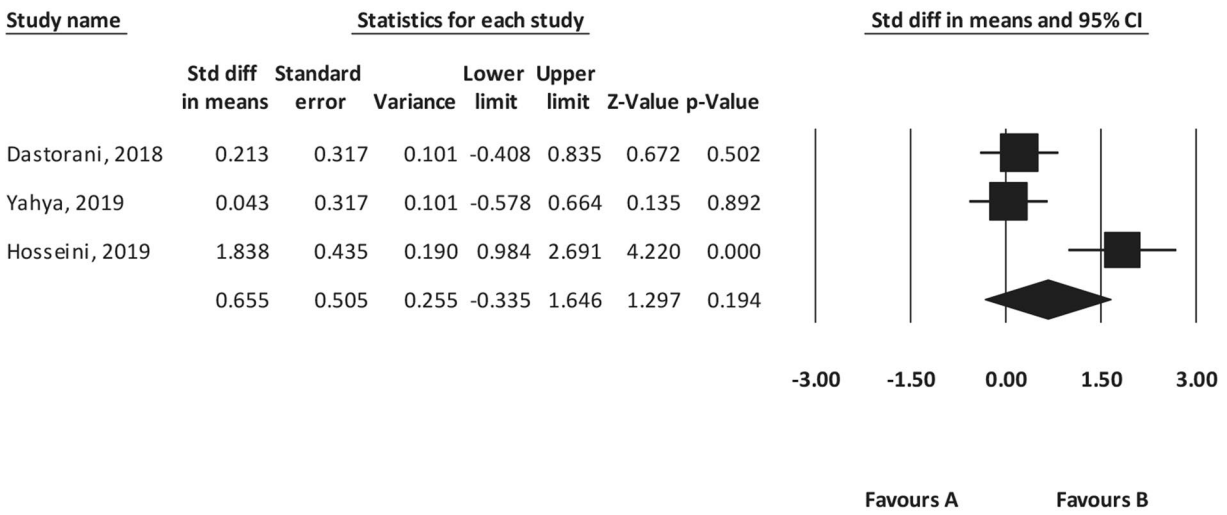
Fig. 6 The forest plot of studies included in the meta-analysis for FSH based on the fixed effects model

production of the male sex hormone testosterone and the female sex hormone estrogen. DHEAS is mainly produced by the adrenal glands and smaller amounts made by the testes in men and the ovaries in women [49]. DHEAS levels are typically higher in women with PCOS compared to healthy women [50]. The results of the present study illustrated that taking vitamin D supplementation reduces DHEAS levels. Although DHEAS levels typically increase with age [51], the meta-regression results of the present study revealed no significant relationship between mean age and the effect of vitamin D on DHEAS levels.

The results of the present study demonstrated that taking vitamin D supplementation reduces testosterone levels. This finding is consistent with the systematic review and meta-analysis conducted by Azadi-Yazdi et al. (2017), which reported that vitamin D supplementation reduces total testosterone in women with PCOS [52]. However, the results of the Azadi-Yazdi et al. study should be interpreted with caution, as they only considered the standardized mean difference (SMD) before and after the intervention in the intervention group, without comparing it to the placebo group. In contrast, the current study estimated the SMD before and after the intervention in both the placebo and intervention groups. Additionally, the number of studies included in the meta-analysis on the effect of vitamin D supplementation on testosterone in women with PCOS is larger in the present study (13 articles) compared to the Azadi-Yazdi et al. study (6 articles). Therefore, the results of the current study provide stronger evidence of the effect of vitamin D supplementation in reducing testosterone levels in women with PCOS. However, due to high heterogeneity in some subgroup analyses on testosterone and LH levels, the interpretation should be considered cautiously [27].

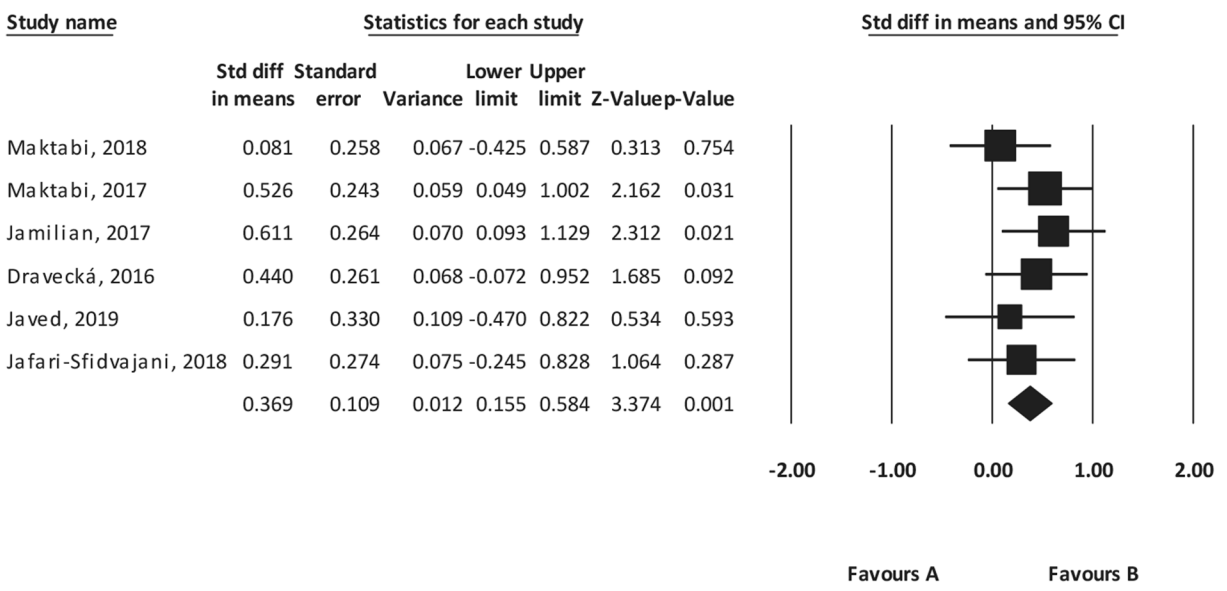
Women with PCOS have elevated serum LH levels and decreased FSH levels. The increased LH stimulates theca cells in the ovary, which in turn stimulates the production of androgens [42]. Based on the results of the present study, although taking vitamin D supplementation reduces LH levels, it does not have a significant effect on FSH levels, which is consistent with the results of the meta-analysis by Pergialiotis et al. (2017) [24].

FAI is a ratio used to assess the abnormal androgen status in humans. FAI is calculated as the total testosterone level divided by SHBG level and then, multiplied by 100. FAI has no unit. Woman's androgens are often



Meta Analysis

Fig. 7 The forest plot of studies included in the meta-analysis for AMH based on the random effects model



Meta Analysis

Fig. 8 The forest plot of studies included in the meta-analysis for FAI based on the fixed effects model

Table 3 The meta-regression of the impact of potential factors

Variable	Hormonal profiles	Number of articles	Sample size (*n*)		*P*-value	Process
			Intervention group	Placebo group		
Year	DHEAS	9	217	208	0.994	Ascending
	SHBG	9	248	236	0.958	Descending
	Testosterone	13	308	323	0.491	Descending
	LH	7	168	143	0.22	Ascending
	FSH	6	159	133	0.437	Descending
	AMH	3	59	52	0.268	Ascending
	FAI	6	169	172	0.225	Descending
Sample size	DHEAS	9	217	208	0.305	Descending
	SHBG	9	248	236	0.558	Ascending
	Testosterone	13	308	323	0.833	Descending
	LH	7	168	143	0.068	Ascending
	FSH	6	159	133	0.382	Ascending
	AMH	3	59	52	0.001	Descending
	FAI	6	169	172	0.372	Ascending
Total dose	DHEAS	9	217	208	0.867	Ascending
	SHBG	9	248	236	0.206	Ascending
	Testosterone	13	308	323	0	Ascending
	LH	7	168	143	0.836	Ascending
	FSH	6	159	133	0.619	Descending
	AMH	3	59	52	0.049	Descending
	FAI	6	169	172	0.99	Ascending
Age	DHEAS	7	155	146	0.58	Descending
	SHBG	8	208	201	0.786	Descending
	Testosterone	11	246	261	0.561	Descending
	LH	5	106	98	0.008	Ascending
	FSH	5	132	106	0.792	Ascending
	AMH	3	59	52	0.26	Ascending
	FAI	5	134	137	0.221	Ascending
Baseline BMI	DHEAS	6	144	137	0.822	Descending
	SHBG	5	190	174	0.098	Ascending
	Testosterone	10	227	243	0.397	Descending
	LH	4	97	87	0.414	Descending
	FSH	4	114	90	0.588	Ascending
	AMH	3	59	52	0.579	Descending
	FAI	3	86	88	0.51	Ascending
Baseline Vitamin D	DHEAS	2	62	62	0.002	Descending
	SHBG	2	70	70	0.49	Ascending
	Testosterone	2	62	62	0.772	Ascending
	LH	2	43	45	0.002	Descending
JBI score	DHEAS	9	217	208	0.585	Ascending
	SHBG	9	248	236	0.793	Ascending
	Testosterone	13	308	323	0.029	Descending
	LH	7	168	143	0.724	Ascending
	FSH	6	159	133	0.633	Descending
	AMH	3	59	52	0.268	Descending
	FAI	6	169	172	0.416	Descending

Table 4 The sub-group analysis of the consumption of the vitamin D based on the duration and frequency of intervention

Hormonal profiles	Subgroups		Number of articles	Sample size (*n*)		I^2	Std diff in means ± Standard error	*P*-value
				Intervention group	Placebo group			
DHEAS	Week of intervention	12 weeks	7	155	163	0.000	0.215 ± 0.113	0.642
		8 weeks	2	62	45	56.14	0.316 ± 0.304	
	Number of times a day	Once a day	5	69	100	0.000	0.287 ± 0.145	0.359
		Twice a day	1	35	35	0.000	0.000 ± 0.239	
		Thrice a day	1	27	27	0.000	0.614 ± 0.279	
		Once a week	1	35	18	0.000	0.007 ± 0.291	
SHBG	Week of intervention	12 weeks	7	178	183	2.15	0.276 ± 0.106	0.309
		8 weeks	2	70	53	0.000	0.496 ± 0.187	
	Number of times a day	Once a day	2	39	41	0.000	0.081 ± 0.239	0.155
		Twice a day	2	60	60	10.26	0.715 ± 0.232	
		Thrice a day	1	35	35	0.000	0.156 ± 0.160	
		Once a week	3	105	98	0.000	0.496 ± 0.187	
Testosterone	Week of intervention	12 weeks	10	237	246	77.66	0.498 ± 0.094	0.062
		8 weeks	3	86	62	0.000	1.099 ± 0.180	
	Number of times a day	Once a day	5	98	104	87.21	0.959 ± 0.437	0.026
		Twice a day	4	113	114	0.000	0.285 ± 0.134	
		Thrice a day	1	27	27	0.000	1.117 ± 0.293	
		Once a week	3	85	63	60.28	0.763 ± 0.175	
LH	Week of intervention	12 weeks	3	64	66	0.000	0.179 ± 0.176	0.009
		8 weeks	4	127	95	49.98	0.941 ± 0.160	
	Number of times a day	Once a day	4	82	82	0.000	0.233 ± 0.157	0.019
		Once a week	2	59	35	67.69	0.153 ± 0.231	
		Thrice a day	1	27	27	0.000	0.957 ± 0.287	
FSH	Week of intervention	12 weeks	2	55	55	0.000	0.200 ± 0.192	0.828
		8 weeks	4	104	78	0.000	0.253 ± 0.152	
	Number of times a day	Once a day	3	72	71	0.000	0.214 ± 0.167	0.998
		Once a week	2	59	35	0.000	0.231 ± 0.215	
		Thrice a day	1	27	27	0.000	0.249 ± 0.273	
AMH	Number of times a day	Once a day	1	15	15	0.000	1.838 ± 0.435	0.002
		Once a week	1	24	17	0.000	0.213 ± 0.317	
		Thrice a day	1	20	20	0.000	0.043 ± 0.317	
FAI	Number of times a day	Once a day	2	60	60	0.000	0.525 ± 0.186	0.435
		Twice a day	2	48	49	0.000	0.117 ± 0.203	
		Thrice a day	1	35	35	0.000	0.526 ± 0.243	
		Once a week	1	26	28	0.000	0.291 ± 0.274	

measured when there is a concern about elevated serum levels, which may be associated with conditions such as hirsutism or PCOS. The standard values for FAI in women range from 7 to 10. FAI is typically increased in women with PCOS. The results of the current study indicated that taking vitamin D supplementation significantly reduces FAI levels and that interventions performed three times a day are more effective.

The study results of Pergialiotis et al. (2017) rejected the effect of vitamin D on the hormonal profile of women with PCOS and reported its effect as mild [24]. The difference between the results of the Pergialiotis et al. study and the findings of the present study can be attributed to the difference in the number of articles included in the meta-analysis, the total sample size of studies, and the effect of potential factors, such as total vitamin D dose, mean age, BMI, baseline vitamin D level, number of weeks of intervention, and frequency of taking vitamin D per day.

Overall, it can be concluded that taking vitamin D supplementation has a positive impact on SHBG, DHEAS,

testosterone, LH, and FAI, and has no significant effect on FSH and AMH levels. However, these results should be interpreted with caution, as the number of studies conducted on some hormonal profile items, such as FSH, FAI, and AMH, was limited. Therefore, it is suggested to perform more primary studies with larger sample sizes to examine all items of the hormonal profile.

Limitations

The present study and the studies included in the meta-analysis come with several limitations:

First, the included studies did not follow a consistent reporting format, which can affect the quality of the data synthesis. Some studies may have used non-random sampling methods, which can introduce selection bias. Second, the included studies had varying study designs, which can contribute to the heterogeneity of the results. Third, the limited number of studies for certain hormonal profile items, such as FSH, FAI, and AMH, restricted the ability to perform robust subgroup analyses. Fourth, the inability to access the full-text versions of conference abstracts may have led to the exclusion of potentially relevant studies. Moreover, the meta-analysis exhibited relatively high heterogeneity among studies on some hormonal profile items, such as testosterone, LH, and AMH. To address this, the researchers performed subgroup analyses, which were able to reduce the heterogeneity to some extent. However, there was still high heterogeneity among some subgroups, likely due to factors such as sample size, demographic characteristics, and study methodology. These limitations should be taken into consideration when interpreting the findings of the present study and when designing future research in this area.

Conclusion

The results of the present systematic review and meta-analysis, based on the available randomized clinical trials, indicate a significant positive effect of vitamin D supplementation on certain hormonal profile items in women with PCOS. Specifically, vitamin D supplementation was found to have a beneficial impact on SHBG, DHEAS, testosterone, LH, and FAI. Furthermore, the findings suggest that 8-week interventions had a more positive effect compared to 12-week interventions. Additionally, the impact of vitamin D on the hormonal profile of women with PCOS was influenced by potential factors such as dose, age, BMI, baseline vitamin D level, and frequency of vitamin D intake per day. Given these findings, the results of the present study should be considered and incorporated by obstetricians and midwives in the management and care of women with PCOS.

Abbreviations

SID	Scientific Information Database
WoS	Web of Science
MeSH	Medical Subject Headings
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
JBI	Joanna Briggs Institute
FAI	Free Androgen Index
SHBG	Sex hormone-binding globulin
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone
DHEAS	Dehydroepiandrosterone sulfate
AMH	Anti-Müllerian hormone
BMI	Body Mass Index

Acknowledgements

This study is the result of research project (IR.KUMS.REC.1401.086) approved by the Kermanshah University of Medical Sciences. We would like to thank the esteemed officials of that center for accepting the financial expenses of this study. We also thank the officials of the Systematic Review and Meta-Analysis Center (SYRMAN) for their guidance and advice in conducting this research.

Authors' contributions

M.K and M.R contributed to the design. M.K, M.R, and F.R participated in most of the study steps. M.K and M.R prepared the manuscript. M.K and R.R assisted in designing the study and helped in the interpretation of the study. All authors have read and approved the content of the manuscript.

Funding

This study is supported by Deputy for Research and Technology, Kermanshah University of Medical Sciences (IR) (IR.KUMS.REC.1401.086). This deputy has no role in the study process.

Availability of data and materials

Datasets are available through the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Ethics approval was received from the ethics committee of the deputy of research and technology, Kermanshah University of Medical Sciences (IR.KUMS.REC.1401.086).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 15 June 2023 Accepted: 4 August 2024
Published online: 24 August 2024

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