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REVIEW

# The effect of probiotics, prebiotics, and synbiotics on hormonal and inflammatory indices in women with polycystic ovary syndrome: a systematic review and meta-analysis

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## Abstract

**Introduction** Polycystic ovary syndrome (PCOS) is among the most prevalent endocrine disorders in women and can lead to many other disorders and chronic diseases. Thus, early diagnosis and treatment of this syndrome is important. Using probiotics, prebiotics, and synbiotics supplementations to treat PCOS seems appropriate because of their useful effects and low complications.

**Aims** To assess the effects of probiotics, prebiotics, and synbiotics on hormonal indices such as testosterone, dehydroepiandrosterone sulfate (DHEA-S), sex hormone binding globulin, Free Androgen Index (FAI), and inflammatory indices, such as high sensitive C reactive protein (hsCRP), malondialdehyde (MDA), total glutathione (GSH), nitric oxide (NO), and total antioxidant capacity (TAC) as the primary outcomes and the hirsutism score as the secondary outcome.

**Methods** All published articles from the beginning until 10 November 2018 in English (Cochrane Library, Web of Sciences, Google Scholar, PubMed, Scopus, and ProQuest) and Persian (SID and Magiran) databases were searched. The effect of interventions on the outcomes was reported with a standard mean difference (SMD) and confidence interval of 95%. In case of high heterogeneity, the random effect model was used instead of the fixed effect model. The statistical heterogeneity of the included clinical trials was tested using the Chi square test and $I^2$.

**Results** Thirteen studies with 855 participants with PCOS(438 women in the intervention group and 417 women in the control group) were included in the meta-analysis. Results of the meta-analysis showed that the SHBG (SMD: 0.56; 95% CI 0.26–0.86; $P=0.0002$) and NO (SMD: 0.38; 95% CI 0.09–0.68; $P=0.01$) concentration increased significantly in the probiotics and synbiotics groups compared to the placebo group. FAI (SMD: − 0.58; 95% CI − 0.95 to − 0.21; $P=0.002$) and MDA (SMD: − 0.76; 95% CI − 1.46 to − 0.05; $P=0.03$) concentration in the probiotics and synbiotics groups reduced significantly compared to the placebo group. The results of meta-analyses on other hormonal and inflammatory indices such as testosterone, DHEAS, GSH, hsCRP, TAC, and hirsutism score showed that there were no significant differences between the intervention and control groups.

**Conclusion** Using synbiotics and probiotics in women with polycystic ovary syndrome improve hormonal (FAI, SHBG) and inflammatory (NO, MDA) indices in these patients.

**Keywords** Probiotic · Symbiotic · Prebiotic · Polycystic ovary syndrome · Systematic review · Meta-analysis

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## Introduction

Polycystic ovary syndrome (PCOS) is among the most prevalent endocrine disorders in women, which is also associated with a spectrum of symptoms [1, 2]. Hirsutism, hyperandrogenism, oligoovulation, anovulation, polycystic ovaries, and increased levels of androgen are essential for the diagnosis of PCOS [3–5]. The leading cause of this syndrome is unknown, but environment and genetics have been implied in its development [6]. The prevalence of this syndrome

varies in different countries and depends on its clinical and biochemical properties, which vary among different races and age groups [7, 8].

PCOS results in anovulation induced infertility in about 90% of cases [9]. It is associated with insulin resistance, and hence, an increased risk of obesity and diabetes. These disorders stimulate the progression of hormonal and inflammatory disorders, and oxidative stress [10, 11], so that 50–70% of women with PCOS and insulin resistance will develop metabolic syndrome in the future, which in turn causes other chronic diseases [12–14]. There is also a higher risk of endometrial and breast cancer, and psychological disorders, such as depression and hypersomnia, in these patients [15, 16]. As a result, early diagnosis and treatment may prevent its short- and long-term complications [17].

There are many recommended treatment methods for PCOS, including lifestyle changes (e.g., diet, weight loss, and exercise), surgery, and pharmacotherapy. However, changing one's lifestyle, along with the improvement of quality of life is considered to be the first therapeutic step in these patients [4, 10, 18].

Prebiotics are indigestible and unfermentable compounds that enhance the host's health by reducing the combination and activity of harmful bacteria and increasing useful intestinal bacteria [19, 20]. Prebiotics can improve the host's health by increasing bifidobacteria, inhibiting the growth of pathogens, moderating the immune system, inhibiting rotavirus activity, stimulating intestinal microflora activity, curing diarrhea and irritable bowel syndrome, preventing intestinal inflammation and cancer [21, 22], intervening in lipid metabolism [23], and increasing absorption of Fe, Mg, Ca, and Zn by reducing intestinal pH [24]. Inulin, resistant dextrin, oligofructose, fructooligosaccharide, galactooligosaccharide, and lactulose are among the prebiotics [25, 26].

Probiotics are non-pathological living microorganisms and adequate consumption could have healthful and beneficial effects on the host through balancing the intestinal microbes. The lactic acid-producing bacteria, in particular *lactobacillus* and *bifidobacterium*, are generally a part of the gastrointestinal ecosystem and typically reside at the distal intestine and colon after entering the GI tract [27]. Probiotics are effective in treating lactose intolerance, inflammatory bowel disease, preventing autoimmune diseases, stimulating the immune system [27, 28], reducing cholesterol probably through bile acid deconjugation [27–29], regulating the patient's weight and serum lipids, reducing blood pressure, and preventing and curing infections. They are also beneficial due to their anticancer and anti-inflammatory properties, which prevent atherosclerosis and cancers [27, 28, 30, 31].

The term synbiotic refers to products including both probiotics and prebiotics [32]; for example, a product containing fructooligosaccharides and bifidobacterium. Synbiotics improve the host's health condition via improving survival rate of the probiotic and implantation of useful intestinal microbes [33, 34].

Some studies have reported the effectiveness of prebiotics, probiotics, and synbiotics in improving hormonal and inflammatory indicators in patients with PCOS [35–40]. However, it continues to remain unknown whether these supplements are effective in improving hormonal and inflammatory indicators in patients with PCOS. Thus, this systematic review was designed to answer these questions based on clinical trials.

## Objectives

The present study aimed initially to evaluate the effects of probiotics, prebiotics, and synbiotics on hormonal indicators, such as testosterone, dehydroepiandrosterone sulfate (DHEA-S), sex hormone binding globulin (SHBG), Free Androgen Index (FAI), and inflammatory indicators, such as high sensitive C-reactive protein (hsCRP), malondialdehyde (MDA), total glutathione (GSH), nitric oxide (NO), and total antioxidant capacity (TAC). The second objective of the study was to obtain the hirsutism score.

## Methods

### Data source and identification of studies

This review study investigated clinical trials on the effects of probiotics, prebiotics, and synbiotics on hormonal and inflammatory indicators (primary outcomes) and the hirsutism score (secondary outcome) in women with PCOS. All Farsi and English articles published until November 2018 in the Cochrane Library, Web of Sciences, Google Scholar, ProQuest, PubMed, Scopus, SID, and Magiran database were reviewed. The references in the found articles were also used to find relevant studies. The search strategy was according to the MeSH terminology. The MeSH keywords used alone or in a combination with other terms included "PCO", "Polycystic ovary", "Prebiotic", "Prebiotic supplementation", "Probiotic", "Probiotic supplementation", "Synbiotic", "Synbiotic supplementation", "Inulin", "Resistant Dextrin", "Gut microflora", "*Lactobacillus*" and "Probiotic bacteria".

### Inclusion and exclusion criteria

This study investigated all controlled randomized or quasi-experimental clinical trials into the effects of probiotics, prebiotics, and synbiotics on clinical and paraclinical symptoms of women with PCOS. In addition, the population, intervention, control, outcome (PICO) criteria, including

participants, intervention, comparison, and outcome, were used. The inclusion criteria were women of reproductive age (15–49 years) with PCOS (diagnosed based on the Rotterdam criteria [5]), not taking probiotics, prebiotics, and synbiotics during and 3 months before the study, not taking antibiotics during the study, not having any chronic disease (e.g., Cushing's syndrome, diabetes, hypertension, autoimmune disease, active liver disease, history of heart and kidney diseases, pancreatitis, pulmonary disease, thyroid problem, adrenal hyperplasia, hyperprolactinemia, and female infertility), no smoking, no dieting or partaking in any type of extra physical activity such as aerobics, and not using Omega 3, and multivitamin products.

The intervention included the use of different doses of probiotics, prebiotics, and synbiotics in the form of powder or capsule. The comparison group included the placebo or maltodextrin group. The outcomes included hormonal and inflammatory indicators and the hirsutism score.

### Data extraction

The collected articles were carefully reviewed and two authors separately scrutinized the title and abstract for inclusion criteria. In case of inadequate information in the title and abstract of an article, it was fully reviewed by the authors. In case of contradiction, the consensus was made through discussion with a third author. The article-related data, namely time of the study, name of the author, methodology, type and consumption method of probiotics, prebiotics, and synbiotics, comparison details between treatment regimens, length of treatment, length of follow-up, participants' characteristics, number of randomized participants, number of attritions in follow-up, primary and secondary outcomes, and reported complications, were extracted.

### Assessment of risk of bias in the included studies

The two authors separately evaluated the articles based on the Cochrane handbook criteria [41] for selection, performance, detection, attrition, and reporting bias. The bias risk of each item for clinical trials were categorized as "low risk", "high risk", or "unclear" topics. Then judgments of the two authors were compared and any disagreement was resolved by the third author.

### Statistical method

The statistical analysis was done with the software RevMan version 5.3. The effect of interventions on the outcomes was reported with a confidence interval of 95% for the difference between means. Due to the application of different methods to estimate hormonal and inflammatory levels, the standardized mean difference (SMD) was used instead of mean difference (MD). In case of high heterogeneity, the random effect model was used instead of the fixed effect model. The statistical heterogeneity of the included clinical trials was tested using the Chi square test and $I^2$. In that, $I^2 > 75\%$ and $P$ value $< 0.01$ was characterized as significant heterogeneity, 0–40%: might not be important; 30–60%: may represent moderate heterogeneity, 50–90%: may represent substantial heterogeneity, and 75–100%: considerable heterogeneity [41].

## Results

A total of 2515 articles were found in the various databases. Among them, 2457 articles were excluded because of irrelevant titles and 39 articles were duplicates. Among the 19 full-text reviewed articles, 13 were finally included (Fig. 1).

Table 1 shows the characteristics of the included studies. The sample size varied between 60 [35, 38, 40, 42, 44, 46] and 118 [47] women. The intervention groups received probiotics, prebiotics, and synbiotics in four [39, 40, 42, 43], seven [35, 36, 38, 44–47], and two studies [37, 48], respectively. In all studies, the control group received a placebo, either starch or maltodextrin. In the included studies, the Ferriman-Gallwey (FG) scoring system was used for assessing hirsutism. In four studies [35, 37, 38, 40], the hormone levels were measured with ELISA and in three studies [35, 38, 47], the hsCRP was measured with ELISA. For measuring the inflammatory indices, different methods were used such as spectrophotometry [37, 40], latex-enhanced immunonephelometry [36], immunoturbidimetry [43], a commercial kit [44], and the spectrophotometric method as described by Benzie and Strain, Griess, and Beutler [35, 38].

### Risk of bias of included studies

The risk of random allocation bias was low in 11 studies [35–37, 39, 40, 42–46, 48]. The risk of allocation concealment bias was low in nine studies [35, 37, 39, 40, 42–44, 46, 48]. The risk of bias from the lack of blinding was low in 11 studies [35–37, 39, 40, 42–46, 49]. The risk of bias from the lack of assessor blinding was unclear in all studies. The risk of incomplete outcome bias was low in eight studies [35–38, 40, 45, 46, 48] and the risk of reporting bias was low in six studies [35, 38, 39, 42, 44, 46] (Figs. 2, 3).

### Meta-analysis of included studies

The effect of probiotics, prebiotics, and synbiotics on hormonal and inflammatory indicators and clinical symptoms of PCOS are reported in Figs. 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13.

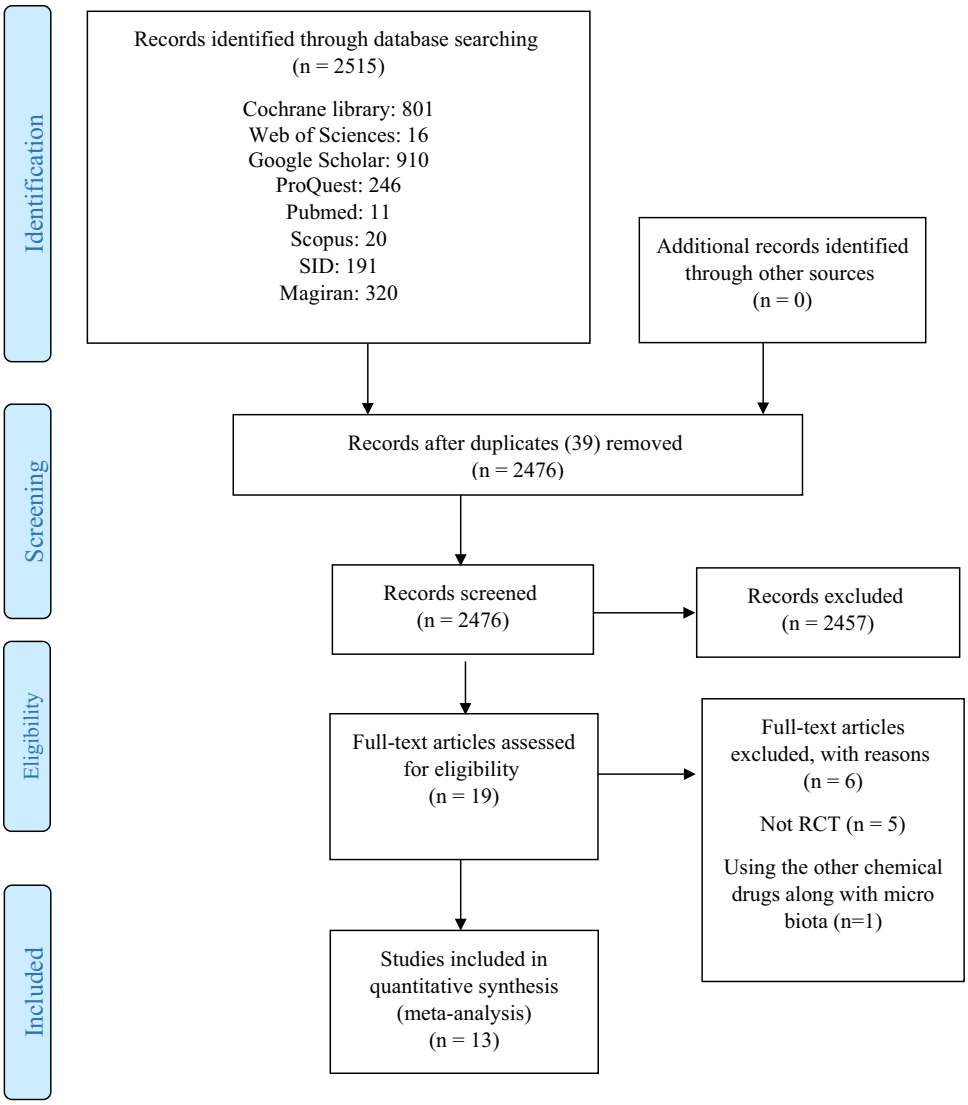


**Fig. 1** PRISMA study flow diagram

## Hormonal indices

### Testosterone

The meta-analysis results showed that the testosterone concentration in the probiotics and synbiotics groups was reduced by 0.05 ng/ml which was lower than in the placebo group; however, this reduction was not statistically significant (SMD: − 0.50; 95% CI − 1.25 to 0.25; $P = 0.19$) and the heterogeneity level was high ($I^2 = 84\%$; $\text{Tau}^2 = 0.37$; $\text{Chi}^2 = 12.30$; $P = 0.002$) (Fig. 4).

### DHEAS

The meta-analysis results showed that the DHEAS concentration in the probiotics, prebiotics and synbiotics groups was reduced by 0.22 µg/ml, which was lower than in the placebo group; however, this reduction was not statistically significant (SMD: − 0.22; 95% CI − 0.51 to 0.07; $P = 0.14$) and the included studies were homogeneous ($I^2 = 0\%$; $\text{Chi}^2 = 1.13$; $P = 0.57$) (Fig. 5).

### SHBG

The meta-analysis results showed that the SHBG concentration in probiotics and synbiotics significantly increased by 0.56 µg/ml higher than in the placebo group (SMD: 0.56; 95% CI 0.26–0.86; $P = 0.0002$) and the included studies were homogeneous ($I^2 = 0\%$; $\text{Chi}^2 = 0.78$; $P = 0.68$) (Fig. 6).

### Fai

The meta-analysis results showed that the FAI concentration in probiotics and synbiotics were significantly reduced by 0.58 µg/ml, which was lower than in the placebo group (SMD: − 0.58; 95% CI − 0.95 to − 0.21; $P = 0.002$), and

**Table 1** Characteristics of included randomized control trials

| Author, year | Country | Study period | Sample size | Study population | Intervention/treatment | Content of intervention and placebo | Outcomes | Result |
|---|---|---|---|---|---|---|---|---|
| Samimi et al. (2018) | Iran | April 2017–June 2017 | 60 | Participant all had PCOS[a] that diagnosed according to the Rotterdam criteria, aged 18–40 years, pregnant women, hyperandrogenism, and/or anovulation, Cushing's syndrome, androgen-secreting tumors, hyperprolactinemia, and thyroid dysfunction, were excluded | Participants were randomized into two groups to receive either one synbiotics capsule ($n=30$) and placebo ($n=30$) per day for 12 weeks | Synbiotics capsule containing *Lactobacillus acidophilus* strain T16 (IBRC-M10785), *Lactobacillus casei* strain T2 (IBRC-M10783), and *Bifidobacterium bifidum* strain T1 (IBRC-M10771) ($2\times10^9$ CFU/g each) plus 800 mg inulin and the placebo that contained starch but no bacteria | Glycemic control, Markers of cardiometabolic risk including lipid profiles and AIP[b] | It showed beneficial effect on insulin resistance, triglyceride, VLDL[c] and AIP |
| Ahmadi et al. (2017) | Iran | August 2015–November 2015 | 60 | Participants were PCOS, aged 18–40 years old with a BMI[d] greater than 19 kg/m$^2$ | Participants were randomly allocated into two treatment groups to intake either probiotic supplements ($n=30$) or placebo ($n=30$) for 12 weeks. Every 4 weeks, participants were given enough supplements to last 3 days after their next scheduled visit and were instructed to return all unused supplements at each visit | Probiotic capsule was consisted of three viable and freeze-dried strains: *Lactobacillus acidophilus* ($2\times10^9$ CFU/g), *Lactobacillus casei* ($2\times10^9$ CFU/g) and *Bifidobacterium bifidum* ($2\times10^9$ CFU/g) and placebo capsule that contained starch but no bacteria | Markers of insulin resistance, weight and BMI loss, FPG[e], serum triglycerides, cholesterol-, VLDL-, LDL[f]-cholesterol and HDL[g]-cholesterol concentrations | It showed beneficial effect on insulin resistance, triglyceride, VLDL and weight loss |
| Karamali et al. (2018) | Iran | January 2017 and August 2017 | 60 | Participants with PCOS, aged 18–40 years old<br>Exclusion criteria were as follows: smokers, taking probiotic supplements, pregnant women, endocrine diseases including thyroid, diabetes and/or impaired glucose tolerance | All Participants were randomly divided into 2 groups to receive either probiotic supplements or placebo (starch) ($n=30$ each group) for 12 weeks. | Probiotic supplements containing *Lactobacillus acidophilus*, *Lactobacillus casei* and *Bifidobacterium bifidum* ($2\times10^9$ CFU/g each) and placebo capsule that contained starch but no bacteria | hs-CRP[h], NO[i], biomarkers of oxidative stress and hormonal profiles | It showed beneficial effect on total testosterone, SHBG[j], FG[k] scores, hs-CRP, TAC[l] and MDA[m] |

**Table 1** (continued)

| Author, year | Country | Study period | Sample size | Study population | Intervention/treatment | Content of intervention and placebo | Outcomes | Result |
|---|---|---|---|---|---|---|---|---|
| Ghanei et al. (2018) | Iran | 2017 | 70 | Participants with PCOS, aged 18–45 years old. Exclusion criteria were thyroid dysfunction, hyperprolactinemia, diabetes, history of premature menopause, smoking, and Cushing's syndrome | Participants were given two probiotic capsules per day and two maltodextrin capsules from the same company for 12 weeks | Probiotic supplements containing of $1\times10^9$ colony forming units (CFU) of each lactobacillus strains (equal to 500 mg) placebo capsule that contained maltodextrin with same color, and size | Inflammatory index | It showed beneficial effect on hsCRP and IL-6[n] |
| Shoaei et al. (2018) | Iran | May 2013–December 2013 | 72 | Participants with PCOS, aged 18–40 years old Exclusion criteria were: chronic heart, kidney, liver, lung or pancreatic disease specially cardiovascular diseases, thyroid disorder, small bowel syndrome, autoimmune disease, allergy to probiotic capsules or placebo, use of chemotherapy, corticosteroid, antibiotic, multivitamin mineral supplements and omega-3 medications and having specific diet or physical activity programs | Participants randomly allocated to one of the two groups: (1) probiotic supplement, (2) placebo, probiotic group received one Familact probiotic capsule (500 mg) and the placebo group received the placebo daily for 8-week | probiotic capsule contained the following bacterial strains: *Lactobacillus casei* $7\times10^9$ CFU/g, *Lactobacillus acidophilus* $2\times10^9$ CFU/g, *Lactobacillus rhamnosus* $1.5\times10^9$ CFU/g, *Lactobacillus bulgaricus* $2\times10^8$ CFU/g, *Bifidobacterium breve* $2\times10^{10}$CFU/g, *Bifidobacterium longum* $7\times10^9$ CFU/g, *Streptococcus thermophiles* $1.5\times10^9$ CFU/g and the placebo that contained starch and maltodextrins but no bacteria | Glycemic index and High sensitive C reactive protein | It showed beneficial effect on FBS[o], HOMA-IR[p] and serum insulin |
| Rashad et al. (2017) | Egypt | 2017 | 118 | Participants were healthy women matched to PCOS women as regard age and ethnic origin | Participants in the intervention group received ten billions probiotic capsules twice daily, after lunch and evening meal for 12 weeks | Probiotic capsule contained *Lactobacillus delbruekii* and *Lactobacillus fermentum* | Metabolic indices and anthropometric indices and hs-CRP | It showed beneficial effect on inflammatory biomarkers; clinical, and MIF[q] levels |

**Table 1** (continued)

| Author, year | Country | Study period | Sample size | Study population | Intervention/treatment | Content of intervention and placebo | Outcomes | Result |
|---|---|---|---|---|---|---|---|---|
| Shabani et al. (2018) | Iran | May 2017–October 2017 | 60 | Participants with PCOS, aged 18–40 years old | Participants with PCOS were randomized into two groups to take either 200 µg/day selenium as selenium yeast plus $8\times10^9$ CFU/day probiotic or placebo ($n=30$ each group) for 12 weeks | Probiotic containing *Lactobacillus acidophilus*, *Lactobacillus reuteri*, *Lactobacillus fermentum* and *Bifidobacterium bifidum* ($2\times10^9$CFU/g each). 200 µg/day selenium | Parameters of insulin metabolism markers of cardio-metabolic risk including lipid profiles, AIP, $AC^r$ and $CRR^s$ | It showed beneficial effect on weight loss and markers of cardio-metabolic risk |
| Karimi et al. (2018) | Iran | September 2015 and July 2016 | 99 | Participants with PCOS aged between 19 and 37 years and BMI ≥ 25 kg/m$^2$ | The participants were randomly assigned to receive either active treatment with synbiotics or placebo<br>The patients were given 6-week supplement capsules. In the next follow-up visit (end of 6 weeks), the patients were given another set of capsules | Each synbiotics capsule (500 mg) contained seven strains of beneficial bacteria (*Lactobacillus acidophilus* $3\times10^{10}$ colony-forming units (CFU)/g, *Lactobacillus casei* $3\times10^9$ CFU/g, *Lactobacillus bulgaricus* $5\times10^8$ CFU/g, *Lactobacillus rhamnosus* $7\times10^9$ CFU/g, *Bifidobacterium longum* $1\times10^9$ CFU/g, *Bifidobacterium breve* $2\times10^{10}$ CFU/g and *Streptococcus thermophilus* $3\times10^8$ CFU/g), prebiotic inulin (fructo-oligosaccharide), and capsules containing starch and maltodextrin, but no bacteria were used as placebo | Glycemic indices, C reactive protein and apelin | It showed beneficial effect on apelin |
| Gholizadeh et al. (2018) | Iran | Oct 2016–May 2017 | 62 | Participants with PCOS aged 18–45 | The participants were divided into an intervention and a control group, three large envelopes were prepared with the same number, each containing 30 envelopes of 20 g of resistant dextrin or the placebo | Prebiotic containing 20 g of resistant dextrin (polysaccharides produced from maize, wheat and other edible starches, NUTRIOSE FM 06 and Roqutte, and placebo containing 20 g maltodextrin, which is an easily absorbed carbohydrate without fiber that is easily digested in the intestines, made by Jiujiang Huirong Trade Company Limited | Hormonal profile, metabolic indices, clinical symptoms, hs-CRP | It showed beneficial effect on hormonal profile, metabolic indices, clinical symptoms, hs-CRP |
| Nasri et al. (2018) | Iran | April–June 2016 | 60 | Participants with PCOS diagnosed according to the Rotterdam criteria, aged 18–40 years | Participants were randomly allocated to receive either synbiotics supplements or placebo ($n=30$ each group) for 12 weeks | Synbiotics supplements were containing *Lactobacillus acidophilus*, *Lactobacillus casei* and *Bifidobacterium bifidum* ($2\times10^9$ CFU/g each) plus 0.8 g inulin | Inflammatory and hormonal indices, hirsutism, anthropometric indices | It showed beneficial effect on SHBG, FG scores, hs-CRP and NO |

**Table 1** (continued)

| Author, year | Country | Study period | Sample size | Study population | Intervention/treatment | Content of intervention and placebo | Outcomes | Result |
|---|---|---|---|---|---|---|---|---|
| Jamilian et al. (2018) | Iran | December–March 2018 | 60 | Participants with PCOS, diagnosed based on the Rotterdam criteria, aged 18–40 years old | Participants were randomized into two groups to intake either $8\times10^9$ CFU/day probiotic plus 200 µg/day selenium ($n=30$) or placebo ($n=30$) for 12 weeks | probiotic containing *Lactobacillus acidophilus*, *Lactobacillus reuteri*, *Lactobacillus fermentum* and *Bifidobacterium bifidum* ($2\times10^9$ CFU/g each)<br>200 µg/day selenium | Hormonal profiles, mental health parameters, biomarkers of inflammation and oxidative stress | It showed beneficial effect on mental health parameters, serum total testosterone, hirsutism, hs-CRP, TAC, GSH[t] and MDA |
| Esmaeilinezhad et al. (2018) | Iran | January–July, 2017 | 92 | Participants with PCOS, aged 15–48 years | Participants were randomly assigned in a 1:1:1:1 ratio, to four groups<br>1. Synbiotics pomegranate juice<br>2. Pomegranate juice<br>3. Synbiotics beverage<br>4. Control group | Synbiotics pomegranate juice: 2 L ($2\times1$-l) of pomegranate juice containing inulin and lactobacillus per week, for 8 weeks in disposable bottles. (each liter of pomegranate juice contains 20 g of inulin + $2\times10^8$CFU/g lactobacillus). pomegranate juice: 2 l ($2\times1$-l) of pomegranate juice per week, for 8 weeks in disposable bottles. synbiotics beverage: 2 l ($2\times1$-l) of synbiotics beverage per week, for 8 weeks in disposable bottles. (each liter of beverage contains 1 l of water + 20 g of inulin + $2\times10^8$ CFU/g lactobacillus + pomegranate flavoring). Control group: 2 L ($2\times1$-l) of placebo beverage per 1 week, for 8 weeks in disposable bottles (each liter of beverage contains 1 l of water + 2 pomegranate flavoring). | Insulin resistance blood glucose, insulin, total testosterone, LH[u] and FSH[v] | It showed beneficial effect on insulin resistance, insulin, testosterone level, BMI, weight and waist circumference |
| Gholizadeh shamasbi et al. (2018) | Iran | Oct 2016–May 2017 | 62 | Participants with PCOS aged 18–45 | The participants were divided into an intervention and a control group, three large envelopes were prepared with the same number, each containing 30 envelopes of 20 g of resistant dextrin or the placebo | Prebiotic containing 20 g of resistant dextrin (polysaccharides produced from maize, wheat and other edible starches, NUTRIOSE FM 06 and Roqutte, and placebo containing 20 g maltodextrin, which is an easily absorbed carbohydrate without fiber that is easily digested in the intestines, made by Jiujiang Huirong Trade Company Limited | Anthropometric indices | It showed beneficial effect on anthropometric indices |

**Table 1** (continued)

[a]Polycystic ovary syndrome
[b]Atherogenic index of plasma
[c]Very low-density lipoprotein
[d]Body mass index
[e]Fasting plasma glucose
[f]Low-density lipoprotein
[g]High-density lipoprotein
[h]High sensitive C reactive protein
[i]Nitric oxide
[j]Sex hormone-binding-globulin
[k]Ferriman–Gallwey
[l]Total antioxidant capacity
[m]Malondialdehyde
[n]Interleucin-6
[o]Fasting blood sugar
[p]Homeostatic model assessment for insulin resistance
[q]Migration inhibitory factor
[r]Atherogenic coefficient
[s]Cardiac risk ratio
[t]Total glutathione
[u]Luteinizing hormone
[v]Follicle stimulating hormone

there was the substantial heterogeneity level ($I^2 = 68\%$; $Chi^2 = 3.12$; $P = 0.08$) (Fig. 7).

## Inflammatory indices

### hsCRP

The meta-analysis results showed that the hsCRP concentration in probiotics, prebiotics, and synbiotics groups were reduced by 0.59 mg/dl, which was lower than in the placebo group; however, this reduction was not statistically significant (SMD: − 0.59; 95% CI − 1.60–0.42; $P = 0.25$), and there was the considerable heterogeneity level ($I^2 = 96\%$; $Tau^2 = 1.78$; $Chi^2 = 148.31$; $P < 0.00001$) (Fig. 8).

### NO

The meta-analysis results showed that the NO concentration in probiotics and synbiotics groups significantly increased by 0.38 mg/dl higher than in the placebo group (SMD: 0.38; 95% CI 0.09–0.68; $P = 0.01$) and the included studies were homogeneous ($I^2 = 0\%$; $Chi^2 = 0.38$; $P = 0.83$) (Fig. 9).

### TAC

The meta-analysis results showed that the TAC concentration in probiotics and synbiotics groups increased by 0.30 mg/dl higher than in the placebo group; however, this increase was not statistically significant (SMD: 0.30; 95% CI − 0.58 to 1.17; $P = 0.51$) and the heterogeneity level was considerable ($I^2 = 88\%$; $Tau^2 = 0.52$; $Chi^2 = 16.72$; $P = 0.0002$) (Fig. 10).

### GSH

The meta-analysis results showed that the GSH concentration in probiotics and synbiotics groups increased by 0.53 mg/dl, which was higher than in the placebo group; however, this increase was not statistically significant (SMD: 0.53; 95% CI − 0.00 to 1.06; $P = 0.05$) and there was the substantial heterogeneity level ($I^2 = 68\%$; $Tau^2 = 0.15$; $Chi^2 = 6.24$; $P = 0.04$) (Fig. 11).

### MDA

The meta-analysis results showed that the MDA concentration in the probiotics and synbiotics groups was reduced by 0.72 mg/dl, which was more than in the placebo group, and this reduction was statistically significant (SMD: − 0.76; 95% CI − 1.46 to − 0.05; $P = 0.03$) and the heterogeneity level was considerable ($I^2 = 81\%$; $Tau^2 = 0.31$; $Chi^2 = 10.42$; $P = 0.005$) (Fig. 12).

## Clinical symptoms

### Hirsutism

The meta-analysis results showed that the hirsutism concentration in probiotics, prebiotics, and synbiotics groups was reduced by 0.12, which was lower than in the placebo group; however, this reduction was not statistically significant (SMD: − 0.12; 95% CI − 0.38 to 0.13; $P = 0.34$) and the heterogeneity was at a moderate level ($I^2 = 50\%$; $Chi^2 = 5.96$; $P = 0.11$) (Fig. 13).

# Discussion

According to the search results, this was the first review study on the effect of probiotics, prebiotics, and synbiotics on hormonal and inflammatory indicators and clinical symptoms in women with PCOS. The meta-analysis results showed that probiotics and synbiotics significantly reduced FAI and MDA and increased NO and SHBG. The use of probiotics, prebiotics, and synbiotics in women with PCOS reduced the serum testosterone, DHEAS, and hsCRP levels and the hirsutism score as compared to the placebo group; however, this difference was not statistically significant. The consumption of probiotics and synbiotics by women with PCOS increased serums TAC and GSH levels; however, the difference with the placebo group was not significant.

An increase in metabolic indices, such as cholesterol as the prerequisite of androgenic hormone generation in these patients, resulted in an increase in serum androgen levels [37, 50]. Among the PCOS pathophysiology, glucose intolerance and insulin sensitivity had an important role in the development of this syndrome. The uptake of probiotics, prebiotics, and synbiotics balanced the colony of intestinal microbes and intestinal pH, improved intestinal decomposition and metabolism of lipids and starch, produced inflammatory cytokines, and improved intestinal digestion and absorption of nutrients [51]. They also reduced cholesterol by reducing its production in the liver, reduced blood glucose by consuming the serum insulin, and reduced insulin resistance which, in turn, reduced the production of androgens, such as testosterone, FAI, DHEAS, and SHBG levels [37, 52, 53]. According to the meta-analysis results, the consumption of probiotics, prebiotics, and synbiotics significantly reduced DHEAS; however, the consumption of probiotics and synbiotics did not significantly reduce testosterone levels. This can be attributed to the short duration of the intervention, which was between 8 and 12 weeks. Moreover, few studies measured the hormones as the outcome [35, 37, 38, 40].

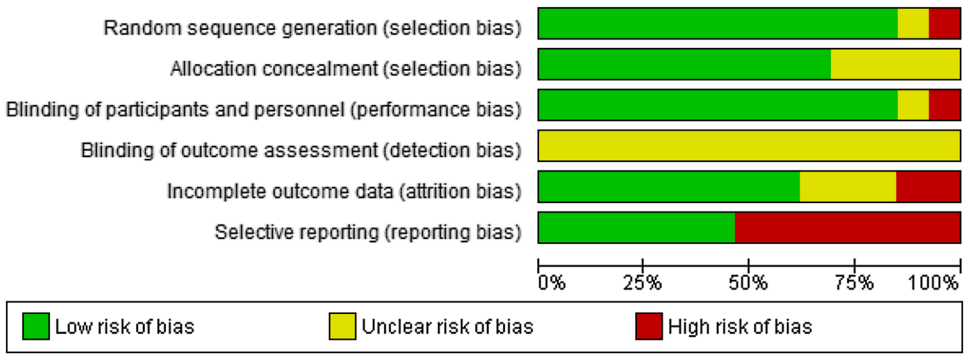


**Fig. 2** Risk of bias graph. Reviewer judgment about each risk of bias items

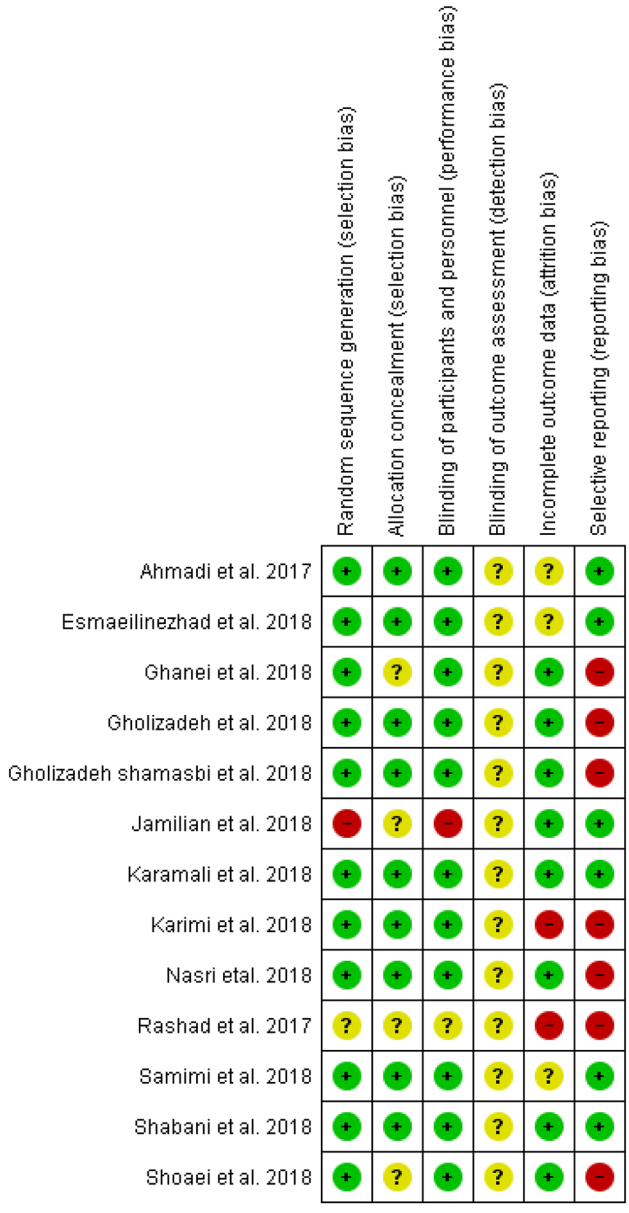


**Fig. 3** Risk of bias summary. Reviewer judgment about each risk of bias item as present (positive sign), unknown (question mark), and absent (negative sign)

This meta-analysis into the effect of probiotics, prebiotics, and synbiotics on clinical symptoms of this syndrome showed that they reduced the hirsutism score in these patients; however, this reduction was not significant. As it was mentioned, reduced levels of male sex hormone in women with PCOS may result in fewer clinical symptoms and improve hirsutism via increasing female sex hormones. As a result, body fat, weight, and male sex hormone levels decrease with reducing serum cholesterol and increasing leptin, peptide YY, glucagon-like peptide-1, and ghrelin, which may reduce clinical symptoms, such as hirsutism [54, 55]. The probable reason for insignificant reduction of hirsutism symptoms after receiving probiotics, prebiotics, and synbiotics may be its short-term use, as clinical symptoms in this syndrome are developed long after an increase in serum androgens and progress with time. As a result, the short-term consumption of these supplements may not result in rapid improvement of these symptoms. This is because; the improvement of signs may take a long time to appear after the regulation of male sex hormones in the patients' serum [56–58].

Oxidative stress and inflammation increase in patients with PCOS, resulting in insulin resistance through the functional disorder of pancreatic beta cells [59]. It finally causes ovarian dysfunction, which is accelerated with unbalanced antioxidant levels [60]. Reduced hyperandrogenism is correlated with the reduction and improvement of oxidative and inflammatory stress [61, 62].

The meta-analysis results on the effect of probiotics, prebiotics, and synbiotics on inflammatory indicators showed that these compounds reduced hsCRP concentration; however, this reduction was not statistically significant. Consumption of probiotics and synbiotics resulted in a significant decrease in the MDA level. Moreover, an increase in plasma levels of TAC and GSH were observed in the conducted meta-analyses; however, these changes were not significant. Additionally, the consumption of probiotics and synbiotics resulted in a significant increase in the plasma level of NO. Of course, NO plays a dual role in the process of immunoinflammation. On the one hand, NO can

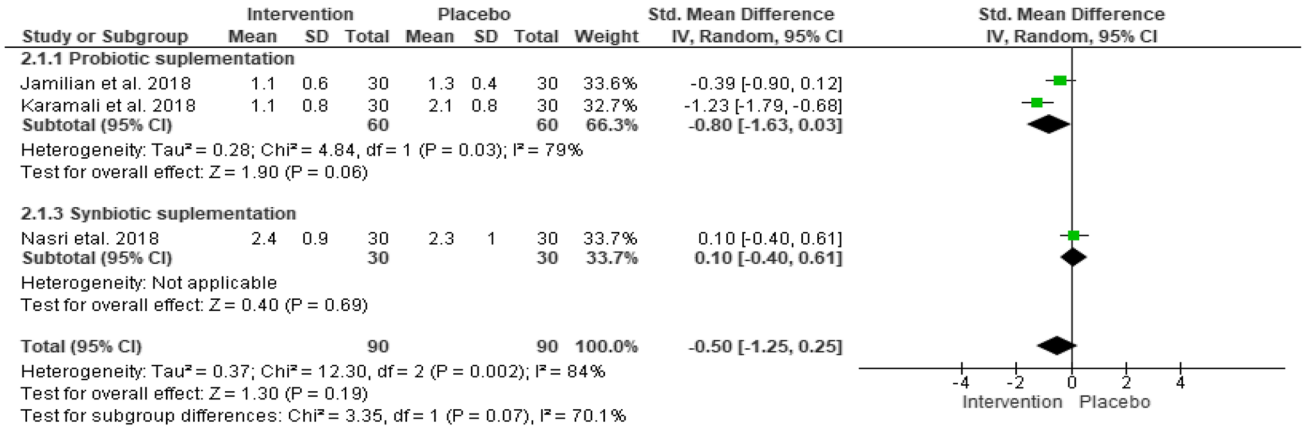


**Fig. 4** Effect of probiotics and synbiotics supplementation on the testosterone level among PCOS patients

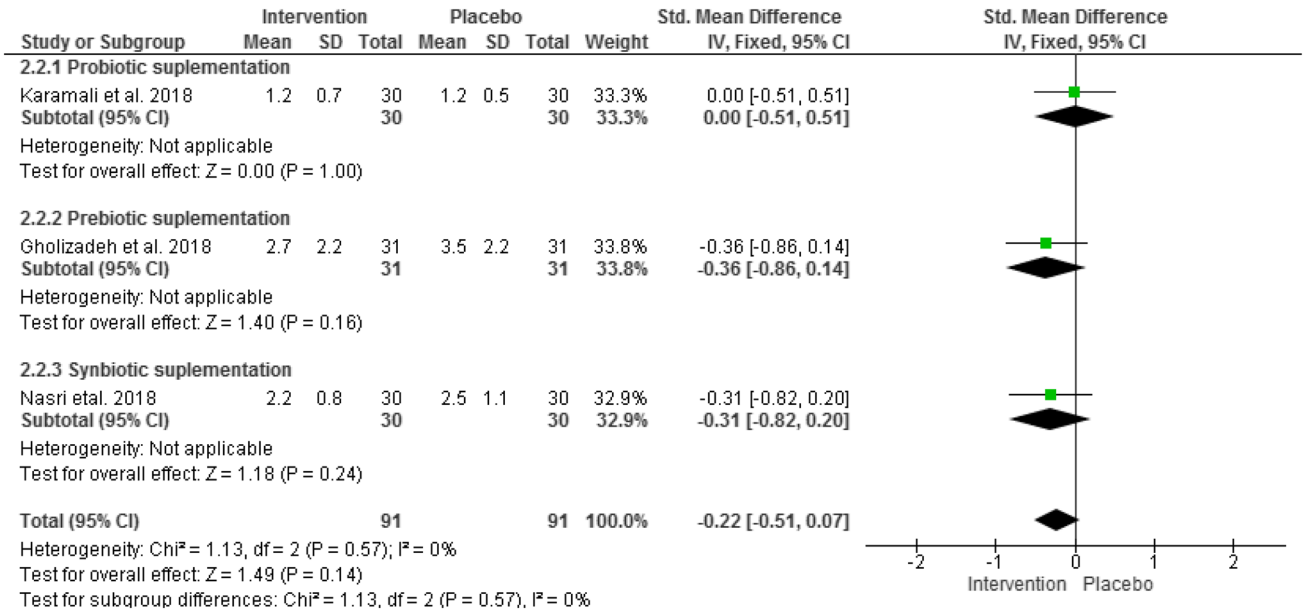


**Fig. 5** Effect of probiotics, prebiotics and synbiotics supplementation on DHEAS level among PCOS patients

kill microorganisms and has a protective effect on the body. On the other hand, NO can damage normal tissue cells to generate pathogenic effects. According to existing research, macrophages and other effector cells, including neutrophils, monocytes, and endothelial cells, are the main effector cells involved in the antimicrobial effects of NO [63].

Oxidative stress is correlated with obesity and hyperandrogenism. Synbiotics can reduce hydroperoxidase and finally increase plasma levels of nitric oxide. They also can reduce MDA by reducing blood lipids and inhibiting lipid peroxidase [64–66]. Probiotics may improve inflammation and oxidative stress by moderating the signaling pathway of inflammatory factors, producing antioxidant metabolites, upregulation of antioxidants activity, and downregulation of ROS-producing enzymes. As a result, the oxidative stress increases following ROS (reactive oxygen species) which may, in turn, increase hyperandrogenemia and insulin resistance. Reduced antioxidants and increased oxidative stress and aggregation of ROS have a significant role in folliculogenesis and oocyte maturity in women with PCOS and their reproductive system [67]. Probiotics may exert anti-inflammatory and anti-oxidative effects through the production of short-chain fatty acids in the intestine [68]. Prebiotics, such as oligofructose, reduce the expression of oxidative and inflammatory markers in the liver [69]. It is a mechanism through which prebiotics improve inflammation

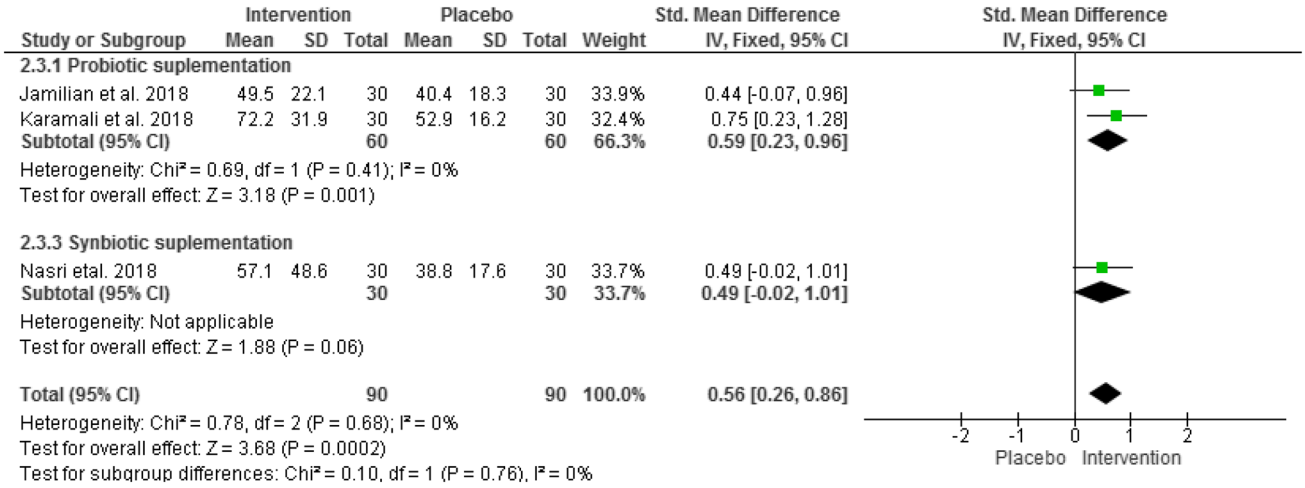


**Fig. 6** Effect of probiotics and synbiotics supplementation on the SHBG level among PCOS patients

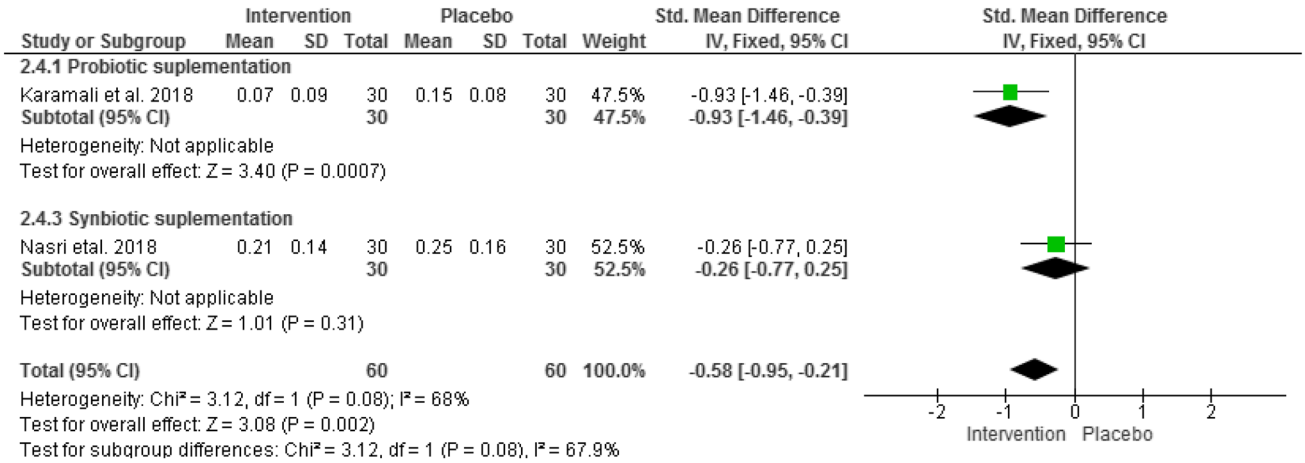


**Fig. 7** Effect of probiotics and synbiotics supplementation on the FAI level among PCOS patients

and antioxidants: the change of intestinal bacteria to butyrogenic-genera, such as peptostreptococcus, fusobacterium, bifidobacterium, which are well-known for their anti-inflammatory properties. An increase in oxidative stress results in an increase in intestinal permeability and endotoxins in blood [70]. Lipopolysaccharide is the main and most important element in the extracellular wall of Gram-negative bacteria and the main inflammatory element in obese people [69]. The lactic acid-producing bacteria have anti-oxidative properties, which eliminate free radicals and secrete antioxidants at the intestinal wall which, in turn, reduce MDA concentration in the blood [71]. However, the differences in the length of use, dose, genotype, and supplement might reduce their effectiveness. In addition, the high dose and prolong use of these supplements may result in significant changes in the inflammatory indicators.

A meta-analysis has recently investigated the effect of probiotics or synbiotics supplementation on QUICKI, triglycerides, fasting insulin, and HDL in women with PCOS and the results have shown that these supplements produce a significant effect on the symptoms of this syndrome. However, the outcomes of the present study are different from the mentioned meta-analysis [72]. This study analyzed the secondary outcomes of some studies instead of the primary outcomes. The limited number of studies into these indicators can be a plausible cause regarding their insignificance. Moreover, the sample size was calculated based on the primary outcomes, which can be a cause for insufficient sample size for evaluating the hormonal and inflammatory outcomes and insignificance of these indices in the meta-analysis.

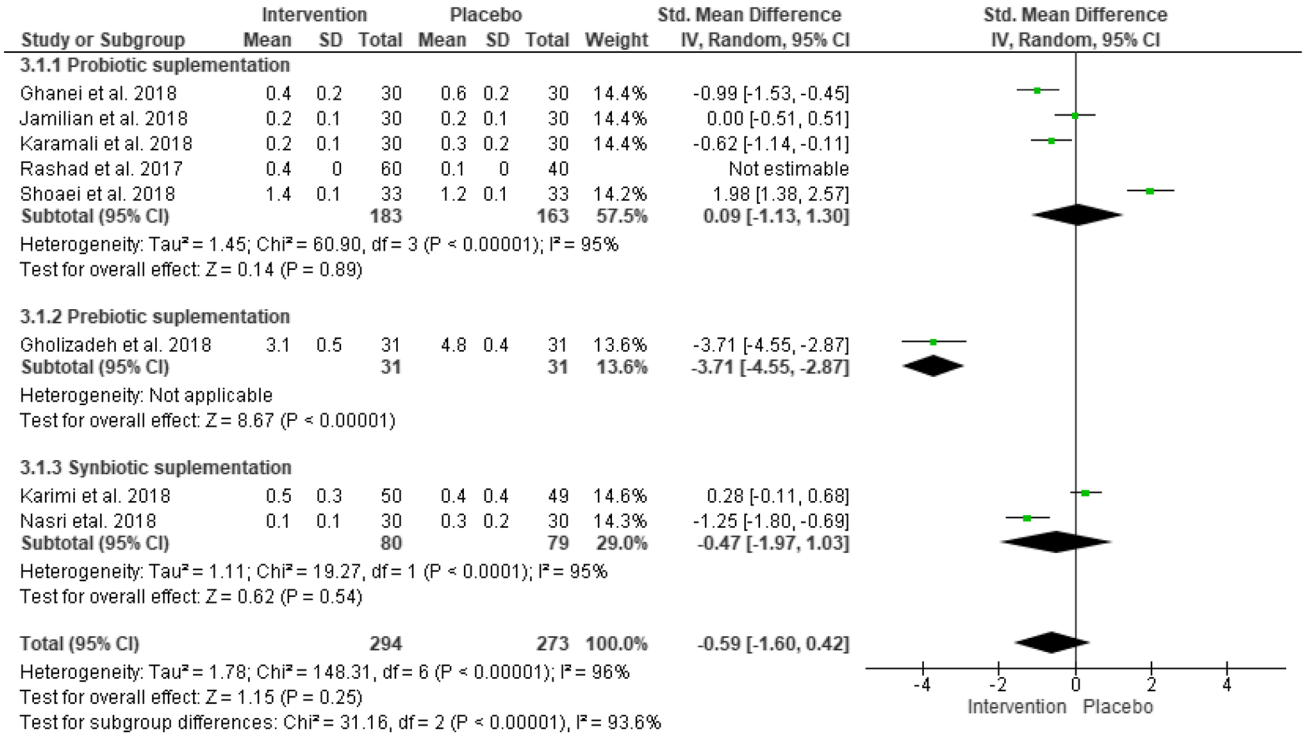


**Fig. 8** Effect of probiotics, prebiotic and synbiotics supplementation on the hsCRP level among PCOS patients

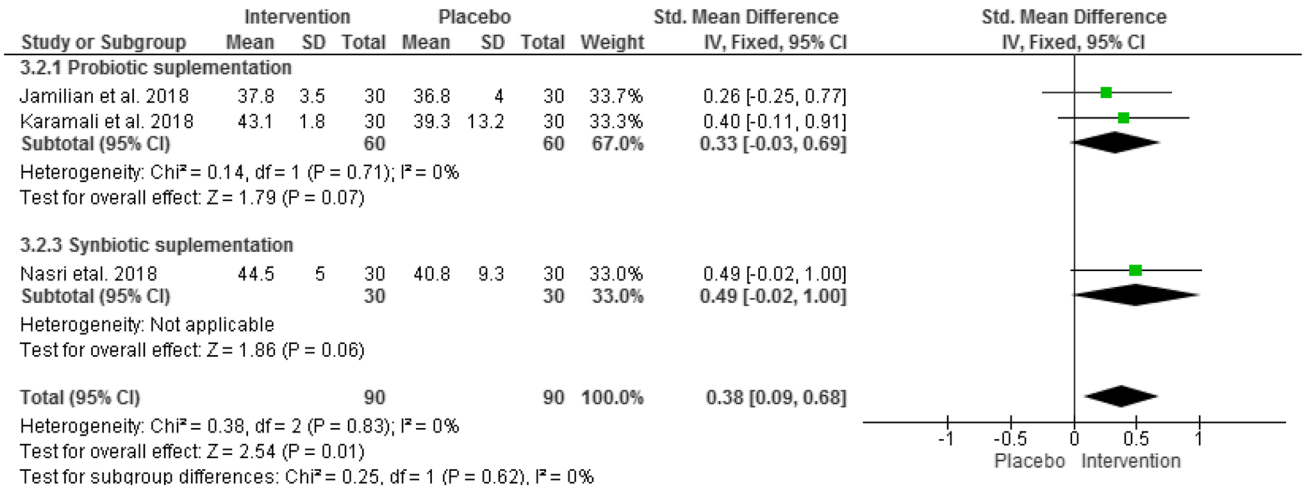


**Fig. 9** Effect of probiotics and synbiotics supplementation on the NO level among PCOS patients

## Limitation

The scant number of studies into the effect of probiotics, prebiotics, and synbiotics on hormonal and inflammatory indicators and clinical symptoms in women with PCOS was a limitation of the present meta-analysis. Therefore, results should be reported carefully. The conduction of all studies in Iran, except one [47], was another limitation of this meta-analysis. There was not a limitation on country searching in our research about the effect of probiotics, prebiotics, and synbiotics on women with PCOs, and unfortunately most of the studies have been conducted in Iran. Although the research environment in clinical trials is not very important, the effect of prebiotics, synbiotics, and probiotics on hormonal and inflammatory indicators, and clinical symptoms in women with PCOS can be affected by ethnicity, race, and climate, and factors related to the lifestyle of Iranians. Therefore, we suggest more clinical trials be done with these

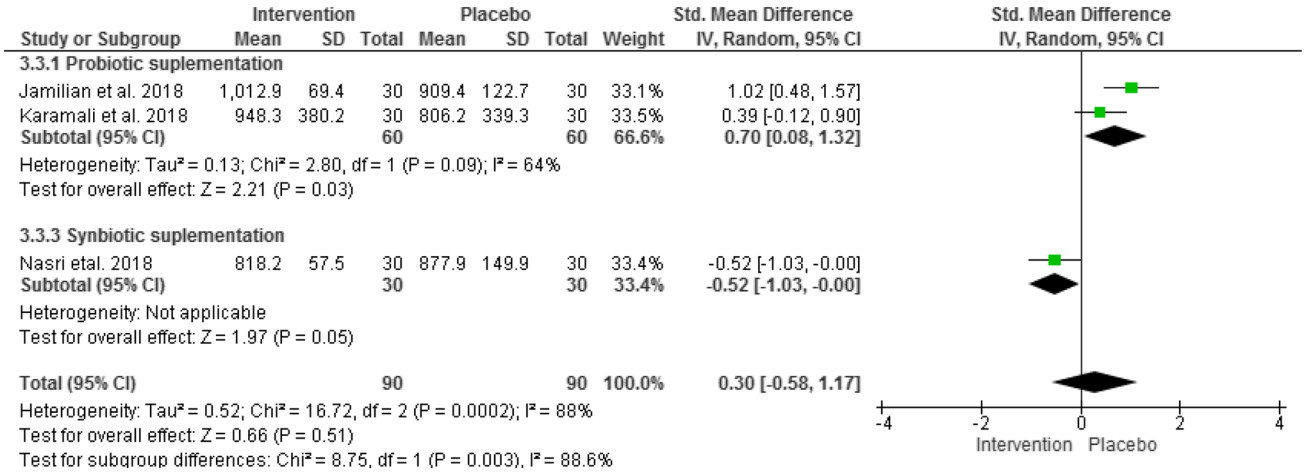


**Fig. 10** Effect of probiotics and synbiotics supplementation on the TAC level among PCOS patients

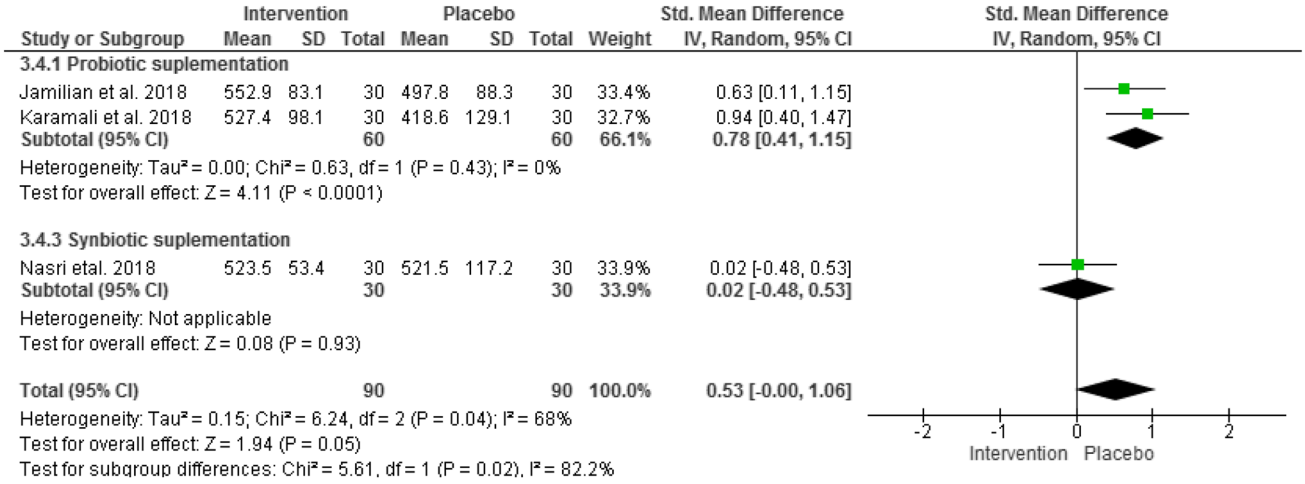


**Fig. 11** Effect of probiotics and synbiotics supplementation on the GSH level among PCOS patients

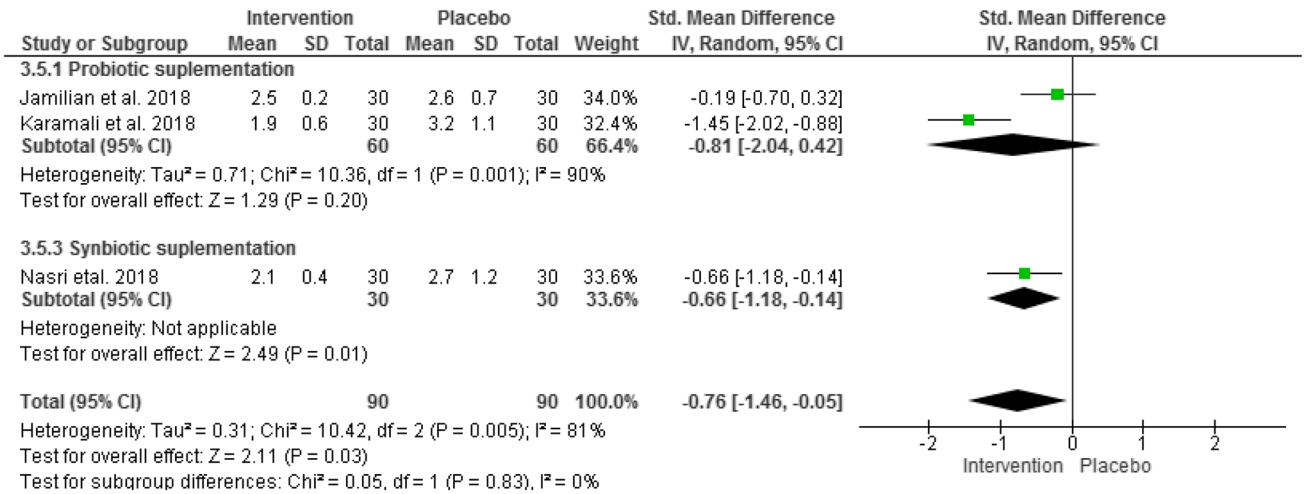


**Fig. 12** Effect of probiotics and synbiotics supplementation on the MDA level among PCOS patients

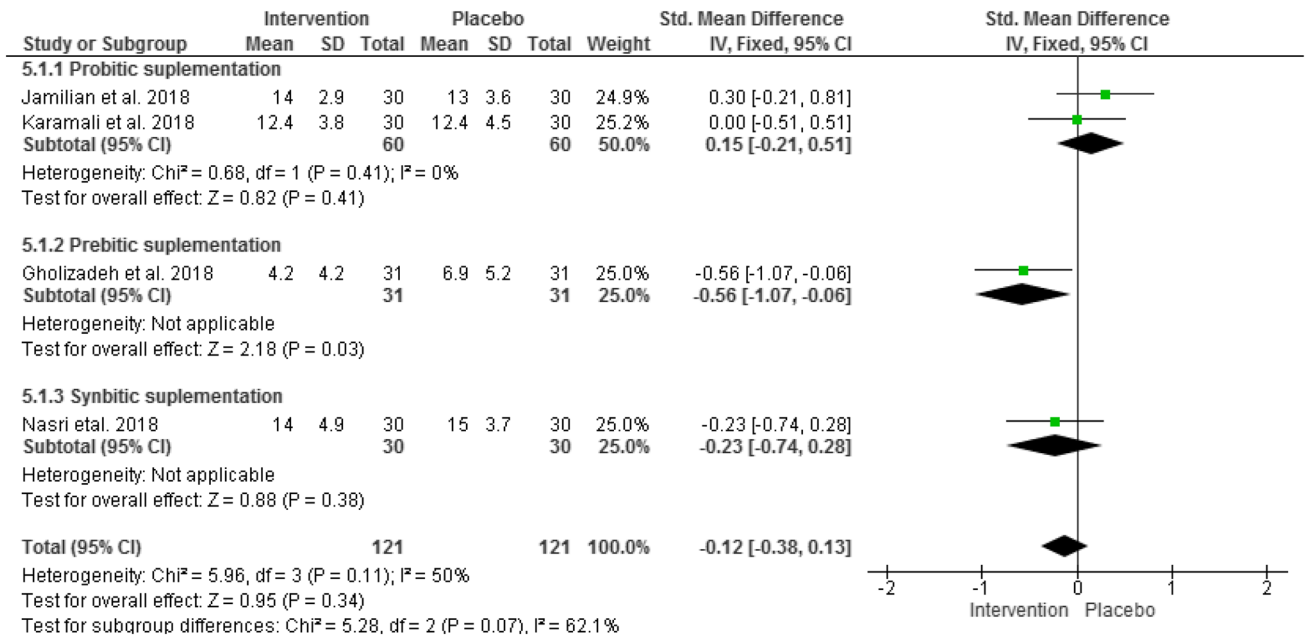


**Fig. 13** Effect of probiotics, prebiotics, and synbiotics supplementation on the hirsutism score among PCOS patients

factors in other countries to make sure of their efficacy on PCOS patients.

On the other hand, in all of these studies, metabolic indices were also measured. The sample size was determined based on the metabolic indices in five studies, hsCRP in two studies, and testosterone in other two studies. The sample size estimation method was not mentioned in four studies. Therefore, the sample size might be insufficient for measuring the effect of probiotics, prebiotics, and synbiotics on hormonal and inflammatory indicators, as well as clinical symptoms, and this could affect the results. Additionally, since the bacterial species were the same in most of the studies, we could not do the subgroup meta-analysis according to the mentioned variable.

## Conclusion

This meta-analysis showed that consumption of probiotics and synbiotics had a significant effect on the control of hormonal and inflammatory indicators by significantly reducing FAI and MDA, and increasing SHBG and NO. Although probiotics and synbiotics increased the GSH and TAC levels, this increase was not statistically significant. Moreover, probiotics, prebiotics, and synbiotics reduced the testosterone, DHEAS, hsCRP, and hirsutism score; however, this reduction was not statistically significant. In conclusion, due to the limited number of studies on women with PCOS, more clinical studies are needed to determine the suitable dose, length of use, and type of the supplement.

**Author contributions** SGS, SGH, and MM participated in the study design. SGS and SGH searched the literature and selected studies, extracted data, assessed quality, and SGS drafted the manuscript. MM revised the draft and all authors read and approved the final version of the manuscript.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they do have not any conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Ethical standards** For this type of study, formal consent is not required.

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