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The Effects of Probiotic Supplementation on Clinical Symptom, Weight Loss, Glycemic Control, Lipid and Hormonal Profiles, Biomarkers of Inflammation, and Oxidative Stress in Women with Polycystic Ovary Syndrome: a Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract

The purpose of this systematic review and meta-analysis of randomized controlled trials (RCTs) is to determine the effectiveness of probiotic supplementation on clinical symptoms, weight loss, glycemic control, lipid and hormonal profiles, and biomarkers of inflammation and oxidative stress in women with polycystic ovary syndrome (PCOS). Eligible studies were systematically searched from Cochrane Library, Embase, Medline, and Web of Science databases until January 2019. Cochran (Q) and I-square statistics were used to measure heterogeneity among included studies. Data were pooled by using random-effect model and expressed as standardized mean difference (SMD) with 95% confidence interval (CI). Eleven articles were included in this meta-analysis. Probiotic supplementation significantly decreased weight (SMD − 0.30; 95% CI, − 0.53, − 0.07; $P = 0.01$), body mass index (BMI) (SMD − 0.29; 95% CI, − 0.54, − 0.03; $P = 0.02$), fasting plasma glucose (FPG) (SMD − 0.26; 95% CI, − 0.45, − 0.07; $P < 0.001$), insulin (SMD − 0.52; 95% CI, − 0.81, − 0.24; $P < 0.001$), homeostatic model assessment for insulin resistance (HOMA-IR) (SMD − 0.53; 95% CI, − 0.79, − 0.26; $P < 0.001$), triglycerides (SMD − 0.69; 95% CI, − 0.99, − 0.39; $P < 0.001$), VLDL-cholesterol (SMD − 0.69; 95% CI, − 0.99, − 0.39; $P < 0.001$), C-reactive protein (CRP) (SMD − 1.26; 95% CI, − 2.14, − 0.37; $P < 0.001$), malondialdehyde (MDA) (SMD − 0.90; 95% CI, − 1.16, − 0.63; $P < 0.001$), hirsutism (SMD − 0.58; 95% CI, − 1.01, − 0.16; $P < 0.001$), and total testosterone levels (SMD − 0.58; 95% CI, − 0.82, − 0.34; $P < 0.001$), and also increased the quantitative insulin sensitivity check index (QUICKI) (SMD 0.41; 95% CI, 0.11, 0.70; $P < 0.01$), nitric oxide (NO) (SMD 0.33; 95% CI 0.08, 0.59; $P = 0.01$), total antioxidant capacity (TAC) (SMD 0.64; 95% CI, 0.38, 0.90; $P < 0.001$), glutathione (GSH) (SMD 0.26; 95% CI, 0.01, 0.52; $P = 0.04$), and sex hormone binding globulin (SHBG) levels (SMD 0.46; 95% CI, 0.08, 0.85; $P = 0.01$). Probiotic supplementation may result in an improvement in weight, BMI, FPG, insulin, HOMA-IR, triglycerides, VLDL-cholesterol, CRP, MDA, hirsutism, total testosterone, QUICKI, NO, TAC, GSH, and SHBG but did not affect dehydroepiandrosterone sulfate levels, and total, LDL, and HDL cholesterol levels in patients with PCOS.

Keywords Probiotic · Weight loss · Glycemic control · Lipids profiles · Inflammation · Oxidative markers · Meta-analysis · Polycystic ovary syndrome

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting 6–10% of women of reproductive age. PCOS can be characterized by a list of dysmetabolic features including glucose intolerance, insulin resistance, lipid abnormalities, and increased low-grade inflammation, especially among women with the classic phenotype of PCOS [1, 2]. About 44–70% of patients with PCOS have been found to be insulin resistant [3, 4]. Insulin resistance and increased inflammatory markers such as C-reactive protein (CRP) levels in women with PCOS are associated with an elevated risk of developing metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), and cardiovascular disease [5–7].

Probiotics are suggested to improve insulin resistance and CRP among patients with metabolic syndrome and related disorders [8, 9]. Findings on the effects of probiotics on glycemic control and CRP levels among women with PCOS are controversial. In a study by Samimi et al. [10], synbiotic supplementation for 12 weeks among women with PCOS significantly improved markers of insulin metabolism; however, it did not affect fasting glucose levels. In addition, Lactobacillus supplementation for 12 weeks among women with PCOS significantly improved inflammatory markers through increasing interleukin 10 (IL-10), and reducing high sensitivity C-reactive protein (hs-CRP), and IL-6 [11]. Conversely, 8-week probiotic supplementation trials prescribed to patients with PCOS showed no effect on parameters related to insulin metabolism and CRP levels [12].

This study aims to systematically review the previous randomized clinical trials (RCTs) on the effects of probiotic supplementation on clinical symptoms, weight loss, glycemic control, lipid and hormonal profiles, and biomarkers of inflammation and oxidative stress among women with PCOS and to summarize the available findings in a meta-analysis, if possible.

Methods

Search Strategy

Eligible studies were identified through systematically searching the Cochrane Library, Embase, Medline, and Web of Science databases until 30th of January 2019. To increase search sensitivity, the authors manually reviewed the reference list of the relevant studies. Articles studying the association between probiotic supplementation and clinical symptoms, weight loss, glycemic control, lipid and hormonal profiles, and biomarkers of inflammation and oxidative stress were retrieved by including the following search terms and text words: patients ("PCOS"), intervention ("probiotic," OR "synbiotic," OR "symbiotic," AND "supplementation," OR "intake"), and outcomes ("weight" OR "body max index (BMI)" OR "weight loss" OR "fasting plasma glucose (FPG)" OR "Insulin" OR "homeostatic model assessment for insulin resistance (HOMA-IR)" OR "quantitative insulin sensitivity check index (QUICKI)" OR "glycemic control" OR "triglycerides" OR "very-low-density lipoprotein-cholesterol (VLDL-cholesterol)" OR "total cholesterol" OR "low-density lipoprotein-cholesterol (LDL-cholesterol)" OR "high-density lipoprotein-cholesterol (HDL-cholesterol)" OR "lipid profiles" OR "C-reactive protein (CRP)" OR "nitric oxide (NO)" OR "total antioxidant capacity (TAC)" OR "glutathione (GSH)" OR " malondialdehyde (MDA)" OR "inflammation markers" OR "oxidative stress markers" OR "modified ferriman-gallwey (mF-G) or hirsutism" OR "total testosterone" OR "dehydroepiandrosterone sulfate levels (DHEAS)" OR "sex hormone binding globulin (SHBG)" OR "hormonal profiles"). The strategy searches were individually performed by two researchers. The search strategy was restricted to RCTs published in English. After papers were screened by their titles and/or abstracts, the full text versions of related RCTs were retrieved for further assessment.

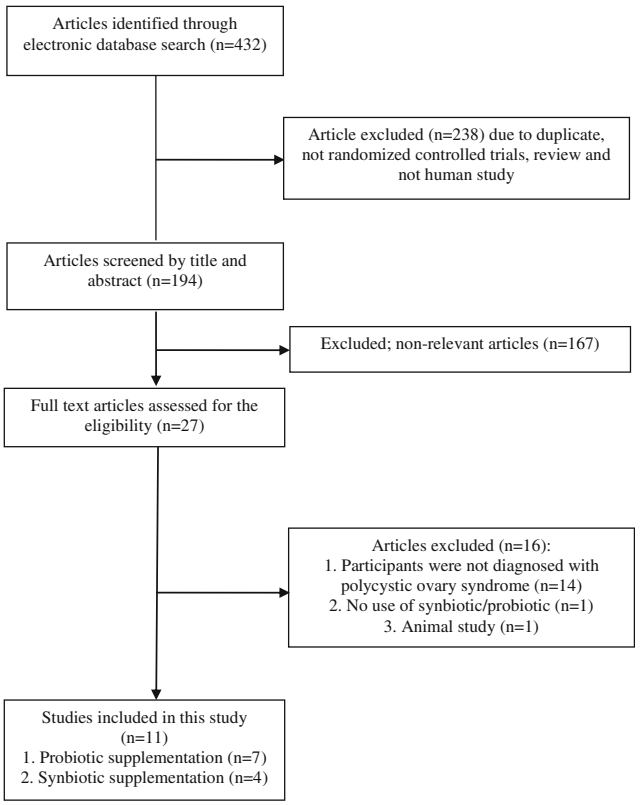


Fig. 1 Literature search and review flowchart for selection of studies

Inclusion and Exclusion Criteria

We included studies that reported using human subjects with RCTs, included women with PCOS, and administrated probiotic and/or synbiotic supplementation as interventions. RCTs that did not report mean (SD) changes of clinical symptoms, weight loss, glycemic control, lipid and hormonal profiles, and biomarkers of inflammation and oxidative stress for the intervention and placebo groups, abstracts without full article, case reports, and RCTs that did not catch at least required score of quality assessment process were excluded.

Quality Assessment

Two independent investigators (VO and MA) have assessed the quality of included studies and extracted data using the Cochrane Collaboration Risk of Bias tool and the standard forms of Microsoft Excel 2007, respectively. The Cochrane Collaboration Risk of Bias tool includes the following criteria: randomization generation, allocation concealment, blinding of subjects and outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. The following data of eligible

Table 1 Characteristics of included studies

Authors (ref)	Publication years	Control/ intervention (sample size)	Age (control vs. intervention)	Duration (week)	Intervention
Samimi et al. [10]	2018	30/30	27.3 ± 6.1, 27.0 ± 5.6	12 weeks	Synbiotic capsule contained *Lactobacillus acidophilus*, *Lactobacillus casei*, *and Bifidobacterium bifidum* (2×10^9 CFU/g each) plus 800 mg inulin
Karimi et al. [13]	2018	49/50	29 ± 5.1, 28.1 ± 5.5	12 weeks	Synbiotic capsule (500 mg) contained *Lactobacillus acidophilus* 3×10^{10} CFU/g, *Lactobacillus casei* 3×10^9 CFU/g, *Lactobacillus bulgaricus* 5×10^8 CFU/g, *Lactobacillus rhamnosus* 7×10^9 CFU/g, *Bifidobacterium longum* 1×10^9 CFU/g, *Bifidobacterium breve* 2×10^{10} CFU/g and *Streptococcus thermophilus* 3×10^8 CFU/g + prebiotic inulin (fructo-oligosaccharide)
Ahmadi et al. [14]	2017	30/30	24.8 ± 5.1, 25.2 ± 5.4	12 weeks	Probiotic capsule contained *Lactobacillus acidophilus*, *Lactobacillus casei and Bifidobacterium bifidum* (2×10^9 CFU/g each)
Shoaei et al. [12]	2015	33/32	25.72 ± 0.1, 26.5 ± 0.1	8 weeks	Probiotic capsule (500 mg) contained *Lactobacillus casei* 7×10^9 CFU/g, *Lactobacillus acidophilus* 2×10^9 CFU/g, *Lactobacillus rhamnosus* 1.5×10^9 CFU/g, *Lactobacillus bulgaricus* 2×10^8 CFU/g, *Bifidobacterium breve* 2×10^{10} CFU/g, *Bifidobacterium longum* 7×10^9 CFU/g, *Streptococcus thermophiles* 1.5×10^9 CFU/g
Karamali et al. [15]	2018	30/30	27.7 ± 4.7, 27.2 ± 4.6	12 weeks	Probiotic capsule contained *Lactobacillus acidophilus*, *Lactobacillus casei* and *Bifidobacterium bifidum* (2×10^9 CFU/g each)
Ghanei et al. [11]	2018	30/30	28.96 ± 0.98, 30.06 ± 1.-06	12 weeks	Probiotic capsule (1000 mg) contained *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus fermentum*, and *Lactobacillus Gasseri* (1×10^9 CFU of each)
Nasri et al. [16]	2018	30/30	25.9 ± 5.2, 25.7 ± 5.5	12 weeks	Synbiotic capsule contained *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum* (2×10^9 CFU/g each) plus 800 mg inulin
Shabani et al. [17]	2018	30/30	26.8 ± 5.1, 27.7 ± 6.9	12 weeks	Probiotic capsule contained *Lactobacillus acidophilus*, *Lactobacillus reuteri*, *Lactobacillus fermentum*, and *Bifidobacterium bifidum* (2×10^9 CFU/g each) + 200 mcg selenium
Jamilian et al. [18]	2018	30/30	25.6 ± 3.8, 26.0 ± 5.3	12 weeks	Probiotic capsule contained *Lactobacillus acidophilus*, *Lactobacillus reuteri*, *Lactobacillus fermentum*, and *Bifidobacterium bifidum* (2×10^9 CFU/g each) + 200 mcg selenium
Esmaeilinezhad (a) et al. [19]	2018	22/22	29.30 ± 7.46, 30.04 ± 6.-39	8 weeks	Synbiotic pomegranate juice 2 lit per week contained Lactobacillus (4×10^8 CFU/g) plus 40 g inulin
Esmaeilinezhad (b) et al. [19]	2018	21/21	30.60 ± 7.43, 29.52 ± 5.-82	8 weeks	Synbiotic beverage 2 lit per week contained Lactobacillus (4×10^8 CFU/g) plus 40 g inulin
Ostadmohammadi et al. [20]	2019	30/30	25.4 ± 5.1, 24.4 ± 4.7	12 weeks	Probiotic capsule contained *Lactobacillus acidophilus*, *Lactobacillus reuteri*, *Lactobacillus fermentum*, and *Bifidobacterium bifidum* (2×10^9 CFU/g each) + 50,000 IU vitamin D every 2 weeks

RCTs were extracted: first authors' name, year of publication, mean age of participants, mean (SD) changes of glucose metabolism (including weight, BMI, FPG, insulin, HOMA-IR, QUICKI, triglycerides, VLDL-, total-, LDL-, and HDL-cholesterol, CRP, NO, TAC, GSH, MDA, mF-G or hirsutism, total testosterone, DHEAS, SHBG, total sample size, number of participants in the intervention and control groups, study design, type of intervention, and duration of intervention. When there were disagreements among the investigators, a third author (ZA) would resolve the dispute through a guided discussion.

Statistical Methods

All statistical analyses of the present study were conducted by using STATA version 12.0 (Stata Corp., College Station, TX) and RevMan software (Cochrane Review Manager, version 5.2). Heterogeneity between studies

Table 2 Estimation of the standardized difference means of weight loss, glycemic control, lipid and hormonal profiles, and biomarkers of inflammation and oxidative stress with CI 95% between the intervention and control groups

Variable		Number of study	Standardized mean difference	CI 95%	*P* value	Heterogeneity		
						I^2 (%)	*Q*	*P* value
Weight	Change intervention vs. placebo group	9	− 0.30	− 0.53, − 0.07	0.01	42.5	13.91	0.08
BMI	Change intervention vs. placebo group	9	− 0.29	− 0.54, − 0.03	0.02	50.7	16.23	0.03
FPG	Change intervention vs. placebo group	7	− 0.26	− 0.45, − 0.07	< 0.01	0.0	2.35	0.88
Insulin	Change intervention vs. placebo group	7	− 0.52	− 0.81, − 0.24	< 0.001	52.2	12.55	0.05
HOMA-IR	Change intervention vs. placebo group	7	− 0.53	− 0.79, − 0.26	< 0.001	44.5	10.82	0.09
QUICKI	Change intervention vs. placebo group	7	0.41	0.11, 0.70	< 0.01	55.5	13.47	0.03
Triglycerides	Change intervention vs. placebo group	3	− 0.69	− 0.99, − 0.39	< 0.001	0.0	0.28	0.86
VLDL-cholesterol	Change intervention vs. placebo group	3	− 0.69	− 0.99, − 0.39	< 0.001	0.0	0.27	0.87
Total cholesterol	Change intervention vs. placebo group	3	− 0.26	− 0.67, 0.15	0.22	48.4	3.88	0.14
LDL-cholesterol	Change intervention vs. placebo group	3	− 0.12	− 0.66, 0.42	0.66	70.2	6.71	0.03
HDL-cholesterol	Change intervention vs. placebo group	3	0.04	− 0.25, 0.33	0.79	0.0	0.44	0.81
CRP	Change intervention vs. placebo group	7	− 1.26	− 2.14, − 0.37	< 0.01	94.6	111.45	< 0.001
NO	Change intervention vs. placebo group	4	0.33	0.08, 0.59	0.01	0.0	2.95	0.39
TAC	Change intervention vs. placebo group	4	0.64	0.38, 0.90	< 0.001	0.0	1.95	0.58
GSH	Change intervention vs. placebo group	4	0.26	0.01, 0.52	0.04	0.0	2.00	0.57
MDA	Change intervention vs. placebo group	4	− 0.90	− 1.16, − 0.63	< 0.001	0.0	1.72	0.63
mF-G	Change intervention vs. placebo group	4	− 0.58	− 1.01, − 0.16	< 0.01	62.6	8.02	0.04
Total testosterone	Change intervention vs. placebo group	6	− 0.58	− 0.82, − 0.34	< 0.001	10.4	5.58	0.34
DHEAS	Change intervention vs. placebo group	2	0.06	− 0.77, 0.89	0.88	80.8	5.21	0.02
SHBG	Change intervention vs. placebo group	4	0.46	0.08, 0.85	0.01	55.7	6.77	0.08

BMI, body max index; *FPG*, fasting plasma glucose; *HOMA-IR*, homeostatic model assessment for insulin resistance; *QUICKI*, quantitative insulin sensitivity check index; *VLDL-cholesterol*, very-low-density lipoprotein-cholesterol; *LDL-cholesterol*, low-density lipoprotein; *HDL-cholesterol*, high-density lipoprotein; *CRP*, C-reactive protein; *NO*, nitric oxide; *TAC*, total antioxidant capacity; *GSH*, glutathione; *MDA*, malondialdehyde; *mF-G*, modified ferriman-gallwey; *DHEAS*, dehydroepiandrosterone sulfate; *SHBG*, sex hormone binding globulin

was assessed by using the Cochran Q test and I-squared statistic (I^2). I^2 higher than 50% with P value < 0.05 represented significant heterogeneity. Because of the different indications between included RCTs were used random-effects models to perform our meta-analyses. To estimate the standardized mean difference (SMD) and 95% confidence intervals (CIs), the inverse variance method and Cohen statistics were applied. The Egger's regression method was conducted on the included studies to detect potential publication bias. Additional subgroup analyses (such as type and duration of interventions) and sensitivity analyses were performed to examine the source of heterogeneity and the contribution of one by one RCTs, respectively. P values < 0.05 were considered as statistically significant.

Results

Search Results and Trial Flow

The step by step method applied for the article screening and selection process is outlined in Fig. 1. Through the screening and selection process, 11 studies with 12 effect sizes of 432 citations were obtained to be suitable for the meta-analysis. Table 1 outlines the characteristics of the included primary RCTs. All included studies were randomized, double-blind, and placebo-controlled trials. Nine studies investigated the effect of probiotic supplementation on weight, nine studies on BMI, four studies on FPG, four studies on insulin, seven studies on HOMA-IR, seven studies on QUICKI, three studies on triglycerides, three studies on VLDL-cholesterol, three studies on total cholesterol, three studies on LDL-cholesterol, three studies on HDL-cholesterol, seven studies on CRP, four studies on NO, four studies on TAC, four studies on GSH, four studies on MDA, four studies on mF-G, six studies on total testosterone, two studies on DHEAS, and four studies on SHBG levels. The intervention duration among selected primary studies were varied between 8 and 12 weeks (Table 2). The studies' sample sizes were ranged between 42 and 99 women. The authors' judgements about quality of each trial and risk of bias for included primary studies are summarized in Fig. 2.

Pooled Effects of Probiotic on Clinical Symptom, Weight Loss, and Metabolic Profiles

The forest plots for the effects of probiotic supplementation on glucose metabolism are presented in Fig. 3. The findings showed that probiotic supplementation significantly decreased weight (SMD − 0.30; 95% CI, − 0.53, − 0.07; P = 0.01), BMI (SMD − 0.29; 95% CI, − 0.54, − 0.03; P = 0.02), FPG (SMD − 0.26; 95% CI, − 0.45, − 0.07; P < 0.001), insulin (SMD − 0.52; 95% CI, − 0.81, − 0.24; P < 0.001), HOMA-IR (SMD − 0.53; 95% CI, − 0.79, − 0.26; P < 0.001), triglycerides (SMD − 0.69; 95% CI, − 0.99, − 0.39; P < 0.001), VLDL-cholesterol (SMD − 0.69; 95% CI, − 0.99, − 0.39; P < 0.001), CRP (SMD − 1.26; 95% CI, − 2.14, − 0.37; P < 0.001), MDA (SMD − 0.90; 95% CI, − 1.16, − 0.63; P < 0.001), mF-G (SMD − 0.58; 95% CI, − 1.01, − 0.16; P < 0.01), and total testosterone levels (SMD − 0.58; 95% CI, − 0.82, − 0.34; P < 0.001), and also increased QUICKI

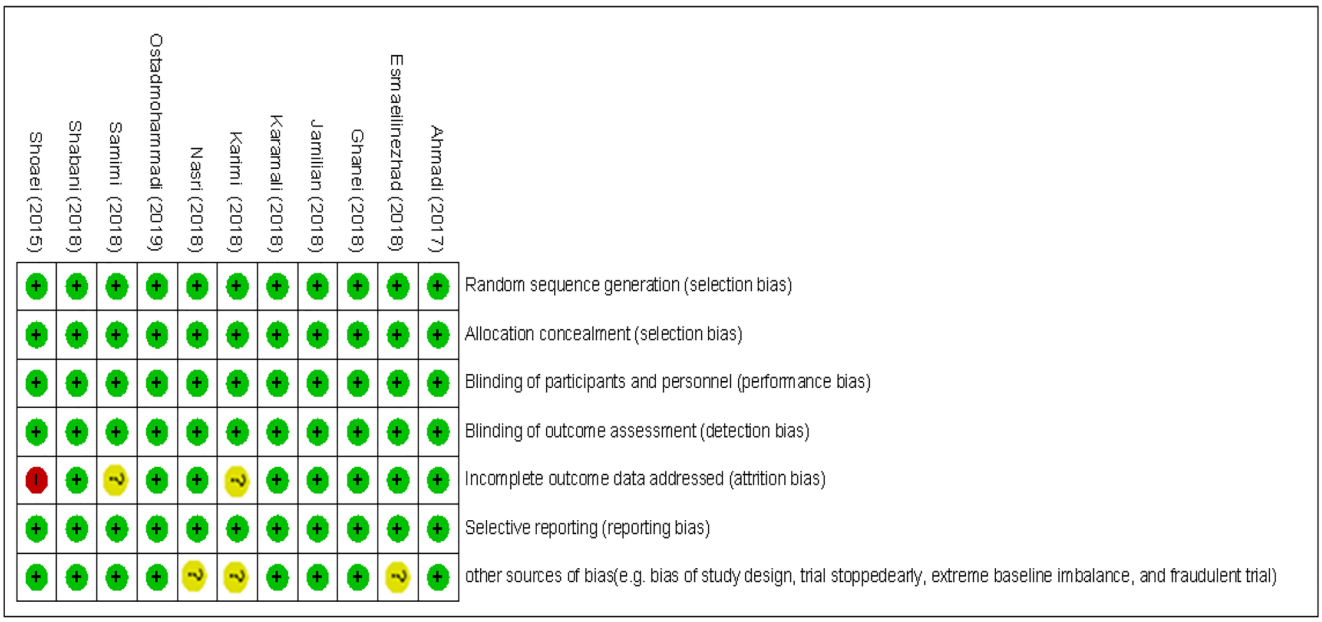


Fig. 2 The methodological quality of included studies

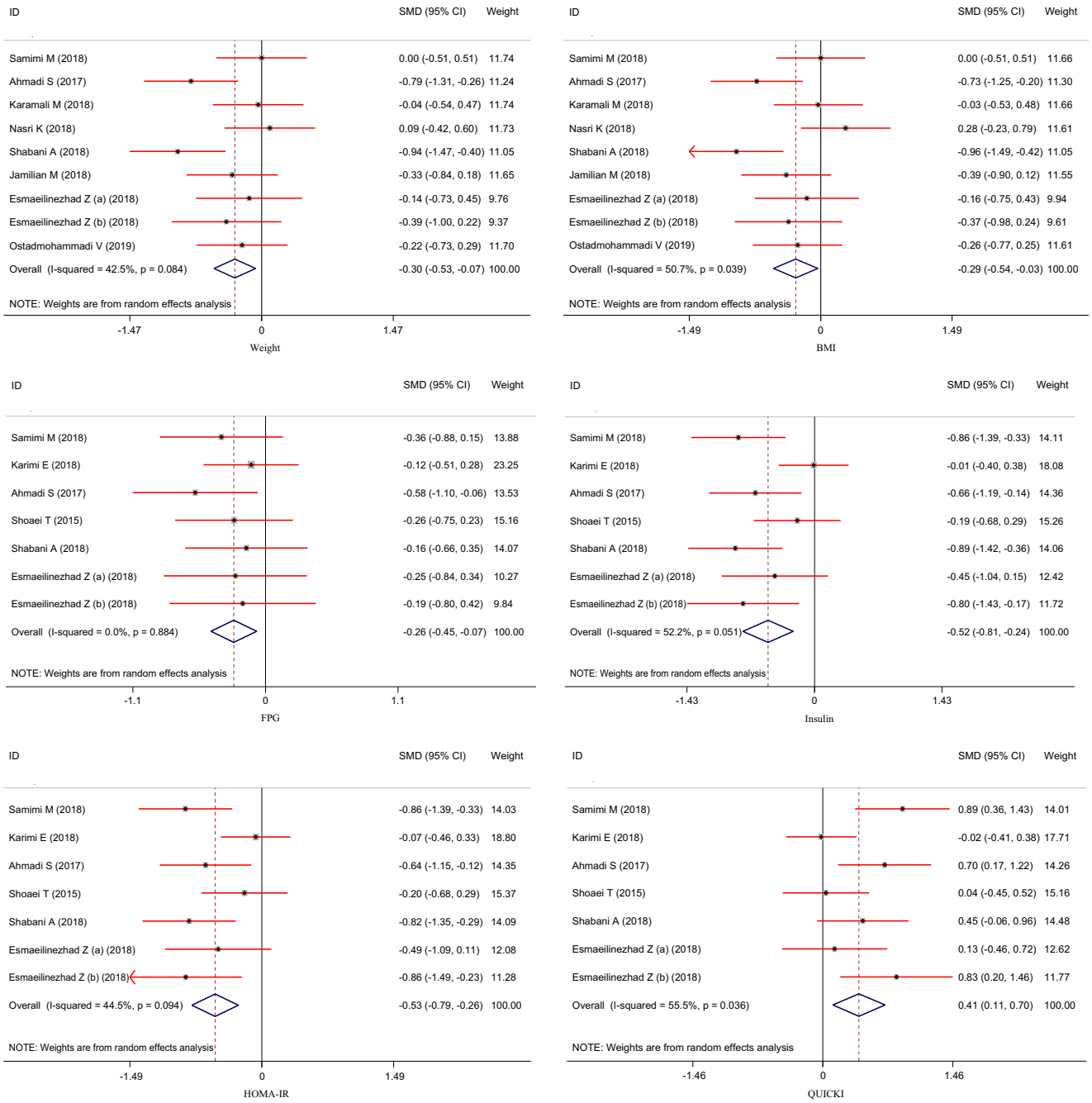


Fig. 3 Meta-analysis clinical symptom, weight loss and metabolic profiles in probiotic and placebo groups (CI = 95%)

(SMD 0.41; 95% CI, 0.11, 0.70; $P < 0.001$), NO (SMD 0.33; 95% CI, 0.08, 0.59; $P = 0.01$), TAC (SMD 0.64; 95% CI, 0.38, 0.90; $P < 0.001$), GSH (SMD 0.26; 95% CI, 0.01, 0.52; $P = 0.04$), and SHBG levels (SMD 0.46; 95% CI, 0.08, 0.85; $P = 0.01$).

Probiotic supplementation had no significant effect on total cholesterol (SMD − 0.26; 95% CI, − 0.67, 0.15; $P = 0.22$), LDL-cholesterol (SMD − 0.12; 95% CI, − 0.66, 0.42; $P = 0.66$), HDL-cholesterol (SMD 0.04; 95% CI, − 0.25, 0.33; $P = 0.79$), and DHEAS levels (SMD 0.06; 95% CI, − 0.77, 0.89; $P = 0.88$).

Subgroup and Sensitivity Analysis

According to existence heterogeneity, subgroup analyses were conducted based on potential suspected variables including, type of interventions (synbiotic vs. probiotic

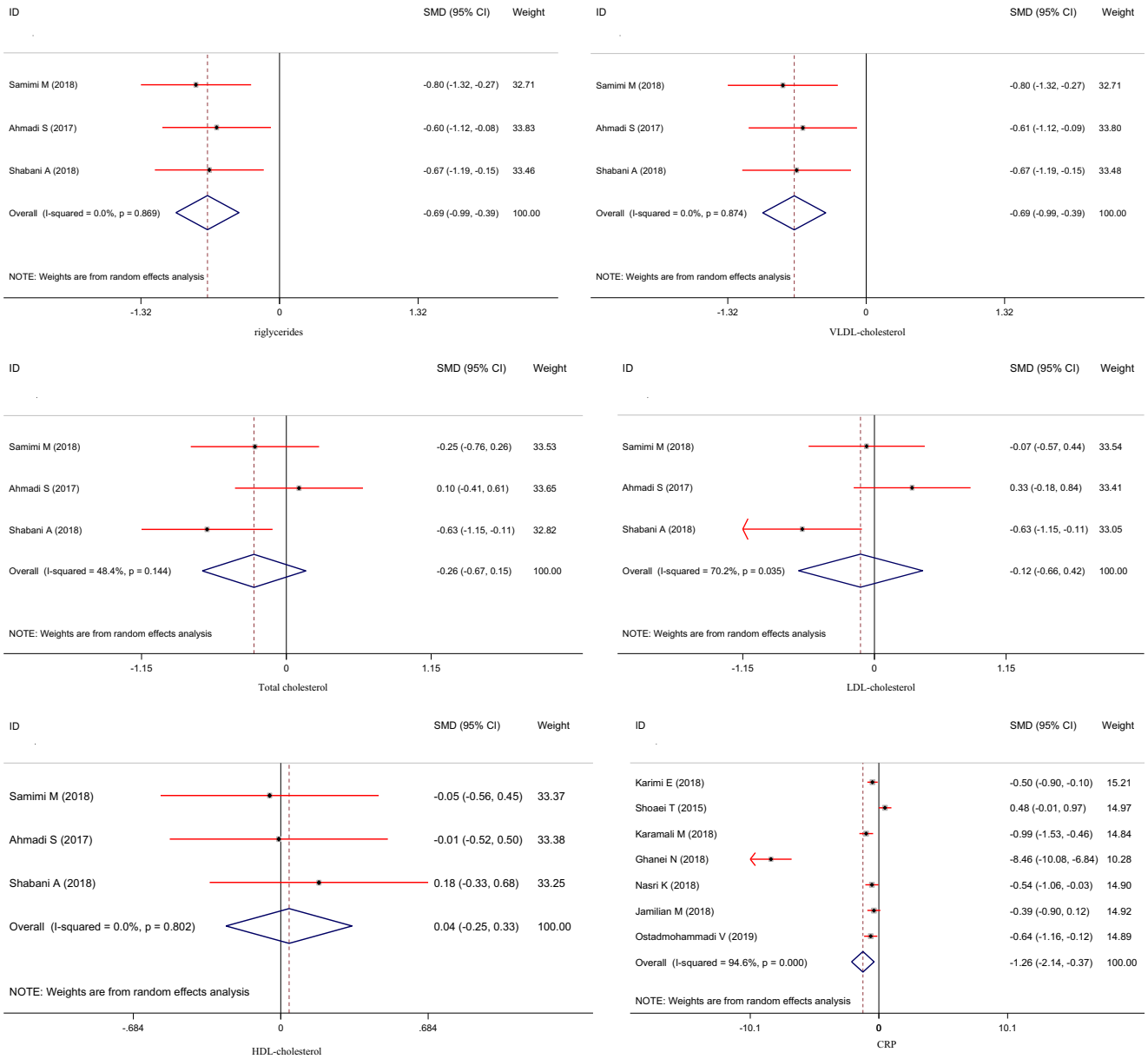


Fig. 3 (continued)

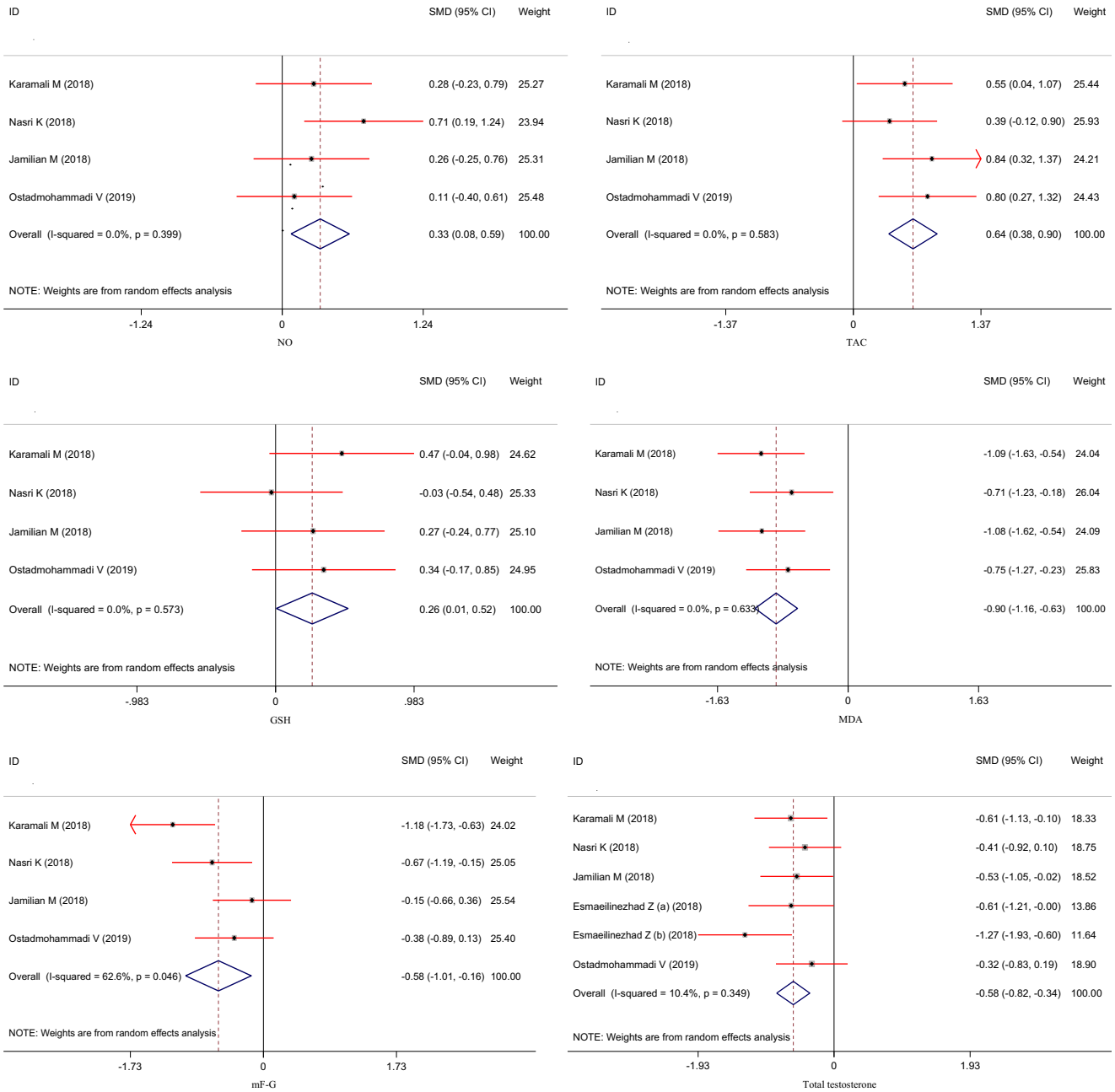
capsule) and duration of the intervention (< 12 weeks vs. ≥ 12 weeks) (Table 3).

Sensitivity analyses were conducted and the results remained consistent with the pooled effect for the effect of probiotic supplementation on weight, FPG, insulin, HOMA-IR, QUICKI, triglycerides, VLDL-cholesterol, LDL-cholesterol, HDL-cholesterol, CRP, TAC, MDA, mf-G, total testosterone, and DHEAS levels. In sensitivity analysis, we found significant difference between the pre- and post-sensitivity analysis for BMI after omitting Shabani et al. [17] study (SMD − 0.19; 95% CI, − 0.41, 0.01), total cholesterol after omitting Ahmadi et al. [14] study (SMD − 0.43; 95% CI, − 0.80, − 0.06), for NO after omitting Nasri et al. [16] study (SMD 0.21; 95% CI, − 0.08, 0.50), for GSH after omitting Karamali et al. [15] study (SMD 0.19; 95% CI, − 0.10, 0.48), and for SHBG after omitting Karamali et al. [15] study (SMD 0.29; 95% CI, − 0.00, 0.58).

The lower and higher pooled SMDs in the sensitivity analyses for glucose metabolisms and CRP levels are summarized in Table 4.

Publication Bias

Results of Egger's test showed no evidence of significant publication bias for weight ($B = -4.40$, $P = 0.54$), BMI ($B = -4.53$,



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$P = 0.57$), FPG ($B = -1.43$, $P = 0.46$), QUIKI ($B = 6.17$, $P = 0.11$), total cholesterol ($B = -98.89$, $P = 0.24$), LDL-cholesterol ($B = -110.72$, $P = 0.44$), HDL-cholesterol ($B = 407.54$, $P = 0.15$), and GSH ($B = 130.86$, $P = 0.06$). There was evidence of publication bias on insulin ($B = -6.96$, $P = 0.04$), HOMA-IR ($B = -6.58$, $P = 0.03$), triglycerides ($B = -43.88$, $P = 0.02$), VLDL ($B = -43.71$, $P = 0.01$), CRP ($B = -12.49$, $P = 0.01$), NO ($B = 68.06$, $P = 0.01$), TAC ($B = 49.11$, $P < 0.001$), MDA ($B = -34.92$, $P < 0.001$), mF-G ($B = -44.38$, $P = 0.02$), total testosterone ($B = -8.52$, $P = 0.02$), and SHBG ($B = 53.80$, $P = 0.01$). The authors applied the non-parametric method (Duval and Tweedie) to estimate the results of censored trials. Findings showed that summary affected the size on profiles that had evidences of publication bias. No significant changes were noted between the pre- and post-intervention after including censored studies.

Discussion

To the authors' knowledge, this paper is the first meta-analysis of RCTs that has evaluated the effect of probiotic

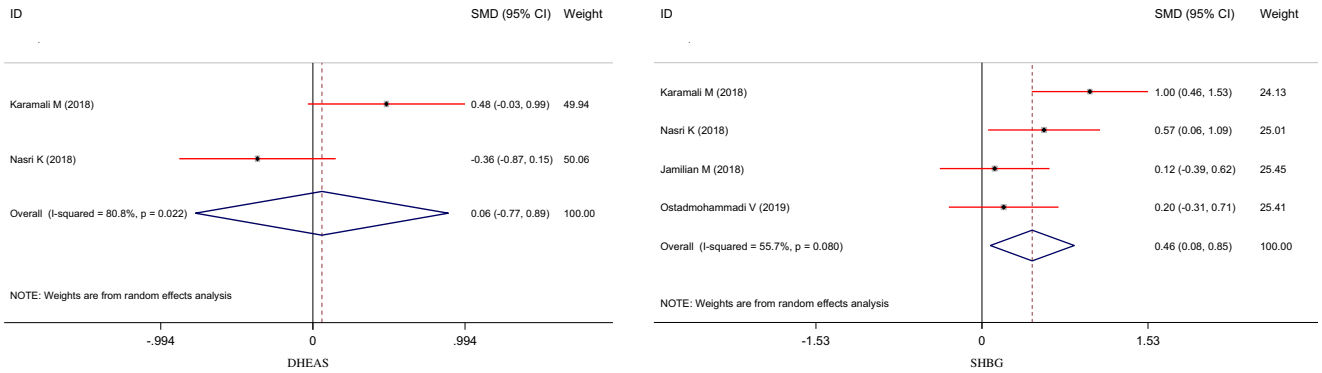

Fig. 3 (continued)

supplementation on glucose metabolism and CRP levels among patients with PCOS. The findings showed that probiotic supplementation may result in an improvement in weight, BMI, FPG, insulin, HOMA-IR, triglycerides, VLDL-cholesterol, CRP, MDA, hirsutism, total testosterone, QUICKI, NO, TAC, GSH, and SHBG but did not affect dehydroepiandrosterone sulfate levels, and total-, LDL-, and HDL-cholesterol levels in patients with PCOS.

The hypothesis that probiotics may be involved in maintenance of healthy gut microbiota, management of glycemic control, and can modulate inflammatory marker has received much attention recently. Two previous meta-analyses among patients with diabetes concluded that probiotics supplementation significantly decreased insulin resistance and HbA1c levels [21, 22]. In addition, a recent meta-analysis, with 11 RCTs and 614 subjects, demonstrated similar results [23]. They observed that probiotic administration to people with diabetes significantly decreased FPG, HbA1c, insulin, and HOMA-IR. In another meta-analysis of 12 RCTs with a total population of 684 patients with diabetes, probiotic administration was associated with significant reductions in both HbA1c and insulin levels [24]. Insulin resistance plays an important role in approximately 70–80% of obese women and in 15–30% of lean women diagnosed with PCOS [1], and represents the pathogenic association between metabolic and reproductive status in PCOS. Moreover, the decrease in insulin sensitivity has been attributed to post-receptor changes in intracellular signaling pathways of insulin occurring in women with PCOS [25]. It must be kept in mind that in the current meta-analysis study, insulin and QUICKI remained unchanged and is opposing to the current study's hypothesis. This may have occurred for a few different reasons. The shorter duration of the intervention might be one possible explanation for the observed discrepancy. Most of the included RCTs were performed between 8 and 12 weeks, which is far shorter than those observational studies conducted with patients diagnosed with other metabolic diseases. Longer duration of RCTs is required to obtain a more reliable conclusion. Additionally, the absence of significant effect on insulin and QUICKI in Asians participants may have attributed to the included PCOS subjects in RCTs. The subjects recruited in the observational studies had different baseline insulin levels and QUICKI. Thus, it was assumed that early intervention with probiotic supplementation among women with PCOS may be important as the beneficiary effect of probiotic on insulin and QUICKI may increase, when individuals have longer supplementation duration and similar baseline levels of insulin and QUICKI. Probiotics may improve the glycemic control through modulating reducing inflammatory cytokines [26] and upregulation in the expression of peroxisome proliferator-activated receptor gamma gene [27, 28].

We found that probiotic supplementation among patients with PCOS did not affect CRP levels. CRP is an important inflammatory factor for patients with diabetes and other metabolic disorders progression and complications [29]. A previous meta-analysis also reported non-significant effects of probiotics on CRP concentrations in people with T2DM [24]. In a meta-analysis conducted among people with T2DM, no significant effects were observed by probiotics supplementation on CRP [21]. In another meta-analysis, probiotic supplementation was given to colorectal cancer patients and CRP levels significantly decreased CRP [30]. Overall, in addition to those findings above, different study designs, sample size, different dosages of probiotic and/or synbiotic used, the use of various probiotic preparations and differences in strain-specific efficacy [31–33] along with characteristics of study participants might explain the discrepancies among the different studies. These results suggested that although probiotics have an important function in intestinal immunological modulation [34], the evidence for an effect on CRP concentrations in patients with PCOS is scarce. Alteration in microbial composition and diversity of the human gastrointestinal tract is considered essential for improvement in metabolic disorders, oxidative stress, inflammation, and proliferation [35]. The intestinal

Table 3 The effects of probiotic supplementation on weight loss, glycemic control, lipid and hormonal profiles, and biomarkers of inflammation and oxidative stress with CI 95% between based on subgroup analysis

Variable		Number of SMD included	Subgroups	Pooled effect estimate	95% CI	I^2 (%)	Overall I^2 (%)
BMI	Type of intervention	4	Synbiotic capsule	− 0.03	− 0.30, 0.25	0.0	50.7
		5	Probiotic capsule	− 0.47	− 0.79, − 0.14	48.6	
	Duration of study (week)	7	≥ 12 weeks	− 0.29	− 0.61, 0.02	62.5	
		2	< 12 weeks	− 0.26	− 0.68, 0.17	0.0	
Insulin	Type of intervention	4	Synbiotic capsule	− 0.50	− 0.93, − 0.06	63.5	52.2
		3	Probiotic capsule	− 0.57	− 0.98, − 0.16	47.5	
	Duration of study (week)	4	≥ 12 weeks	− 0.58	− 1.03, − 0.13	70.5	
		3	< 12 weeks	− 0.44	− 0.78, − 0.09	11.5	
QUICKI	Type of intervention	4	Synbiotic capsule	0.44	− 0.05, 0.92	70.2	55.5
		3	Probiotic capsule	0.38	0.01, 0.77	41.3	
	Duration of study (week)	4	≥ 12 weeks	0.48	0.06, 0.90	66.1	
		3	< 12 weeks	0.30	− 0.17, 0.77	51.2	
LDL-cholesterol	Type of intervention	1	Synbiotic capsule	− 0.07	− 0.57, 0.44	–	70.2
		2	Probiotic capsule	− 0.15	− 1.09, 0.79	85.0	
	Duration of study (week)	3	≥ 12 weeks	− 0.12	− 0.66, 0.42	70.2	
		–	< 12 weeks	–	–	–	
CRP	Type of intervention	2	Synbiotic capsule	− 0.52	− 0.83, − 0.20	0.0	94.6
		5	Probiotic capsule	− 1.73	− 3.13, − 0.33	96.4	
	Duration of study (week)	6	≥ 12 weeks	− 1.57	− 2.54, − 0.60	94.6	
		1	< 12 weeks	0.48	− 0.01, 0.97	–	
mF-G	Type of intervention	1	Synbiotic capsule	− 0.67	− 1.19, − 0.15	–	62.6
		3	Probiotic capsule	− 0.56	− 1.16, 0.04	74.5	
	Duration of study (week)	4	≥ 12 weeks	− 0.58	− 1.01, − 0.16	62.6	
		–	< 12 weeks	–	–	–	

BMI, body max index; *QUICKI*, quantitative insulin sensitivity check index; *LDL-cholesterol*, low-density lipoprotein; *CRP*, C-reactive protein; *mF-G*, modified ferriman-gallwey

microbiota can be modulated by several factors including, surgery, aging, environmental exposures, radiation, medicines, lifestyle, diet, and host genetic background [36]. Another important way of modulating the intestinal microbiota is probiotics supplementation. Modifications to the microbial community can prevent or treat various gastrointestinal disorders such as irritable bowel syndrome and inflammatory bowel disease [37], as well as systemic diseases such as eczema [38], respiratory infections [39], asthma [40], and diabetes [23]. Probiotics intake may change gut dysbiosis by the several effects such as reducing microbial genotoxicity, altering the metabolites produced by the microbiota, competing with the pathogenic bacteria, increasing the intestinal barrier, and increasing the innate immune response [41, 42]. Therefore, microbiota changed following probiotic supplementation can promote the intestinal homeostasis and regulate metabolic disorders, as well as inflammatory responses.

The current meta-analysis had a few limitations. There were few eligible RCTs and most of them had a modest

Table 4 The assess of contribution one by one trials in association between probiotic supplementation and weight loss, glycemic control, lipid and hormonal profiles, and biomarkers of inflammation and oxidative stress using sensitivity analysis

Variable	Pre-sensitivity analysis			Upper and lower of effect size	Post-sensitivity analysis		
	No. of studies included	Pooled SMD (random effect)	95% CI		Pooled SMD (random effect)	95% CI	Excluded studies
Weight	9	− 0.30	− 0.53, − 0.07	Upper	− 0.21	− 0.40, − 0.02	Shabani
				Lower	− 0.34	− 0.53, − 0.16	Nasri
BMI	9	− 0.29	− 0.54, − 0.03	Upper	− 0.19	− 0.41, 0.01	Shabani
				Lower	− 0.35	− 0.59, − 0.12	Nasri
FPG	7	− 0.26	− 0.45, − 0.07	Upper	− 0.21	− 0.41, − 0.01	Ahmadi
				Lower	− 0.30	− 0.52, − 0.08	Karimi
Insulin	7	− 0.52	− 0.81, − 0.24	Upper	− 0.45	− 0.75, − 0.16	Shabani
				Lower	− 0.62	− 0.85, − 0.39	Karimi
HOMA-IR	7	− 0.53	− 0.79, − 0.26	Upper	− 0.47	− 0.74, − 0.19	Samimi
				Lower	− 0.62	− 0.84, − 0.40	Karimi
QUICKI	7	0.41	0.11, 0.70	Upper	0.49	0.20, 0.78	Karimi
				Lower	0.32	0.03, 0.60	Samimi
Triglycerides	3	− 0.69	− 0.99, − 0.39	Upper	− 0.63	− 1.00, − 0.26	Samimi
				Lower	− 0.73	− 1.10, − 0.36	Ahmadi
VLDL-cholesterol	3	− 0.69	− 0.99, − 0.39	Upper	− 0.63	− 1.00, − 0.26	Samimi
				Lower	− 0.73	− 1.10, − 0.36	Ahmadi
Total cholesterol	3	− 0.26	− 0.67, 0.15	Upper	− 0.07	− 0.43, 0.28	Shabani
				Lower	− 0.43	− 0.80, − 0.06	Ahmadi
LDL-cholesterol	3	− 0.12	− 0.66, 0.42	Upper	0.12	− 0.25, 0.51	Shabani
				Lower	− 0.34	− 0.89, 0.20	Ahmadi
HDL-cholesterol	3	0.04	− 0.25, 0.33	Upper	0.08	− 0.27, 0.44	Samimi
				Lower	− 0.03	− 0.38, 0.32	Shabani
CRP	7	− 1.26	− 2.14, − 0.37	Upper	− 0.42	− 0.81, − 0.04	Ghanei
				Lower	− 1.56	− 2.53, − 0.59	Shoaei
NO	4	0.33	0.08, 0.59	Upper	0.41	0.11, 0.70	Ostadmohammadi
				Lower	0.21	− 0.08, 0.50	Nasri
TAC	4	0.64	0.38, 0.90	Upper	0.72	0.42, 1.03	Nasri
				Lower	0.57	0.27, 0.87	Jamilian
GSH	4	0.26	0.01, 0.52	Upper	0.35	0.06, 0.65	Nasri
				Lower	0.19	− 0.10, 0.48	Karamali
MDA	4	− 0.90	− 1.16, − 0.63	Upper	− 0.83	− 1.14, − 0.53	Karamali

Table 4 (continued)

Variable	Pre-sensitivity analysis			Upper and lower of effect size	Post-sensitivity analysis		
	No. of studies included	Pooled SMD (random effect)	95% CI		Pooled SMD (random effect)	95% CI	Excluded studies
				Lower	− 0.96	− 1.27, − 0.65	Nasri
mF-G	4	− 0.58	− 1.01, − 0.16	Upper	− 0.39	− 0.68, − 0.09	Karamali
				Lower	− 0.73	− 1.18, − 0.27	Jamilian
Total testosterone	6	− 0.58	− 0.82, − 0.34	Upper	− 0.48	− 0.72, − 0.25	Esmaeilinezhad (b)
				Lower	− 0.63	− 0.89, − 0.38	Ostadmohammadi
DHEAS	2	0.06	− 0.77, 0.89	Upper	0.48	− 0.03, 0.99	Nasri
				Lower	− 0.36	− 0.87, 0.14	Karamali
SHBG	4	0.46	0.08, 0.85	Upper	0.58	0.13, 1.03	Jamilian
				Lower	0.29	− 0.00, 0.58	Karamali

BMI, body max index; *FPG*, fasting plasma glucose; *HOMA-IR*, homeostatic model assessment for insulin resistance; *QUICKI*, quantitative insulin sensitivity check index; *VLDL-cholesterol*, very-low-density lipoprotein-cholesterol; *LDL-cholesterol*, low-density lipoprotein; *HDL-cholesterol*, high-density lipoprotein; *CRP*, C-reactive protein; *NO*, nitric oxide; *TAC*, total antioxidant capacity; *GSH*, glutathione; *MDA*, malondialdehyde; *mF-G*, modified ferriman-gallwey; *DHEAS*, dehydroepiandrosterone sulfate; *SHBG*, sex hormone binding globulin

number of participants. The dose response association between supplementation dose, glycemic control, and inflammatory markers was unable to be evaluated due to the low number of studies included. The number of studies evaluating lipid profiles and inflammatory cytokines in women with PCOS were low. Therefore, we did not analyze these variables in the current meta-analysis. Inflammatory cytokines are signals in the intestinal immune system, contributing to the understanding of gut inflammation status, which would affect the overall condition of inflammation among women with PCOS. It would be interested to assess gut microbiome changes by probiotic treatment. Unfortunately, we were unable to examine the gut microbiome changes following probiotic supplementation as a treatment option, because none of the studies evaluated that.

Conclusions

Probiotic supplementation may result in an improvement in weight, BMI, FPG, insulin, HOMA-IR, triglycerides, VLDL-cholesterol, CRP, MDA, hirsutism, total testosterone, QUICKI, NO, TAC, GSH, and SHBG, but did not affect dehydroepiandrosterone sulfate levels, and total-, LDL-, and HDL-cholesterol levels in patients with PCOS.

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Compliance with Ethics Requirements

Conflict of Interest The authors declare that they have no conflict of interest.

For Studies with Human Subjects All procedures utilized in the selected papers were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Authors of the selected papers obtained informed consent from all patients for being included in their studies.

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