Effect of Diet on Insulin Resistance in Polycystic Ovary Syndrome

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Objective: The effect of diet on insulin resistance (IR) in polycystic ovary syndrome (PCOS) is controversial. Thus, we conducted this systematic review and meta-analysis to evaluate whether diet could reduce IR in women with PCOS while providing optimal and precise nutrition advice for clinical practice.

Design: The search was conducted in 8 databases through June 30, 2019. The systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. A random-effects model was adopted to calculate the overall effects.

Results: A total of 19 trials (1193 participants) were included. The analysis showed that diet was significantly related to improvements in IR and body composition (eg, homeostasis model assessment of insulin resistance, fasting insulin, fasting plasma glucose, body mass index [BMI], weight, and waist circumference) in PCOS patients. The Dietary Approaches to Stop Hypertension diet and calorie-restricted diets might be the optimal choices for reducing IR and improving body composition, respectively, in the PCOS population. Additionally, the effects were associated with the course of treatment. The longer the duration, the greater the improvement was. Compared with metformin, diet was also advantageous for weight loss (including BMI and weight) and had the same effects on insulin regulation.

Conclusion: Overall, our findings suggest that diet is an effective, acceptable and safe intervention for relieving IR, and professional dietary advice should be offered to all PCOS patients. **(*J Clin Endocrinol Metab* 105: 3346–3360, 2020)**

Key Words: diet, polycystic ovary syndrome, insulin resistance, weight loss

Polycystic ovary syndrome (PCOS), characterized by irregular menstruation, infertility, hirsutism and polycystic ovarian morphology (PCOM), is one of the most common endocrine disorders in women of reproductive age and is prone to increased risks of complications, such as diabetes, cardiovascular diseases, and endometrial cancer, in the long term (1-3). The prevalence ranges from 6% to 21%, depending on the population studied and diagnostic criteria used (4, 5). Although the causes of PCOS have not yet been fully defined, insulin resistance (IR) has been indicated as a key etiological component (6). IR is associated with decreased insulin sensitivity of body tissues caused by anomalous molecular structure, abnormal function and signaling of insulin receptors, or excessive levels of insulin-binding antibodies. Overweight and obesity

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Abbreviations: BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension; FINS, fasting insulin; FPG, fasting plasma glucose; GI, glycemic index; HOMA-IR, homeostasis model assessment of insulin resistance; IR, insulin resistance; MD, mean difference; PCOM, polycystic ovarian morphology; PCOS, polycystic ovary syndrome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT, randomized controlled trial; SMD, standardized mean difference; WC, waist circumference; WHR, waist–hip ratio.

can worsen IR and features of metabolic syndrome (7), which is also a common finding in PCOS (8). With the increased rates of weight gain and prevalence of excess weight in women with PCOS (up to 88%) (9, 10), IR is further exacerbated, which adversely affects the condition and poses a major public health challenge mandating both prevention and treatment.

Several interventions (pharmacological, nonpharmacological, or surgical) have been assessed to target complex outcomes associated with the condition. Metformin, an insulin sensitizer, has been extensively used in PCOS patients with IR. It works by decreasing gluconeogenesis and lipogenesis and enhancing glucose uptake in the liver, skeletal muscle, adipose tissue, and ovaries (11). Side effects, primarily gastrointestinal, are common, and long-term use may cause vitamin B12 deficiency (11). However, the efficacy of metformin in terms of improving clinical outcomes remains uncertain (12). Considering recurrent symptoms after drug withdrawal, as well as side effects, it is not the first choice for treatment in the long term. Physical activity, as a part of lifestyle intervention, has also been recommended for managing the signs and symptoms of PCOS (13). Although structured exercise can deliver well-established benefits to women with PCOS in metabolism, physique, and psychology, due to general (such as lack of time, fatigue, weather, family matters) and PCOS-specific (social physique anxiety, appearance evaluation, depression) barriers (14, 15), most populations tend to remain inactive. Therefore, optimal management strategies with more safety and acceptability are needed.

Women with PCOS often have coexisting IR. Overall, 75% of lean women and 95% of obese women with PCOS have IR (16). In recent years, the role of diet in IR has become a focus in both reproductive and endocrine research. Emerging evidence has suggested that well-adjusted, balanced diets, such as the Dietary Approaches to Stop Hypertension (DASH) diet, the Mediterranean diet, low-glycemic index (GI) diets, and vegetarian diets, are beneficial for ameliorating IR, regulating metabolism, controlling body weight, and preventing future related complications (17-20). The International Evidence-based Guideline for the Assessment and Management of PCOS also emphasized the importance of diet in PCOS and recommended dietary and exercise interventions as the first-line management for women with PCOS, mostly overweight and obese patients (21). However, despite the general recommendations, there is a lack of specific clinical application, as patients with PCOS seem reluctant to follow the recommendations on diet and exercise (22) and they are not willing to adopt self-help methods (23). The main barrier is that PCOS patients have limited access to professional nutrition treatment due to inadequate knowledge of current nutrition care for this population. Hence, we conducted this systematic review and meta-analysis of randomized controlled trials (RCTs) to define the association of diet with IR in PCOS and provide precise and targeted nutrition suggestions. Given the adverse effects of obesity on IR, especially visceral adiposity, we assessed not only homeostasis model assessment of insulin resistance (HOMA-IR), fasting insulin (FINS), and fasting plasma glucose (FPG) but also body composition outcomes, including body mass index (BMI), weight, waist circumference (WC), and waist–hip ratio (WHR).

Materials and Methods

This systematic review was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (24) and has been registered in the International prospective register of systematic reviews (PROSPERO) under the number CRD42019140454.

Data sources and searches

Databases such as the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE, Web of Science, Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), VIP information database, and Wanfang Data were searched from inception to June 30, 2019. We also checked reference lists and conference proceedings manually to obtain additional relevant data. No restrictions were imposed on language or publication date. The details of the search strategy in PubMed are as follows:

1. diet [MeSH] OR diet [Title/Abstract] OR food [MeSH] OR food [Title/Abstract] OR feeding behavior [MeSH] OR dietary pattern [Title/Abstract] OR feeding pattern [Title/Abstract] OR eating behavior [Title/Abstract] OR food selection [Title/Abstract] OR dietary habit [Title/Abstract] OR dietary approach [Title/Abstract] OR food habit [Title/Abstract] OR eating habit [Title/Abstract] OR diet habit[Title/Abstract] OR lifestyle[Title/Abstract]
2. Polycystic Ovary Syndrome [MeSH] 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 Polycystic Ovary Syndrome [Title/Abstract] OR Sclerocystic Ovaries [Title/Abstract] OR Ovary, Sclerocystic [Title/Abstract] OR Sclerocystic Ovary[Title/Abstract] OR Polycystic ovary syndrome [Title/Abstract]
3. random* [tw]
4. (#1 AND #2 AND #3)

Selection criteria

Two review authors undertook the study selection independently following the eligibility and exclusion criteria described previously. Studies that met the following inclusion criteria were included: (1) parallel controlled RCTs, (2) evaluation of the effects of diet on IR, (3) women with a clear diagnosis of PCOS, (4) studies with exercise/medication as a cointervention in both intervention/control arms were also considered, and (5) the outcomes should refer to the following aspects: HOMA-IR, FINS, FPG, BMI, WC, WHR, and weight. The exclusion criteria were as follows: (1) quasi-randomized trials, cohort or case-control studies, reviews, meta-analyses, case reports, animal or cell experiments, (2) women with other causes for hyperandrogenism and abnormal ovulation, or any serious medical, psychiatric, or neurological problems, (3) interventions focusing on single dietary components (eg, vitamins, calcium), and (4) studies with unavailable data and unreported target outcomes.

Titles and abstracts of all potential studies were scanned to eliminate duplicated and ineligible studies. When the information was insufficient to make a decision, we sought further details from the original authors. Any discrepancies were resolved by discussion or consensus with the corresponding author.

Data extraction

Two reviewers performed data extraction independently. Data were cross-checked to minimize potential errors, and disagreements were handled through discussion with the corresponding author. The following information was extracted from the included trials: (1) study characteristics, including first author, year of publication, and location; (2) participants, including sample size and diagnostic criteria for PCOS; (3) interventions, including dietary protocols, frequency, and duration of treatment; and (4) outcome data at baseline and follow-up.

Assessment of risk of bias in included studies

Two authors assessed the methodological quality of eligible trials via a Cochrane Collaboration tool. Studies were evaluated as low, unclear risk, or high bias based on the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. We judged studies with data loss over 20% as having a high risk of attrition bias. If ≥1 feature was unclear, the risk of bias was unclear. If ≥1 feature was negative, the study was allocated a high risk of bias (25).

Data synthesis and statistics

Statistical analysis was performed by Review Manager 5.3 in accordance with the guidelines described in the Cochrane Handbook for Systematic Reviews of Interventions (26). For dichotomous data, the results were expressed as RR with 95% confidence intervals. For continuous data, the results were pooled for meta-analysis as the mean difference (MD) with 95% confidence intervals if all studies reported the same scales. When data were reported on different methods or scales, the standardized mean difference (SMD) was calculated. $P < .05$ represented statistical significance. The random-effects method was preferred for calculating summary effect measures since clinical heterogeneity was inevitable. Statistical heterogeneity within comparisons was evaluated by Cochran's Q test and quantified by the I-squared (I^2) statistic. I^2 values <50% were deemed moderate, those 50% to 75% were deemed substantial, and those >75% were deemed considerable heterogeneity (27). Subgroups were analyzed when there were more than three studies and were categorized according to the type of dietary interventions and intervention duration (≤12 weeks or >12 weeks). To assess the robustness of the evidence, we conducted a sensitivity analysis by restricting studies to those deemed at low risk of bias. Egger's test and funnel plots were generated to investigate the potential publication bias when there were more than ten trials included in the analysis; otherwise, the power of tests would be too low to distinguish chance from real asymmetry.

Results

Study selection and characteristics

A total of 447 studies were identified by the preliminary search, and 5 additional studies were found by checking the reference lists and review articles manually. After removing 148 duplicated studies, 304 records were assessed by screening titles and abstracts. Among them, 227 items were excluded due to apparent ineligibility, such as meta-analyses, reviews, case reports, and animal or cell experiments. Seventy-seven articles were selected for full-text revision, and 58 of these were excluded for the following reasons: (1) inappropriate study design (n = 18), (2) inappropriate outcome reported (n = 9), (3) participants without PCOS (n = 20), (4) inability to obtain the full text (n = 8), and (5) lack of suitability for meta-analysis (n = 3). Only 1 trial (reported in 3 articles) conducted in Sweden comparing diet with exercise (28-30), due to limited number and small sample size (n = 38), was not included in the meta-analysis. Finally, 19 RCTs (1193 participants) were eligible for meta-analysis. Details of the selection process are shown in a PRISMA flow diagram (Fig. 1).

The general characteristics of the included studies are outlined in Table 1. Except for the trial conducted by Gower et al. (crossover study) (36), all of them were parallel-design and single-center RCTs conducted in China (40, 43-45, 48, 49), Iran (34, 37, 38, 41, 42, 47), the United States (32, 36), Australia (31, 33), Denmark (35), Egypt (39), and Jordan (46) between 2003 and 2017. A total of 1193 women with a clear diagnosis of PCOS were included in the analysis: 11 trials under the Rotterdam Consensus (35, 37, 38, 41-43, 45-49), 6 trials following NIH (National Institutes of Health) diagnostic criteria (31-34, 36, 39), and 2 trials confirmed by the China Medical Association diagnostic criteria (40, 44). Two trials explicitly focused on obesity (BMI ≥ 30 kg/m^2) (31, 39), 12 trials assessed overweight and obese participants (BMI ≥ 25 kg/m^2)

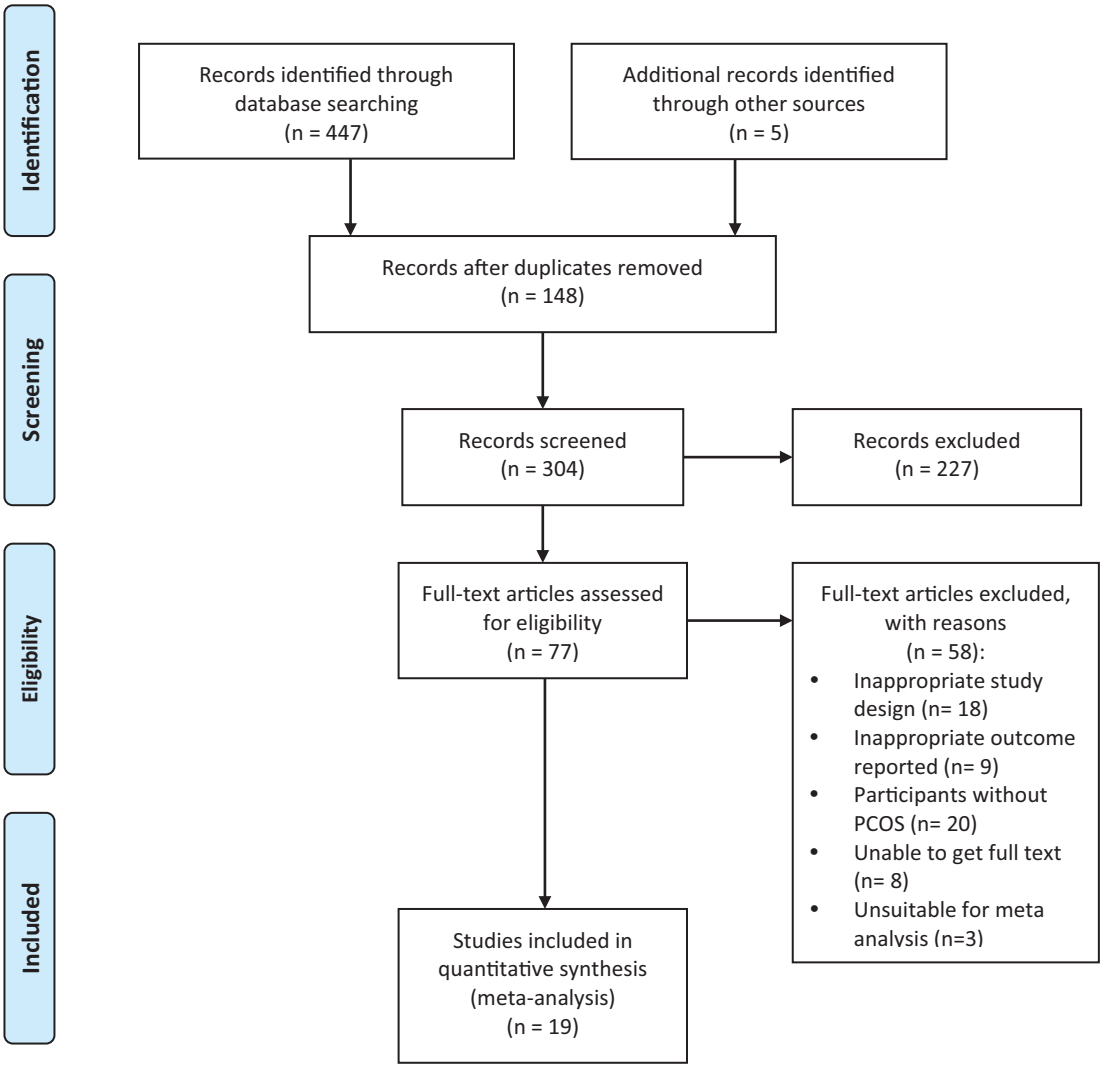

Figure 1. PRISMA flow diagram of studies included in the meta-analysis.

(32-34, 36-38, 41-43, 45-47), while the other 5 did not consider obesity as an inclusion criterion (35, 40, 44, 48, 49). Fifteen trials compared dietary changes with advice, no treatment, or usual diet (31-45), and 4 with metformin (46-49). Regarding dietary patterns, 10 trials evaluated low-carbohydrate diets (31-36, 40, 44, 45, 49); 4 trials evaluated the DASH diet (37, 38, 41, 42); 3 trials evaluated calorie-restricted diets (39, 46, 47); and the remaining 2 evaluated a low-fat diet (48) and a Mediterranean diet (43). The course of interventions ranged from 4 weeks to 1 year. The majority had a short duration (≤12 weeks), and 1 trial by Li lasted for 1 year (44).

Risk of bias assessment

Fourteen studies reported randomization methods in detail (31-35, 37-39, 41, 42, 45-48), with only 1 explaining the allocation concealment (42). Although blinding was performed in 5 trials (34, 37, 38, 41, 42), the outcomes were less prone to be affected, since they were all objective figures detected by machines. Two trials (35, 37) applied the intention-to-treat principle in statistical analysis, and 4 trials were judged as high risk due to the high attrition rate (more than 20%) across intervention groups (31-33, 47). Four trials mentioning trial registration (37, 38, 41, 42) were considered to have a low risk of reporting bias (Fig. 2).

Effects of interventions: diet versus minimal intervention

Fifteen studies with 853 participants compared dietary interventions with advice, usual diets, or no treatment (31-45). A random-effects model was used for statistical analysis due to clinical heterogeneity (Fig. 3). Subgroup analyses were performed by the dietary patterns and treatment duration (all supplementary material and figures are located in a digital research materials repository (50)).

Table 1. Characteristics of trials included in the meta-analysis

First author year (ref)	Country	Diagnostic criteria	Sample size (n)	Intervention arm	Control arm	Duration (month)	Outcomes
Diet versus minimal interventions							
Moran 2003 (31)	Australia	NIH	LCD: 23 C: 22	LCD: 40% carbohydrates, 30% protein and 30% fat (energy restriction (≤6000 kJ/day) for the first 12 wk)	Control: 55% carbohydrates, 15% protein and 30% fat (≤6000 kJ/day) for the first 12 wk)	4	FINS, FPG, weight
Stamets 2004 (32)	USA	NIH	LCD: 17 C: 18	LCD: 40% carbohydrates, 30% protein and 30% fat (1000 kcal/d energy deficit)	Control: 55% carbohydrates, 15% protein and 30% fat (1000 kcal/d energy deficit)	1	WC, WHR, weight
Moran 2010 (33)	Australia	NIH	LCD: 24 C: 22	LCD: 43% carbohydrates, 27% protein and 28% fat (energy restriction (≤6000 kJ/day) for the first 12 wk)	Control: 57% carbohydrates, 16% protein and 27% fat (≤6000 kJ/day) for the first 12 wk)	4	FINS, FPG, BMI, weight
Mehrabani 2012 (34)	Iran	NIH	LCD: 30 C: 30	LCD: 40% low and medium glycemic carbohydrates, 30% protein and 30% fat (500–1000 kcal/d energy deficit depending on BMI)	Control: 55% carbohydrates, 15% protein and 30% fat (500–1000 kcal/d energy deficit depending on BMI)	3	HOMA-IR, FINS, WC, weight
Sørensen 2012 (35)	Denmark	Rotterdam	LCD: 29 C: 28	LCD: 30% carbohydrates, 40% protein and 30% fat	Control: 57% carbohydrates, 16% protein and 27% fat	6	FPG, BMI, WC, WHR, weight
Gower 2013 (36)	USA	NIH	LCD: 30 C: 30	LCD: 41% carbohydrate, 19% protein and 40% fat (GI: 50)	Control: 55% carbohydrates, 18% protein and 27% fat (GI: 60)	2	HOMA-IR, FINS, FPG
Asemi 2014 (37)	Iran	Rotterdam	DASH: 27 C: 27	DASH: 52% carbohydrates, 18% proteins, and 30% total fats; rich in fruits, vegetables, whole grains, low-fat dairy products and low in saturated fats, cholesterol, refined grains, and sweets, with sodium was less than 2400 mg/day (calorie-restricted 350-700 kcal depending on BMI)	Control: 52% carbohydrates, 18% protein, and 30% total fat. The macronutrient composition was designed based on Iranian traditional dietary patterns	2	BMI, weight
Asemi 2015 (38)	Iran	Rotterdam	DASH: 27 C: 27	DASH: 52% carbohydrates, 18% proteins, and 30% total fats; rich in fruits, vegetables, whole grains, low-fat dairy products, and low in saturated fats, cholesterol, refined grains and sweets, with sodium less than 2400 mg/day (calorie-restricted: 350-700 kcal depending on BMI)	Control: 52% carbohydrates, 18% protein, and 30% total fat. The macronutrient composition was designed based on Iranian traditional dietary patterns (calorie-restricted:350–700 kcal depending on BMI)	2	HOMA-IR, FINS, FPG, BMI, weight
Marzouk 2015 (39)	Egypt	NIH	CRD: 30 C: 30	CRD: daily caloric intake reduced by 500 kcal/d; 50-55% carbohydrates (low GI), 15%-20% protein and 30% fat	Followed the same healthy food of the intervention group without restriction in calories	6	BMI, WC, weight
Cheng 2016 (40)	China	CMA	LCD: 40 C: 40	LCD: <30% carbohydrates, ≥40% protein and 30% fat	General advice on a healthy diet	6	FINS, BMI, WC
Azadi 2017 (41)	Iran	Rotterdam	DASH: 30 C: 30	DASH: 50%-55% carbohydrate, 15-20% protein and 25-30% fat; rich in fruits, vegetables, whole grains, low-fat dairy products, and low in saturated fats, cholesterol, refined grains and sweets, with sodium less than 2400 mg/day (calorie restricted: 350-500 kcal depending on BMI)	Control:50%-55% carbohydrate, 15-20% protein and 25-30% fat (calorie-restricted: 350–500 kcal depending on BMI)	3	BMI, WC, WHR, weight

Table 1. Continued

First author year (ref)	Country	Diagnostic criteria	Sample size (n)	Intervention arm	Control arm	Duration (month)	Outcomes
Foroozanfard 2017 (42)	Iran	Rotterdam	DASH: 30 C: 30	DASH: 52-55% carbohydrate, 16-18% protein and 30% fat; rich in fruits, vegetables, whole grains, low-fat dairy products, and low in saturated fats, cholesterol, refined grains and sweets, with sodium less than 2400 mg/day (calorie restricted: 350-700 kcal depending on BMI)	Control: 52-55% carbohydrate, 16-18% protein and 30% fat. The macronutrient composition was designed based on Iranian traditional dietary patterns (calorie-restricted: 350–700 kcal depending on BMI)	3	HOMA-IR, FINS, FPG, BMI, weight
Xu 2017 (43)	China	Rotterdam	MD: 20 C: 20	Mediterranean diet: high intake of vegetables, legumes, fruits, nuts, cereals, and olive oil but a low intake of saturated lipids and meat, moderate intake of fish, low to moderate intake of dairy products, and regular but moderate intake of alcohol (usually wine)		3	BMI, weight
Li 2017 (44)	China	CMA	LCD: 39 C: 39	LCD: <30% carbohydrates, ≥40% protein and 30% fat		12	FINS, weight
Sun 2017 (45)	China	Rotterdam	LCD: 32 C: 32	a. LCD: weight loss period: approximately 50 g/d carbohydrates; weight maintain period: <40% carbohydrates; b. metformin: 1.5 g/d	Metformin: 1.5 g/d	3	HOMA-IR, FINS, FPG, BMI, WC, weight
Diet versus metformin							
Qublan 2007 (46)	Jordan	Rotterdam	CRD: 24 C: 22	CRD: caloric intake 1200-1400 kcal/d; 50% carbohydrates, 25% protein and 25% fat	Metformin: 850 mg, twice a day	6	FINS, FPG, BMI
Esfahanian 2013 (47)	Iran	Rotterdam	CRD: 20 C: 20	NR	Metformin: 1000 mg/day in divided doses and built gradually to 2000 mg/day	3	HOMA-IR, FINS, FPG, BMI, WC, WHR
Li 2017 (48)	China	Rotterdam	LF: 37 C: 38	LF: 50-65% carbohydrates, 18-33% protein and 8-14% fat; daily caloric intake reduced by 200 kcal/d	Metformin: 500 mg, twice or three times/day	3	HOMA-IR, FINS, FPG, BMI, WC, WHR, weight
Ge 2017 (49)	China	Rotterdam	LCD: 97 C: 82	a. LCD: weight loss period (BMI ≥25 kg/m^2): 20-25% carbohydrates, 18-33% protein and 8-14% fat; weight maintain period: 40-45% carbohydrates, 25–30% protein and 30% fat; b. fertility treatment	Fertility treatment	3	HOMA-IR, FINS, FPG, BMI, WHR, weight

Abbreviations: BMI, body mass index; CAM, China Medical Association diagnostic criteria (2011); CRD, calorie-restricted diet; C, control; FINS, fasting insulin; FPG, fasting plasma glucose; HOMA-IR, homeostatic assessment of insulin resistance; LCD, low-carbohydrate diet; LF, low-fat; MD, Mediterranean diet; NIH, National Institutes of Health diagnostic criteria(1990); NR, not reported; Rotterdam, European Society for Human Reproductive and Embryology/American Society for Reproductive Medicine diagnostic criteria (2003); TC, total cholesterol; TG, triglyceride; WC, waist circumference; WHR, waist-hip ratio.

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HOMA-IR. Five trials (266 participants) reported the effects of diet on HOMA-IR (34, 36, 38, 42, 45). The pooled data indicated a significant decrease in HOMA-IR among participants with dietary interventions (MD = –0.78, 95% CI –0.92 to –0.65; $P < .00001$; $I^2 = 24\%$) (Fig. 3). Subgroup analysis showed that the DASH diet brought more benefits compared with the low-carbohydrate diet (Table 2 and (50)).

FINS. Nine trials (500 participants) were identified (31, 33, 34, 36, 38, 40, 42, 44, 45). Overall analysis revealed that dietary interventions were superior in reducing FINS than other treatments (MD = –4.24 mIU/L, 95% CI –5.37 to –3.10 mIU/L; $P < .00001$; $I^2 = 80\%$) (Fig. 3). In subgroup analysis, we found that the effects might be associated with treatment time, as the reduction over a long duration was better than that over a short duration, indicating that the longer the duration, the greater the decrease in FINS. Regarding dietary patterns, the DASH diet was as effective as the low-carbohydrate diet (Table 2 and (50)).

FPG. Six studies (272 participants) examined the relationship between diet and changes in FPG (33, 35, 36, 38, 42, 45). Meta-analysis showed that dietary interventions led to a greater decrease than other interventions (MD = –0.11 mmol/L, 95% CI –0.17 to –0.04 mmol/L; $P = .002$; $I^2 = 0\%$) (Fig. 3). The results of subgroup analysis revealed that the DASH diet could significantly affect FPG, while the effects of the low-carbohydrate diet were uncertain. Notably, diet might work more quickly than other interventions, as data from trials showed a significant decrease within 12 weeks; however, the difference became nonsignificant when studies were restricted to a long duration (Table 2 and (50)).

BMI. In total, nine studies (450 participants) mentioned the changes in BMI (33, 35, 37-40, 42, 43, 45). Adherence to dietary treatment was found to reduce BMI more obviously (MD = –1.01 kg/m^2, 95% CI –1.38 to –0.64 kg/m^2; $P < .00001$; $I^2 = 54\%$) (Fig. 3). The subgroup analysis indicated that the calorie-restricted diet was more beneficial than other diet patterns, including the DASH diet, low-carbohydrate diet, and Mediterranean diet. The effects of diet on BMI seemed to concern the length of intervention time; however, no significant changes were found between groups (Table 2 and (50)).

Weight. Twelve trials with 557 participants in total were included in the analysis of WT (31-35, 37-39, 41-45). A significant difference was found between the diet and control groups (MD = –1.74 kg, 95% CI –2.42 to –1.05 kg; $P < .00001$; $I^2 = 59\%$) (Fig. 3). The pooled data of the subgroup analysis did not show significant differences when grouped by treatment duration, but there was a tendency to lose more weight over time. Classified by diet approaches, the results indicated that the calorie-restricted diet was more advantageous than other diet patterns, such as the DASH diet, low-carbohydrate diet, and Mediterranean diet (Table 2 and (50)).

WC. In total, 5 studies (227 participants) mentioned the changes in WC (32, 35, 39, 41, 45). Adherence to the diet treatment was found to have a significant overall effect on WC (MD = –3.25 cm, 95% CI –5.29 to 1.22 cm; $P = .002$; $I^2 = 41\%$) (Fig. 3). In addition to the DASH diet, calorie-restricted diets and low-carbohydrate diets significantly reduced the WC in PCOS patients. In addition, women with long durations showed greater reduction (Table 2 and (50)).

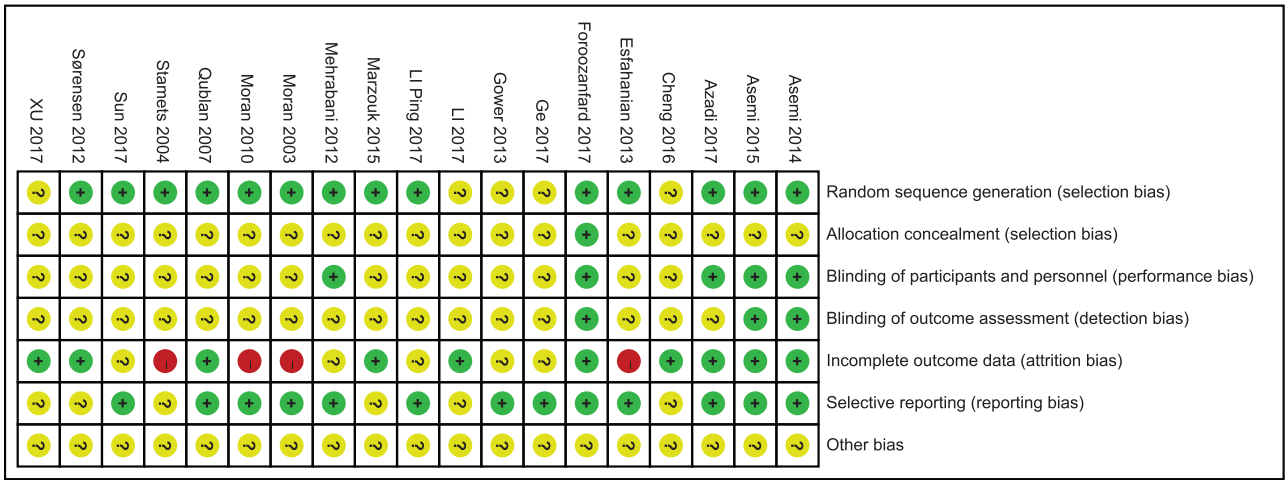

Figure 2. Risk of bias summary. Green: low risk of bias, yellow: unclear risk of bias, red: high risk of bias.

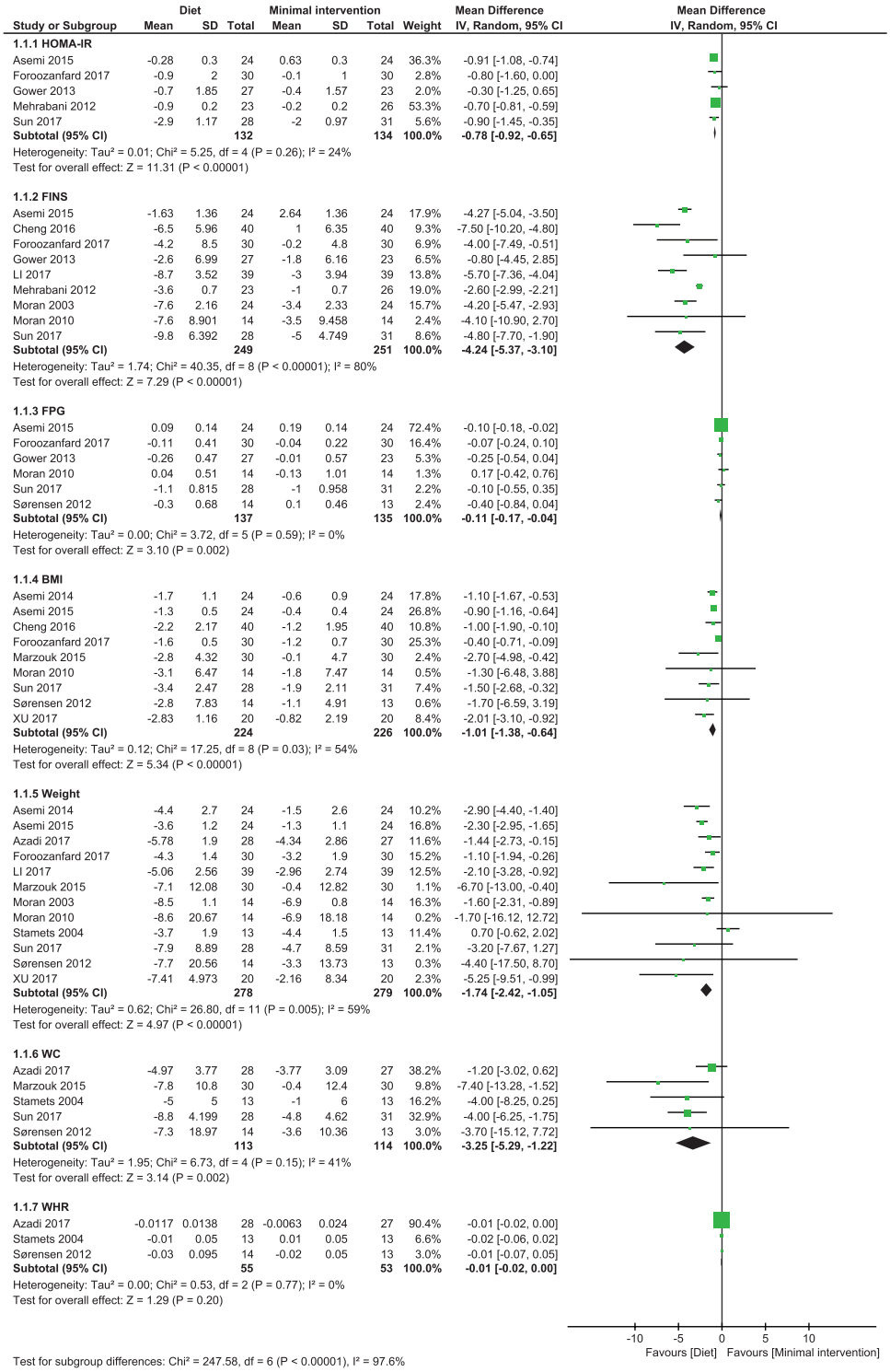

Figure 3. Forest plots of comparison between diet intervention and minimal treatment.

WHR. Three trials (108 participants) were involved in the analysis (32, 35, 41), and no significant changes were observed (MD = –0.01, 95% CI –0.02 to 0.00; $P = .20$; $I^2 = 0\%$) (Fig. 3).

Effects of interventions: diet versus metformin

Four studies with 340 participants compared dietary interventions with metformin (46-49), and the random-effects model was applied in the statistical analysis (Fig. 4). Subgroup analyses were performed by the dietary patterns and treatment duration (see (50)).

HOMA-IR. Three trials with 253 participants evaluated HOMA-IR between diet and metformin treatments (47-49). The pooled data showed no differences between

Table 2. Effect estimates and heterogeneity of subgroup analysis for outcomes (diet versus minimal intervention)

Outcome	Subgroup	Trial (n)	Sample size (n)	Effect estimate MD (95% CI)	I^2	*P*
HOMA-IR	**Diet type**					
	DASH diet	2	108	–0.91 (–1.07, –0.74)	0%	<.00001
	low-carbohydrate diet	3	158	–0.70 (–0.81, –0.59)	0%	<.00001
FINS (mIU/L)	**Diet type**					
	DASH	2	108	–4.26 (–5.01, –3.51)	0%	< .00001
	Low-carbohydrate diet	7	392	–4.29 (–5.83, –2.74)	81%	< .00001
	Intervention duration					
	≤12 weeks	5	266	–3.40 (–4.66, –2.13)	77%	< .00001
	>12 weeks	4	234	–5.37 (–6.86, –3.88)	46%	< .00001
FPG (mmol/L)	**Diet type**					
	DASH diet	2	108	–0.09 (–0.17, –0.02)	0%	.010
	Low-carbohydrate diet	4	164	–0.20 (–0.41, –0.00)	0%	.05
	Intervention duration					
	≤12 weeks	4	217	–0.10 (–0.17, –0.03)	0%	.003
	>12 weeks	2	55	–0.15 (–0.71, –0.40)	57%	.59
BMI (kg/m^2)	**Diet type**					
	DASH	3	156	–0.76 (–1.17, –0.36)	74%	.0002
	Low-carbohydrate diet	4	194	–1.20 (–1.90, –0.49)	0%	.0008
	Calorie-restricted diet	1	60	–2.70 (–4.98, –0.42)	NR	.02
	Mediterranean diet	1	40	–2.01 (–3.10, –0.92)	NR	.0003
	Intervention duration					
	≤12 weeks	5	255	–0.97 (–1.40, –0.55)	72%	<.00001
	>12 weeks	4	195	–1.25 (–2.06, –0.43)	0%	.003
Weight (kg)	**Diet type**					
	DASH	4	211	–1.88 (–2.65, –1.11)	58%	<.00001
	Low-carbohydrate diet	6	246	–1.24 (–2.47, –0.01)	59%	.05
	Calorie-restricted diet	1	60	–6.70 (–13.00, –0.40)	NR	.04
	Mediterranean diet	1	40	–5.25 (–9.51, –0.99)	NR	.02
	Intervention duration					
	≤12 weeks	7	336	–1.67 (–2.70, –0.65)	75%	.001
	>12 weeks	5	221	–1.79 (–2.39, –1.18)	0%	<.00001
WC (cm)	**Diet type**					
	DASH	1	55	–1.20 (–3.02, 0.62)	NR	.20
	low-carbohydrate diet	3	112	–3.99 (–5.95, –2.03)	0%	<.0001
	Calorie-restricted diet	1	60	–7.40 (–13.28, –1.52)	NR	.01
	Intervention duration					
	≤12 weeks	3	140	–2.76 (–4.88, –0.64)	52%	.01
	>12 weeks	2	87	–6.62 (–11.85, –1.39)	0%	.01

Abbreviations: BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension; FINS, fasting insulin; FPG, fasting plasma glucose; HOMA, homeostatic assessment of insulin resistance; MD, mean difference; NR, not reported; WC, waist circumference.

groups (MD = –0.09, 95% CI –0.46 to 0.28; P = .63; I^2 = 38%) (Fig. 4).

FINS. The pooled effect size of 4 data sets (299 participants) (46-49) represented no advantages of diet in improving FINS compared with metformin (MD = –0.15 mIU/L, 95% CI –1.34 to 1.04 mIU/L; P = .81; I^2 = 45%) (Fig. 4). No significant change was found in the subgroup analysis (Table 3 and (50)).

FPG. Four trials (299 participants) mentioned FPG in comparison with diet and metformin (46-49). The results of the meta-analysis showed no significant difference (MD = 0.01 mmol/L, 95% CI –0.13 to 0.15 mmol/L; P = .85; I^2 = 53%) (Fig. 4). No significant change was found in the subgroup analysis (Table 3 and (50)).

BMI. Four trials with 299 participants assessed the impact of diet on BMI (46-48). Meta-analysis showed that dietary interventions resulted in a greater decrease in BMI than metformin (MD = -2.49 kg/m^2, 95% CI –2.73 to –2.25 kg/m^2; P < .00001; I^2 = 0%), with no heterogeneity (Fig. 4). Regarding dietary approaches, both the low-carbohydrate diet and low-fat diet were more effective than metformin in reducing BMI, and the effect of the low-carbohydrate diet was more prominent. The calorie-restricted diet seemed no better than metformin in reducing BMI. Additionally, diet worked more quickly than metformin, and the advantages were obvious within 12 weeks (Table 3 and (50)).

Weight. Two studies mentioned the weight changes of 223 women assigned to diet and metformin randomly

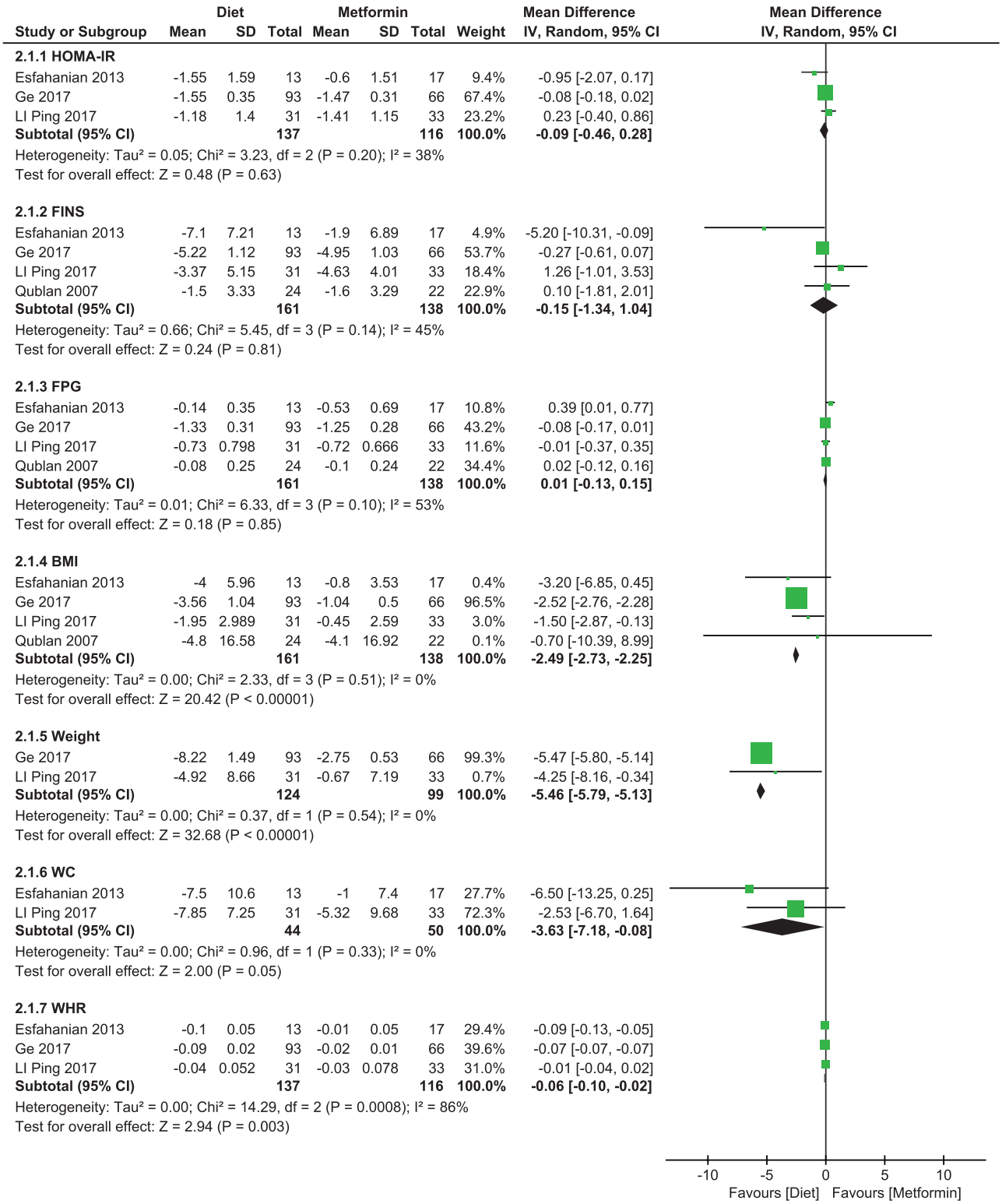

Figure 4. Forest plots of comparison between diet intervention and metformin.

(48, 49). Based on the pooled data, a significant reduction in weight was observed in the diet group (MD = –5.46 kg, 95% CI –5.79 to –5.13 kg; $P < .00001$; $I^2 = 0\%$) (Fig. 4).

WC. Two trials (94 participants) reported this outcome (47, 48). Compared with the control groups, the diet groups had significantly smaller WC measurements (MD = –3.63 cm, 95% CI –7.18 to –0.08 cm; $P = .05$; $I^2 = 0\%$) (Fig. 4).

WHR. The analysis of 3 trials (253 participants) indicated that dietary interventions had no additional

Table 3. Effect estimates and heterogeneity of subgroup analysis for outcomes (diet versus metformin)

Outcome	Subgroup	Trial (n)	Sample size (n)	Effect estimate MD (95% CI)	I^2	*P*
FINS (mIU/L)	**Diet type**					
	Calorie-restricted diet	2	76	–2.00 (–7.08, 3.08)	72%	.44
	Low-carbohydrate diet	1	159	–0.27 (–0.61, 0.07)	NR	.12
	Low-fat diet	1	64	1.26 (–1.01, 3.53)	NR	.28
	Intervention duration					
	≤12 weeks	3	253	–0.37 (–2.39, 1.65)	62%	.72
	>12 weeks	1	46	0.10 (–1.81, 2.01)	NR	.92
FPG (mmol/L)	**Diet type**					
	Calorie-restricted diet	2	76	0.16 (–0.19, 0.51)	69%	.37
	Low-carbohydrate diet	1	159	–0.08 (–0.17, 0.01)	NR	.09
	Low-fat diet	1	64	–0.01 (–0.37, 0.35)	NR	.96
	Intervention duration					
	≤12 weeks	3	253	0.06 (–0.21, 0.32)	64%	.68
	>12 weeks	1	46	0.02 (–0.12, 0.16)	NR	.78
BMI (kg/m^2)	**Diet type**					
	Calorie-restricted diet	2	76	–2.89 (–6.30, 0.52)	0%	.10
	Low-carbohydrate diet	1	159	–2.52 (–2.76, –2.28)	NR	<.00001
	Low-fat diet	1	64	–1.50 (–2.87, –0.13)	NR	.03
	Intervention duration					
	≤12 weeks	3	253	–2.43 (–2.88, –1.98)	9%	<.00001
	>12 weeks	1	46	–0.70 (–10.39, 8.99)	NR	.89

Abbreviations: BMI, body mass index; FINS, fasting insulin; FPG, fasting plasma glucose; MD, mean difference; NR, not reported.

benefits of adjusting WHR (MD = –0.06, 95% CI –0.10 to –0.02; *P* = .003; I^2 = 86%) compared with metformin (47-49) (Fig. 4).

Meta-regression, sensitivity analysis, and publication bias

Meta-regression analyses were possible only for weight (diet versus minimal intervention). Neither the dietary patterns (regression coefficient β = .557; SE = 0.364; *P* = .392) nor the treatment duration (regression coefficient β = .631; SE = 0.597; *P* = .637) had an association with the study effect size. Meta-regression analyses were attempted to explain the heterogeneity among the studies, but inferences were limited by the paucity of available studies.

When excluding trials deemed as high risk of bias, the overall estimates remained unchanged, except the outcome of WC and WHR in the comparison of diet and metformin, indicating that the majority of conclusions were stable and not affected by the quality of trials included. However, compared with metformin, the results of WC and WHR should be interpreted with caution.

Given the limited number of studies (<10), Egger's test and the forest plot may be low-powered. Thus, we could conduct tests on body weight only in the comparison of diet and minimal inventions. The *P* value of Egger's test was .464, indicating that there was no evidence of publication bias in our study. The funnel plot did not show major asymmetries (Fig. 5).

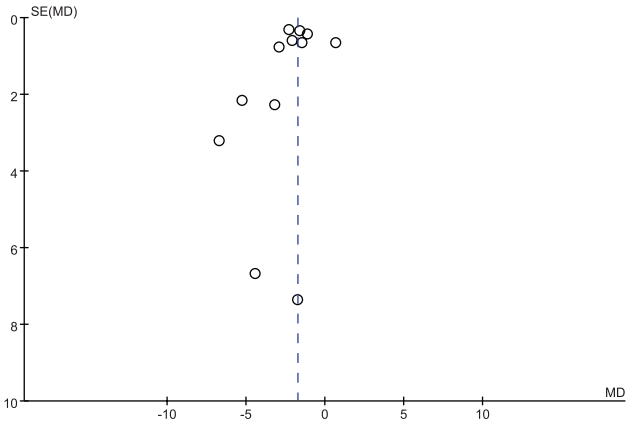

Figure 5. Funnel plot of weight (diet intervention versus minimal treatment).

Discussion

In this systematic review and meta-analysis, dietary changes were significantly related to decreased IR and body composition in PCOS patients. The positive effects of diet were comparable to those of metformin and were more beneficial in weight loss, especially for a quick decline in BMI. We also found a trial comparing diet versus exercise, indicating that diet was more favorable in terms of HOMA-IR and showed a trend of more weight loss (28-30).

The results of our meta-analysis showed that the DASH diet seemed to be more effective in improving insulin sensitivity in PCOS, which was consistent with previous meta-analyses conducted in the general or

type 2 diabetes population (51, 52). The DASH diet is rich in fruits, vegetables, whole grains, nuts, legumes, fat-free/low-fat dairy and low in saturated fat, cholesterol, red and processed meats, and refined grains and sweets (53). Although there is no limit to the content of carbohydrates, as a kind of low GI diet, the DASH diet still helps improve insulin sensitivity and control glycemia. Recent studies have shown that the type of carbohydrate in the diet is more important than the ratio (54, 55). Diets with low GI have been reported to improve insulin sensitivity and lower blood glucose (56, 57), as they can increase satiety and produce less hypoglycemia. The combination of foods from the DASH dietary pattern, such as fruits, vegetables, whole grains, nuts, and legumes, are rich sources of dietary fiber and micronutrients. High fiber is an essential part of the diet for IR. Several studies have indicated that the consumption of dietary fiber is inversely correlated with FINS, HOMA-IR, and the Matsuda insulin index (58, 59) and contributes to superior responses of insulin and glucose (60). Most importantly, given its lack of calorie restriction and richness in nutrients with strong satiety, the DASH diet is easy for people to adhere to, thus it might provide both short- and long-term health benefits in women with PCOS (61, 62).

We also found that the calorie-restricted diet may be the optimal dietary pattern for weight loss, indicating that long-term weight loss and metabolic improvement might be independent of macronutrient composition in the diet. Updated meta-analyses and clinical trials also suggested that the greater energy restriction is, the greater the weight loss will be, regardless of where the restriction comes from (carbohydrates, protein, or fat) (63, 64). It has been reported that weight reduction induced by low-calorie diets is associated with reduced fat mass and preserved lean body mass (65). Moreover, calorie-restricted diets may positively affect glycemic control by enhancing insulin sensitivity (66), improving β-cell function and lowering the elevated levels of glucose and HbA1c (67-69).

The Mediterranean diet, one of the healthiest dietary approaches, has been reported to have the strongest association with lower insulin levels, lower HOMA-IR values, and higher levels of insulin sensitivity (70). However, due to limited number of studies in our analysis (only 1 trial evaluated the effects of Mediterranean diet), the advantages of Mediterranean diet in IR improvement were not apparent, and we were uncertain about its role in PCOS population.

Furthermore, we also found that the effects were associated with treatment duration. The longer the duration, the greater the improvement was (except FPG, where the effects of diet were obvious within 12 weeks). Considering that PCOS is a lifelong disease, especially with metabolic disorders, treatment should be long term, dynamic, and adapted to the changing circumstances, personal needs and expectations of the individual patient (71).

Our research has unique strengths. First, to the best of our knowledge, this study is a frontier analysis to evaluate the role of diet on IR in women with PCOS, as previous studies mainly focus on the impact of exercise or lifestyle changes (72, 73). Second, we conducted a detailed analysis of the results and performed subgroup analysis based on different dietary patterns and treatment durations, 2 factors that may have significant impacts on the conclusions. Through analysis, we elucidated specific and optimal recommendations, providing good guidance for clinical practice. Third, we evaluated not only the effects of diet with minimal interventions but also those of metformin, making the conclusions more comprehensive and practical.

However, there were several limitations to be taken into consideration. First, the evidence involved few countries and ethnic groups, which made the results difficult to generalize. Second, given the limited number of trials and small sample size in certain outcomes, the findings might be insufficient to ensure a significant difference. Third, heterogeneity was observed in some results. Different dietary patterns, dosages of metformin, and characteristics of the studied populations (eg, different phenotypes and countries) might account for the potential sources.

More well-designed studies are warranted to confirm the effect of dietary intervention on IR in PCOS. First, PCOS is a heterogeneous condition with different phenotypes. However, no included trials targeted a specific phenotype, which made the results difficult to generalize. Future work should focus on the relationship between IR in particular phenotypes and dietary interventions, thus investigating the effects accordingly. Second, the effects on IR may depend not only on the components of dietary patterns but also on eating habits and meal energy content. Physicians should pay more attention to these factors mentioned above when designing RCTs and assess whether these issues would influence the observed effects and to what degree. Third, the duration of most included trials was within 12 weeks. Studies with longer follow-up periods will help to comprehensively unravel the effects of dietary interventions in the long run. Fourth, given that not all women with PCOS are overweight or obese, the impact of diet independent of weight loss is of great clinical interest.

Conclusion

Based on this review, our results suggest that diet benefits IR and weight management in women with PCOS. The DASH diet and calorie-restricted diets might be the optimal choices for reducing IR and improving weight management, respectively. Additionally, the effects were associated with the course of treatment. Overall, diet is an effective, acceptable and safe intervention, providing options for patients who cannot tolerate the gastrointestinal side effects induced by metformin. However, due to the limited number of studies and the small sample size included, the results should be interpreted with caution. More RCTs with rigorous designs and large samples are needed to confirm the evidence and further explore the optimal dietary patterns.

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Data Availability: All data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

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