REVIEW

Effects of Dietary Glycemic Index and Glycemic Load on Cardiometabolic and Reproductive Profiles in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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ABSTRACT

Women with polycystic ovary syndrome (PCOS) exhibit cardiometabolic (e.g., insulin resistance) and associated reproductive disruptions. Lifestyle modification (e.g., diet) is recommended as the first-line therapy to manage PCOS; however, a favorable dietary regimen remains unclear beyond energy restriction. We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to summarize evidence on impacts of dietary glycemic index (GI) or glycemic load (GL) on cardiometabolic and reproductive profiles to update the International Evidence-based Guideline for the Assessment and Management of PCOS. Databases of MEDLINE, Cochrane, Web of Science, and Scopus were searched through 30 October 2019, and confirmed on 25 March 2020, to identify RCTs (≥8 wk) comparing the effects of diets with lower (LGI/LGL) and higher (HGI/HGL) GI/GL on glucoregulatory outcomes, lipid profile, anthropometrics, and androgen status in PCOS. The primary outcome was HOMA-IR. Data were pooled by random-effects models and expressed as weighted mean differences and 95% CIs. The risk of bias was assessed by the Cochrane tool. Ten RCTs ($n = 403$) were eligible. Eight evaluated LGI and 2 LGL diets. LGI diets decreased HOMA-IR (−0.78; −1.20, −0.37; $I^2 = 86.6\%$), fasting insulin (−2.39; −4.78, 0.00 μIU/mL; $I^2 = 76.8\%$), total cholesterol (−11.13; −18.23, −4.04 mg/dL; $I^2 = 0.0\%$), LDL cholesterol (−6.27; −12.01, −0.53 mg/dL; $I^2 = 0.0\%$), triglycerides (−14.85; −28.75, −0.95 mg/dL; $I^2 = 31.0\%$), waist circumference (−2.81; −4.40, −1.23 cm; $I^2 = 53.9\%$), and total testosterone (−0.21; −0.32, −0.09 nmol/L; $I^2 = 8.6\%$) compared with HGI diets (all: $P \leq 0.05$) without affecting fasting glucose, HDL cholesterol, weight, or free androgen index (all: $P \geq 0.07$). Some results were contradictory and only described narratively for 2 RCTs that evaluated LGL diets, since inclusion in meta-analyses was not possible. LGI diets improved glucoregulatory outcomes (HOMA-IR, insulin), lipid profiles, abdominal adiposity, and androgen status, conceivably supporting their inclusion for dietary management of PCOS. Further RCTs should confirm these observations and address whether LGI diets improve more patient-pressing complications, including ovulatory cyclicity, infertility, and cardiovascular disease risk in this high-risk population. This review was registered at www.crd.york.ac.uk/PROSPERO as CRD42020175300. *Adv Nutr* 2021;12:161–178.

Keywords: diet, cardiovascular diseases, metabolic diseases, insulin, glucose, dyslipidemias, obesity, hyperandrogenism, polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder and the leading cause of anovulatory infertility affecting up to 18% of reproductive-aged women (1, 2). PCOS is characterized by hyperandrogenism, menstrual irregularity, and/or polycystic ovarian morphology. In addition to reproductive disruption, women with PCOS often exhibit cardiometabolic aberrations, including insulin resistance (IR) and compensatory hyperinsulinemia dyslipidemia, and visceral adiposity and are at risk for developing metabolic syndrome and type 2 diabetes (2–5).

The relation between diet, as a modifiable environmental factor, and components of the female reproductive axis has biological plausibility (**Figure 1**). A favorable diet can improve PCOS health outcomes (6). Accordingly, the International Evidence-based Guideline for the Assessment and Management of PCOS recommends lifestyle modifications, including dietary interventions, as the first-line therapy

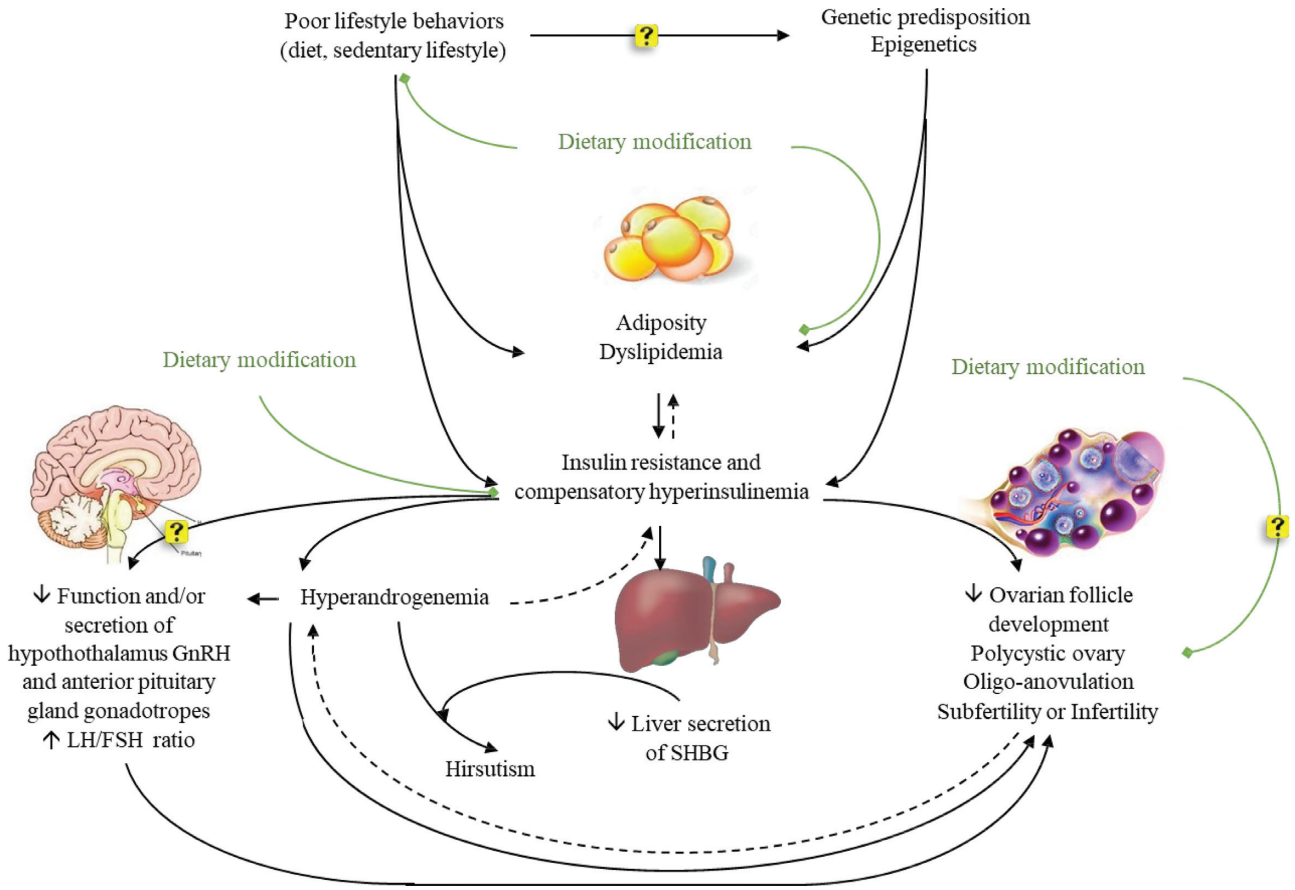

FIGURE 1 Intersection of diet with the etiological and pathophysiological theories of PCOS. Black lines represent the mechanisms of developing PCOS in direct (solid lines) and feedback loops (dotted lines). Green lines represent the proposed mechanism that diet, as a modifiable environmental factor, can positively affect the clinical and biochemical aberrations of PCOS. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; PCOS, polycystic ovary syndrome; SHBG, sex hormone–binding globulin.

to manage PCOS metabolic complications (7). While the guideline focuses on weight loss for women with overweight or obesity, and prevention of weight gain for women of normal weight, the success and sustainability of weight-loss diets have been debated. We and others have shown women with PCOS have a propensity for obesity (8, 9), perceive an inevitability for weight gain (10–12), exhibit poor adherence to energy-restricted diets (10, 13–15), and have a tendency for longitudinal weight regain (16, 17). A Cochrane review reported attrition rates of ~46% in PCOS (18), which increase with the duration of intervention (8, 14–16, 19, 20), attributed to psychosocial, physiological, or appetite-regulation factors (21–23). At present, no consensus exists for a unique dietary composition to facilitate PCOS health outcomes beyond energy restriction per se (7). Understanding the most favorable dietary type and composition is critical for sustainable and successful management strategies that set the foundation for healthy pregnancy and lifelong wellness in this clinical population.

The glycemic index (GI) represents the effects of the carbohydrate portion of a particular food on postprandial glucose concentrations compared with white bread or glucose as a reference containing an equivalent amount of carbohydrate (24–27). The glycemic load (GL) is the product of the GI and total dietary carbohydrate, thereby accounting for the total glycemic effect of food (25, 27). Previous systematic reviews and meta-analyses have shown the benefits of low-GI and/or low-GL diets on glucoregulatory status (28–32), metabolic syndrome rate (33), lipid profile (34, 35), and weight loss (36) in non-PCOS populations who share pathophysiological

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Supplemental Table 1–3 and Supplemental Figures 1–4 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances.
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Abbreviations used: DASH, Dietary Approaches to Stop Hypertension; FAI, free androgen index; GI, glycemic index; GL, glycemic load; HGI, higher glycemic index; HGL, higher glycemic load; IR, insulin resistance; LGI, lower glycemic index; LGL, lower glycemic load; PCOS, polycystic ovary syndrome; PICOTS, Population, Intervention, Comparison, Outcome, Time, and Study Design; RCT, randomized controlled trial; SAE, serious adverse event; TC, total cholesterol; TG, triglyceride; TT, total testosterone; WC, waist circumference; WMD, weighted mean difference.

underpinnings with PCOS. Low-GI foods have also been proposed to decrease the sensation of hunger, which could translate into reduced energy intake in the short term (37, 38), as described in the glucostatic theory (39), albeit their long-term effects remain unknown (39, 40). The overlapping pathophysiological processes between women with PCOS and individuals with similar clinical aberrations [e.g., metabolic syndrome, dyslipidemia, type 2 diabetes (3, 41, 42)] whose cardiometabolic status improved following low-GI and/or -GL diets (43–47) potentially support the unique benefits of these diets on PCOS health outcomes per se. Namely, IR and hyperinsulinemia are established as the key/central pathophysiological factors associated with a wide cascade of metabolic and reproductive disruptions in PCOS (41, 42) (Figure 1). Diets with low-GI and/or -GL, in turn, are known to increase insulin sensitivity and function (48–52). These interconnections between diet, metabolic, and reproductive aberrations are consistent with the notion that the low-GI and/or -GL diets likely modulate hyperinsulinemia and IR and, subsequently, other associated metabolic and reproductive disruptions of PCOS. However, the presence and magnitude of these associations remain inconclusive. Some studies (15, 16, 19, 53, 54) support the benefits of adherence to low-GI or -GL diets on improving insulin sensitivity, dyslipidemia, weight loss, hyperandrogenism, or menstrual cyclicity; however, others identified no differences between low-GI and/or -GL and high-GI and/or -GL diets on some of these outcomes (16, 55–58). The inconsistency may stem, in part, from the small sample sizes of individual trials that likely limit their statistical power to capture any true effects of low-GI and/or -GL diets on PCOS outcomes. The paucity of available randomized controlled trials (RCTs), secondary to difficulties in conducting lifestyle interventions in PCOS and high attrition rates of available interventions, has also contributed to inconclusive reports (6). Collectively, whether or not women with PCOS benefit from low-GI or -GL diets remains unknown.

To address this knowledge gap, we conducted a systematic review and meta-analysis of RCTs to summarize and quantitatively pool evidence on the effects of modification of dietary GI and GL on cardiometabolic and reproductive profiles in women with PCOS. The primary outcome of our study was to assess whether a low-GI or -GL diet results in a greater decrease in IR, as assessed by the HOMA-IR. We hypothesized that low-GI and/or -GL diets would be more effective than high-GI and/or -GL diets at decreasing hyperinsulinemia and IR, thereby improving associated cardiometabolic and reproductive complications in women with PCOS.

Methods

The work presented herein was planned and conducted according to the Cochrane Handbook for Systematic Reviews of Interventions, version 6.0 (59). Reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (60). This review was registered at www.crd.york.ac.uk/PROSPERO as CRD42020175300.

Review question (PICOTS)

The PICOTS [Population (P), Intervention (I), Comparison (C), Outcome (O), Time (T), and Study Design (S)] criteria were defined before the literature search and are detailed in **Supplemental Table 1**. Concisely, our study question was, in women with PCOS (P), does a lower-GI/-GL (LGI/LGL) diet (I), compared with a higher-GI/-GL (HGI/HGL) isocaloric/hypocaloric diet (C), improve cardiometabolic and reproductive health outcomes (O) over ≥8 wk (T) in RCTs (S)? The cutoff for the intervention duration was chosen to allow observation of clinically meaningful changes in the outcomes of interest (61–63).

Primary and secondary outcomes

Our primary outcome of interest was HOMA-IR as a marker of insulin resistance. Secondary outcomes included fasting insulin, fasting glucose, lipid profile [total cholesterol (TC), LDL cholesterol, HDL cholesterol, and triglycerides (TGs)], waist circumference (WC), body weight, total testosterone (TT), and free androgen index (FAI; Supplemental Table 1).

Data sources and search strategy

A systematic search of published literature was conducted in the electronic databases of MEDLINE, Cochrane Database of Systematic Reviews, Institute for Scientific Information (ISI) Web of Science, and Scopus through 30 October 2019, using a search strategy based on the PICOTS framework (Supplemental Table 1). Details of the subject headings and key terms used in search strategy for MEDLINE are available (**Supplemental Table 2**) and translated for use in other databases, where appropriate. Further, manual searches of reference lists from included trials supplemented the electronic database searches. No restriction on language was imposed in the search. Unpublished literature was beyond the scope of the present work and not included. No additional research meeting the criteria was found for inclusion as of 25 March 2020.

Inclusion and exclusion criteria

Studies were included if they met the PICOTS criteria described in Supplemental Table 1. Briefly, parallel or crossover RCTs on reproductive-age women with PCOS were included in which a difference in GI/GL of diets between the intervention and comparator groups was reported. The difference constituted lower and higher GI/GL diets in the intervention and comparator arms of individual studies defined in their design.

Exclusion criteria included non–peer-reviewed references; studies without an RCT design; duplicated reports from identical RCTs; studies in adolescents, pregnant women, infertile women without PCOS, or nonhuman models; and in cases in which study data were irretrievable after contacting their corresponding authors.

The screening processes for inclusion and exclusion of studies were completed by 2 investigators (MK and AH) independently using a double-blind coding assignment function of EPPI-Reviewer 4 (EPPI-Centre Software; Social Science Research Unit, UCL Institute of Education) (64) and EndNote version X9.2 (Thomson Reuters). All discrepancies and disagreement about the inclusion and exclusion of studies were resolved by consensus or discussion with a third investigator (PDC).

Data extraction

The following data were extracted using a standardized protocol: *1*) first author's name; *2*) study publication year; *3*) study country; *4*) participants' characteristics, including total sample size and the sample size of participants who completed each of the intervention and control groups, baseline age, and BMI of intervention and control groups, and criteria used to define PCOS; *5*) study design and setting; *6*) study duration; *7*) dietary characteristics, including the type, energy and macronutrient composition, and delivery of diets in the intervention and control groups; and *8*) direction of changes in the cardiometabolic and reproductive outcomes of interest that were reported between the intervention and control groups in each study. We also evaluated additional information, including the attrition rate; and reported adverse events, the use of any other intervention, and the type of assay used to measure TT as informative measures of the study methodology. In the case of any missing or unclear data, 2 attempts were made to contact the corresponding author by e-mail requesting data required for inclusion herein. Data extraction was completed by one of the investigators (MK) and was reviewed by all other authors (AH, PDC, RAP, MEL, and GAZ) for any potential extraction error.

Quality assessment

The Cochrane Risk of Bias Assessment tool (59) was used to evaluate the risk of bias in RCTs using 7 domains of *1*) sequence generation, *2*) allocation concealment (both within the domain of selection bias or allocation bias), *3*) blinding of participants and personnel (performance bias), *4*) blinding of outcome assessors (detection bias), *5*) incomplete outcome data (attrition bias), *6*) selective reporting (reporting bias), and an auxiliary domain of *7*) "other bias." For each bias domain, a judgment of "high," "low," or "unclear" risk of bias was assigned. Quality assessment was completed by 2 investigators (MK and AH) independently for each included study. All discrepancies and disagreements were resolved by consensus or discussion with a third investigator (PDC).

Data synthesis and analysis

Statistical analyses were performed using STATA version 14.0 (StataCorp) or SPSS version 25.0 (IBM Corporation). Effect sizes are expressed as the weighted mean difference (WMD) and 95% CI between the intervention and control groups and were pooled using the generic inverse variance method with a random-effects model. Mean differences and SDs of cardiometabolic and reproductive outcome measures were collected to estimate pooled effects if reported in ≥3 trials. Where net changes were not directly reported in the intervention and control groups, mean changes were calculated by subtracting the postintervention from the baseline values. Accordingly, the SD of the mean changes was calculated for each group using 2 formulas where SD and SEM were only reported in the RCTs, respectively: *1*) SD = square root [(SD baseline)^2 + (SD postintervention)^2 – ($2r$ × SD baseline × SD postintervention)] assuming that $r = 0.5$ and *2*) SD = SEM × square root (n), assuming n is the number of participants (59, 65). Where medians and ranges or IQRs were reported instead of means, we used formulas proposed by Hozo et al. (66) and Wan et al. (67), respectively, to calculate the means and SD values.

The chi-square test was used to evaluate heterogeneity, and the Cochran Q ($P < 0.01$) and I^2 statistics were reported. The I^2 value was calculated as $(Q - df)/Q \times 100\%$, with Q being the χ^2 value and df the corresponding degrees of freedom. Low, moderate, and high heterogeneity were defined according to the cutoffs of 25%, 50%, and 75%, respectively, using the results of the I^2 test values (68). Any sources of heterogeneity were explored using subgroup and sensitivity analyses. We performed a priori subgroup analyses to detect any impact of *1*) participants' age (≤30 or >30 y) on study outcomes, *2*) energy restriction in the intervention and control groups (yes or no), and *3*) duration of the intervention (<16 or ≥16 wk) to allow including ≥2 studies in each of the subgroups. Within- and between-subgroup heterogeneity was evaluated by random-effects and fixed-effects models, respectively. Further, sensitivity analyses were performed by removing 1 study each time and recalculating the effect size to detect the influence of each study on the overall effect size and determine whether an individual trial exerted undue influence. Publication bias was assessed by Begg's rank correlation tests and Egger's regression asymmetry (69, 70). Results were considered significant at $P \leq 0.05$.

Results

Literature search

The systematic search resulted in 346 records (**Figure 2**), of which 10 RCTs published across 13 studies (15, 16, 54, 56–58, 71–77) were deemed eligible and included. All studies comprising a total of 20 experimental arms and 403 participants (202 in the intervention and 201 in the control arms) were included in the systematic review. Three of the 10 studies (54, 76, 77) lacked sufficient data for pooling meta-analyses and were included only in the qualitative assessment. Therefore, the meta-analyses comprised 7 RCTs (15, 16, 56–58, 71–75). The reasons for excluding studies at each stage of the literature screening are reported (Figure 2). The main reasons for excluding the studies at the first and second stages of data screening were unrelated topics and non-RCT designs, respectively.

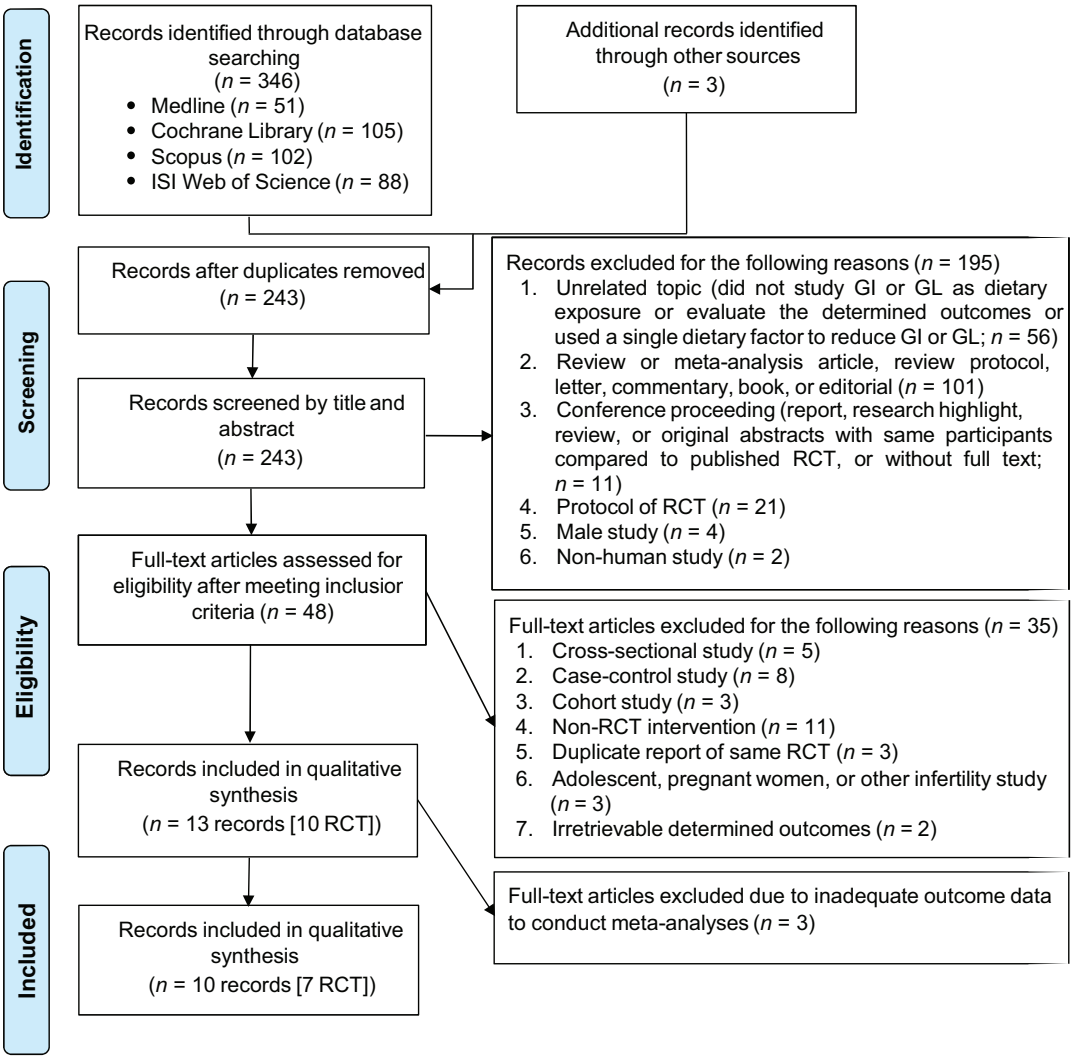

FIGURE 2 Flow diagram of study selection. GI, glycemic index; GL, glycemic load; PCOS, polycystic ovary syndrome; RCT, randomized controlled trial(s).

Study characteristics

General characteristics of the studies included in the present work are described in **Table 1** and summarized herein. Studies were published between 2009 and 2020 and were conducted in the United States (15, 58, 75), Canada (16, 57), the United Kingdom (72), Iran (54, 56, 71, 73, 74), Italy (76), and Mexico (77). The mean age and BMI (kg/m^2) of women ranged from 22.1 to 36.4 y and 28.7 to 42.7, respectively, across the intervention and control arms. The attrition rate ranged from zero (72, 74) to 77% (76) across the evaluated trials.

Most of the included RCTs [7/10, 70% (15, 56, 71–74, 76, 77)] used the Rotterdam criteria (78) to define PCOS, whereas 2 RCTs (published in 3 studies) (54, 58, 75) used NIH (79) and 1 (published in 2 studies) (16, 57) the AEPCOS (Androgen Excess and Polycystic Ovary Syndrome) (80) criteria. All trials were conducted in academic medical centers. Of all included 10 RCTs (13 studies), 9 (11 studies) (15, 16, 54, 56, 57, 71–74, 76, 77) had a parallel design and 1 (2 studies) (58, 75) had a crossover design. Intervention duration ranged between 8 wk (56, 58, 71, 75) to 6 mo (15, 72) across the trials. Most trials focused on the effects of LGI (15, 16, 56–58, 71–75, 77) diets as exposure and only 2 specifically focused on the impacts of LGL diets (54, 76). Dietary interventions were without (15, 16, 57, 58, 75, 76) or with prescribed energy restriction with an energy deficit ranging from 350 to 1000 kcal/d (15, 54, 56, 71–74, 77) (Table 1). The cardiometabolic and reproductive outcomes extracted included glucoregulatory markers [HOMA-IR (16, 58, 71, 74), fasting insulin (16, 58, 71, 72, 74), and fasting glucose (16, 58, 71, 72, 74)], lipid profile [TC (56–58, 72), LDL cholesterol (56–58, 72), HDL cholesterol (56–58, 72), and TGs (56–58, 72)], anthropometrics [body weight (15, 56, 57, 72–75) and WC (57, 71–73)], and androgen status [TT (57, 58, 72–74) and FAI (57, 58, 73, 74)] across the trials.

TABLE 1 General characteristics of the included studies[1]

Author, year (reference), country	Participants' characteristics [*n*, mean age (y), mean BMI (kg/m^2)], and PCOS definition	RCT design (blinding) and setting	Duration	Intervention diet characteristics [type, composition (%, mean, or range), and recommendations]	Control diet characteristics [type, composition (%, mean, or range), and recommendations]	Reported outcomes of interest
Asemi et al., 2014 (56) and 2015 (71), Iran	Total completers, 48 (Intervention, 24; Control, 24) Intervention, age: 22.1; BMI, 30.3; Control, age: 24.7, BMI, 28.6; PCOS definition, Rotterdam	Parallel (yes, investigators and participants); setting, academic medical center	8 wk	LGI: standard DASH dietary pattern; E%: CHO, 52%; F, 30%; P, 18%; fiber: 17 g/d; target energy deficit, 350–700 kcal/d; dietary advice and food exchange list were provided at baseline by a dietitian	HGI: Iranian traditional dietary pattern; E%: CHO, 52%; F, 30%; P, 18%; fiber: 12 g/d; target energy deficit: 350–700 kcal/d; dietary advice and food exchange list were provided at baseline by a dietitian	↓Fasting insulin, ↔fasting glucose, ↓HOMA-IR, ↔TC, ↔LDL-C, ↔HDL-C, ↓TG, ↓weight, ↓WC
Atiomo et al., 2009 (72), UK	Total completers, 11 (Intervention, 6; Control, 5); Intervention, age: 35.3, BMI, 45.1; Control, age: 36.4, BMI, 38.9; PCOS definition, Rotterdam	Parallel (yes, investigators and participants); setting, academic medical center	6 mo	LGI: low-GI diet; E%: NR; fiber: NR; target energy deficit, 600 kcal/d; dietary advice and ideal meal plans were provided at baseline and participants were visited monthly by a dietitian	HGI: conventional healthy diet; E%: NR; fiber: NR; target energy deficit, 600 kcal/d; dietary advice and ideal meal plans were provided at baseline and participants were visited monthly by a dietitian	↔Fasting insulin, ↔fasting glucose, ↔TC, ↔LDL-C, ↔HDL-C, ↔TG, ↔weight, ↔WC, ↔TT
Azadi-Yazdi et al., 2017 (73), Iran	Total completers, 55 (Intervention, 28; Control, 27); Intervention, age: 32.1, BMI, 31.9; Control, age: 31.8; BMI, 30.2; PCOS definition, Rotterdam	Parallel (yes, participants; investigator NR); setting, academic medical center	12 wk	LGI: standard DASH dietary pattern; E%: CHO, 50–55%; F, 25–30%; P, 15–20%; fiber: 18 g/d; target energy deficit, 350–500 kcal/d; dietary advice and a guide weekly menu cycle were provided at baseline, and participants were visited bimonthly by a dietitian	HGI: control diet; E%: CHO, 50–55%; F, 25–30%; P, 15–20%; fiber: 13 g/d; target energy deficit, 350–500 kcal/d; dietary advice and a guide weekly menu cycle were provided at baseline, and participants were visited bimonthly by a dietitian	↓Weight, ↔WC, ↓TT, ↓FAI
Foroozanfard et al., 2017 (63), Iran	Total completers, 60 (Intervention, 30; Control, 30); Intervention, age: 27.1, BMI, 32.3; Control, age: 25.6; BMI, 32.2; PCOS definition, Rotterdam	Parallel (yes, investigators and participants); setting, academic medical center	12 wk	LGI: standard DASH dietary pattern; E%: CHO, 52–55%; F, 30%; P, 16–18%; fiber: 18 g/d; target energy deficit, 350–700 kcal/d; weekly menu cycles and food exchange list were provided at baseline and participants were monitored via phone interviews weekly by a dietitian	HGI: Iranian traditional dietary pattern; E%: CHO, 52–55%; F, 30%; P, 16–18%; fiber: 12 g/d; target energy deficit, 350–700 kcal/d; weekly menu cycles and food exchange list were provided at baseline and participants were monitored via phone interviews weekly by a dietitian	↓Fasting insulin, ↔fasting glucose, ↓HOMA-IR, ↓weight, ↔TT, ↓FAI

(*Continued*)

TABLE 1 (*Continued*)

Author, year (reference), country	Participants' characteristics [*n*, mean age (y), mean BMI (kg/m^2)], and PCOS definition	RCT design (blinding) and setting	Duration	Intervention diet characteristics [type, composition (%, mean, or range), and recommendations]	Control diet characteristics [type, composition (%, mean, or range), and recommendations]	Reported outcomes of interest
Gower et al., 2013 (58), and Goss et al., 2014 (75), USA	Total completers, 50 (Intervention, 27; Control, 23); age: 31.2, BMI, 31.8; PCOS definition, NIH	Crossover (yes, only participants); setting, academic medical center	8 wk in 2 periods; (4-wk washout period)	LGI: low-CHO diet; E%: CHO, 41%; F, 40%; P, 19%; fiber: 22–31 g/d; GI: ∼50; GL: 81–114; no energy restriction was prescribed; target energy intake, 1800–2500 kcal/d; dietary advice and ideal meal plans were provided at baseline and participants were visited monthly by a dietitian	HGI: standard diet; E%: CHO, 55%; F, 27%; P, 18%; fiber: 18–23 g/d; GI: ∼60, GL: 143–192; no energy restriction was prescribed; target energy intake, 1800–2500 kcal/d; dietary advice and ideal meal plans were provided at baseline and participants were visited monthly by a dietitian	↓Fasting insulin, ↓fasting glucose, ↓HOMA-IR, ↓TC, ↓LDL-C, ↓HDL-C, ↔TG, ↔weight, ↓TT, ↔FAI
Kazemi et al., 2018 (16), and 2020 (57), Canada	Total completers, 61 (Intervention, 30; Control, 31); Intervention, age: 27.0, BMI, 32.5; Control, age: 26.9, BMI, 33.3; PCOS definition, AEPCOS 2006 (with AEPCOS 2013 criterion of ≥25 FNPO or OV ≥10 mL for PCO)	Parallel (yes, only investigators); setting, academic medical center	16 wk	LGI: low-GI pulse-based diet; E%: CHO, 52–55%; F, 30%; P, 16–18%; fiber: 33 g/d; GI: ∼35–40; GL: ∼70–100; no energy restriction was prescribed; dietary advice with a focus on consuming low-GI high-fiber pulse foods and limiting high-GI foods, food exchange list, and general healthy eating behaviors were provided at baseline and participants were visited monthly by a dietitian	HGI: standard TLC diet; E%: 52–55%; F, 30%; P, 16–18%; fiber: 25 g/d; GI: ∼50–60; GL: ∼100–110; no energy restriction was prescribed; dietary advice about following the standard TLC diet, food exchange list, and general healthy eating behaviors was provided at baseline and participants were visited monthly by a dietitian	↔Fasting insulin, ↔fasting glucose, ↔HOMA-IR, ↔TC, ↓LDL-C, ↔HDL-C, ↓TG, ↔weight, ↔WC↔TT, ↔FAI
Mehrabani et al., 2012 (54), Iran	Total completers, 49 (Intervention, 23; Control, 26); Intervention, age: 30.5, BMI, 31.9; Control, age: 28.5, BMI, 331.1; PCOS definition, NIH	Parallel (yes, only participants); setting, academic medical center	12 wk	LGL: low-GL hypocaloric diet; E%: CHO, 40%; F, 30%; P, 30%; fiber: NR; focus on carbohydrate intake from low- and medium-GL foods and limiting high-GL foods and refraining from high-GL (≥20) foods; target energy deficit, 500–1000 kcal/d; dietary advice about GI and GL of food, quantification and recording food intake, and food exchange were provided at baseline and participants were visited bi-weekly by a dietitian	HGL: conventional hypocaloric diet; E%: CHO, 55%; F, 30%; P, 15%; fiber: NR; target energy deficit, 500–1000 kcal/d; dietary advice about quantification and recording food intake and food exchange were provided at baseline and participants were visited bi-weekly by a dietitian	↓Fasting insulin, ↔fasting glucose, ↓HOMA-IR, ↔TC, ↔LDL-C, ↔HDL-C, ↔TG, ↔weight, ↓WC, ↔TT, ↔FAI

(*Continued*)

TABLE 1 (*Continued*)

Author, year (reference), country	Participants' characteristics [*n*, mean age (y), mean BMI (kg/m^2)], and PCOS definition	RCT design (blinding) and setting	Duration	Intervention diet characteristics [type, composition (%, mean, or range), and recommendations]	Control diet characteristics [type, composition (%, mean, or range), and recommendations]	Reported outcomes of interest
Panico et al., 2014 (76), Italy	Total completers, 14 (Intervention, 7; Control, 7); age: 23.4, BMI, 28.7; PCOS definition, modified Rotterdam (9 FNPO 2–8 mm and DHEAS >248 μg/dL)	Parallel (NR); setting, academic medical center	3 mo in 2 periods; (washout period, NR)	LGL: low-GL diet; E%: CHO, 44–45%; F, 37–38%; P, 18%; fiber: 25–35 g/d; GI: 63–69; GL: 79–105; no energy restriction was prescribed; target energy intake, 1500–1800 kcal/d; dietary advice at baseline and bi-weekly visits with a dietitian were provided during intervention	HGL: moderately high GL diet; E%: CHO, 50–52%; F, 29–30%; P, 19–20%; fiber: 34–44 g/d; GI, 66–68; GL, 123–134; no energy restriction was prescribed; target energy intake, 1500–1800 kcal/d; dietary advice at baseline and bi-weekly visits with a dietitian were provided during intervention	↔Fasting insulin, ↔fasting glucose, ↔HOMA-IR, ↔TC, ↔TG, ↔weight, ↓TT
Sordia-Hernandez et al., 2016 (77), Mexico	Total completers, 37 (Intervention, 19; Control, 18); Intervention, age: 26.1, BMI, NR; Control, age: 26.1, BMI, NR; PCOS definition, Rotterdam	Parallel (NR); setting, academic medical center	3 mo	LGI: low-GI diet; E%: CHO, 45–50%; F, 30–40%; P, 15–20%; fat composition: 10–15% MUFA, <10% PUFA, <10% SFA; fiber: 20–35 g/d; GI: <45; target energy intake, 1200–1500 kcal/d; dietary advice about complex carbohydrate intake and sources of omega-3 fatty acids and dietary evaluation were provided at baseline, and participants were visited monthly by a dietitian	HGI: normal-GI diet; E%: CHO, 45–50%; F, 30–40%; P, 15–20%; fat composition: 10–15% MUFA, <10% PUFA, <10% SFA; fiber: 20–35 g/d; GI: 50–75; target energy intake, 1200–1500 kcal/d; dietary advice about complex carbohydrate intake and sources of omega-3 fatty acids and dietary evaluation were provided at baseline, and participants were visited monthly by a dietitian	↔Weight
Turner-McGrievy et al., 2014 (15), USA	Total completers, 18 (Intervention, 9, Control, 9); Intervention, age: 28.1, BMI, 42.7; Control, age: 27.4, BMI, 37.2; PCOS criteria, Rotterdam	Parallel (no); setting, academic medical center	6 mo	LGI: vegan low-GI diet; E%: NR; fiber: NR; no energy restriction was prescribed; dietary advice on a vegan diet and a vegan recipe book of high-GI foods to limit and the low-GI foods to include were provided at baseline and participants were visited at baseline and every 3 mo	HGI: conventional hypocaloric diet; E%: NR; fiber: NR; target energy intake: 1200 or 1500 kcal/d; dietary plan for weight loss and a book containing calorie and fat grams of common foods were provided at baseline and participants were visited at baseline and every 3 mo	↔Weight

[1] AEPCOS, Androgen Excess and Polycystic Ovary Syndrome; CHO, carbohydrate; DASH, Dietary Approaches to Stop Hypertension; DHEAS, dehydroepiandrosterone sulfate; E, energy; F, fat; FAI, free androgen index; fiber, total dietary fiber; FNPO, follicle numbers per ovary; GI, glycemic index; GL, glycemic load; HDL-C, HDL cholesterol; HGI, higher glycemic index diet; HGL, higher glycemic load; LDL-C, LDL cholesterol; LGI, lower glycemic index; LGL, lower glycemic load; NR, not reported; OV, ovarian volume; P, protein; PCO, polycystic ovaries; PCOS, polycystic ovary syndrome; RCT, randomized controlled trial; TC, total cholesterol; TG, triglyceride; TLC, therapeutic lifestyle changes; TT, total testosterone; WC, waist circumference. ↓denote decreases in evaluated outcome measures in LGI diets compared to HGI diets and ↔ denote comparable effects of LGI and HGI diets.

Quality assessments

The risk of bias was assessed for each trial (**Supplemental Table 3**) and is summarized herein. Briefly, the generation of random allocation for participants was reported in 8 trials (15, 16, 56–58, 71–75, 77) and unclear in 2 (54, 76). Concealment of allocation sequence was described in 3 trials (16, 54, 57, 74), which had a low risk of bias, whereas 1 trial (15) had a high risk and the other 6 (56, 58, 71–73, 75–77) had an unclear risk. Seven trials (16, 56–58, 71–75) exhibited a low risk of bias, 1 trial (15) had a high risk, and 2 trials (76, 77) had an unclear risk when considering the blinding of the intervention. Seven trials (16, 54, 56, 57, 71–74, 76) had a low risk of bias about blinding their assessors, and 3 (15, 58, 75, 77) had an unclear risk. Two trials (54, 76) had a high risk of bias for complete reporting of their outcome data, and the other 8 (15, 16, 56–58, 71–75, 77) showed a low risk. Trials appeared to have a low risk of bias for selective outcome reporting.

Systematic review

Three studies (54, 76, 77) that were ineligible for pooled meta-analyses were included in the qualitative review herein. The first 2 studies by Mehrabani et al. (54) and Panico et al. (76) focused on the effects of the LGL diets on cardiometabolic and reproductive outcomes; we were unable to conduct meta-analyses for LGL diets given the small number of available trials. Both studies had a comparable duration of the intervention (12 wk); the number of women who completed the intervention in the study by Mehrabani et al. (54) was ~3.5-fold higher, and their participants followed an energy-restricted protocol (energy deficit, 500–1000 kcal/d) when compared with that of Panico et al. (76), as described in Table 1. Mehrabani et al. (54) reported improved metabolic status, including decreased fasting insulin concentrations, HOMA-IR, and WC. Conversely, Panico et al. (76) only reported decreased TT in the LGL diet group. The third study included in the qualitative review was by Sordia-Hernandez et al. (77), where the SD data of weight change in their experimental arms were not reported and, therefore, the data were insufficient for pooling results. However, the investigators reported comparable decreases in the body weight of women with PCOS following a 3-mo intervention that was composed of hypocaloric (energy deficit, 1200–1500 kcal/d) LGI and a normal-GI diet as elaborated in Table 1.

Meta-analyses

Glucoregulatory status.

HOMA-IR. LGI diets decreased HOMA-IR when compared with HGI diets (WMD: −0.78; 95% CI: −1.20, −0.37; $P<0.001$; **Supplemental Figure 1**A) using pooled data from 4 eligible studies (16, 58, 71, 74). High heterogeneity was observed among the studies ($I^2 = 86.6\%$; $P<0.001$).

The result of the subgroup analyses based on energy restriction appeared to explain the observed heterogeneity; HOMA-IR was decreased only in trials that applied energy restriction (WMD: −1.02; 95% CI: −1.46, −0.57; $P<0.001$; **Table 2**). We were unable to conduct subgroup analyses based on participant's age and study duration since only single studies had subsets with younger age (≤30 y) (71) or longer intervention periods (≥16 wk) (16).

The results of sensitivity analyses showed excluding studies by Asemi et al. (WMD: −0.42; 95% CI: −1.00, 0.23; $P = 0.20$) (71) and Foroozanfard et al. (WMD: −0.51; 95% CI: −1.53, 0.50; $P = 0.31$) (74) altered the overall effect size. No evidence of publication bias was found ($P = 1.00$, Begg's test, and $P = 0.90$, Egger's test).

Insulin. LGI diets decreased fasting insulin concentrations when compared with HGI diets (WMD: −2.39; 95% CI: −4.78, −0.00 μIU/mL; $P = 0.05$; Supplemental Figure 1B), as reflected by pooled data from 5 eligible studies (16, 58, 71, 72, 74). However, high heterogeneity was observed among the studies ($I^2 = 76.8\%$; $P = 0.002$).

Results of the subgroup analyses showed participant's age, energy restriction, and study duration explained the sources of heterogeneity (Table 2). Accordingly, decreases in the fasting insulin concentrations following the LGI diet were only evident in younger participants (≤30 y; WMD: −4.07; 95% CI: −5.86, −2.27 μIU/mL; $P<0.001$), trials with prescribed energy restriction (WMD: −3.10; 95% CI: −6.13, −0.06 μIU/mL; $P = 0.04$), and trials with shorter duration (<16 wk; WMD: −3.73; 95% CI: −5.91, −1.55 μIU/mL; $P<0.001$) when compared with older (>30 y) participants, trials without energy restriction, or longer duration (≥16 wk), respectively (Table 2).

Results of sensitivity analyses showed excluding studies by Asemi et al. (WMD: −1.30; 95% CI: −2.95, 0.35 μIU/mL; $P = 0.12$) (71), Foroozanfard et al. (WMD: −1.96; 95% CI: −4.90, 0.98 μIU/mL; $P = 0.19$) (74), and Kazemi et al. (WMD: −2.63; 95% CI: −5.29, 0.03 μIU/mL; $P = 0.53$) (16) altered the overall effect estimates. We observed no evidence of publication bias in the studies ($P = 0.62$, Begg's test, and $P = 0.11$, Egger's test).

Glucose. Pooling data from 5 eligible studies (16, 58, 71, 72, 74) showed no differences between the LGI and HGI diets on fasting glucose concentrations (WMD: −2.21; 95% CI: −6.30, 1.89 mg/dL; $P = 0.29$; Supplemental Figure 1C). High heterogeneity was evident among the studies ($I^2 = 92.9\%$; $P<0.001$).

Results of the subgroup analyses based on study duration appeared to explain the heterogeneity, but participants' age and energy restriction did not explain the heterogeneity (Table 2); decreases in fasting glucose concentrations were more pronounced in the LGI diets with a shorter intervention duration (<16 wk; WMD: −4.13; 95% CI: −7.70, −0.56 mg/dL; $P < 0.02$) in contrast to LGI diets with a longer intervention duration (≥16 wk; Table 2).

None of the individual studies influenced the overall effect sizes, as evidenced by the results of sensitivity analyses. We observed no evidence of publication bias ($P = 0.99$, Begg's test, and $P = 0.58$, Egger's test).

TABLE 2 Subgroup analyses to assess the effects of an LGI diet on glycemic parameters based on anthropometric indices, glucoregulatory status, lipid profile, and androgen status in women with polycystic ovary syndrome[1]

Subgrouped by	Number of trials	Effect size	95% CI	*P* value for effect estimates[2]	I^2, %	*P* value for within-subgroup heterogeneity[2]	*P* value for between-subgroup heterogeneity[3]
Fasting insulin, μIU/mL							
Participant's age							<0.001
>30 y	2	−0.44	2.43 to 1.54	0.66	0.0	0.82	
≤30 y	3	−4.07	−5.86 to −2.27	<0.001	34.9	0.21	
Energy restriction							0.02
Yes	3	−3.10	−6.13 to −0.06	0.04	83.5	0.002	
No	2	−0.89	−3.66 to 1.88	0.53	0.0	0.94	
Study duration							<0.001
≥16 wk	2	−0.47	−2.52 to 1.59	0.65	0.0	0.77	
<16 wk	3	−3.73	−5.91 to −1.55	0.001	53.2	0.11	
Fasting glucose, mg/dL							
Participant's age							0.002
>30 y	2	−1.36	−6.00 to 3.24	0.55	68.4	0.07	
≤30 y	3	−2.85	−7.82 to 2.12	0.26	83.6	0.002	
Energy restriction							0.87
Yes	3	−2.40	−7.28 to 2.47	0.33	96.3	<0.001	
No	2	−0.68	−11.43 to 10.08	0.90	55.0	0.13	
Study duration							<0.001
≥16 wk	2	0.47	−0.95 to 1.88	0.52	0.0	0.35	
<16 wk	3	−4.13	−7.70 to −0.56	0.02	78.7	0.009	
HOMA-IR							
Energy restriction							0.03
Yes	2	−1.02	−1.46 to −0.57	<0.001	93.9	<0.001	
No	2	−0.02	−0.74 to 0.70	0.95	0.0	0.41	
TC, mg/dL							
Participant's age							0.91
>30 y	2	−11.74	−24.95 to 1.47	0.08	0.0	0.35	
≤30 y	2	−10.88	−19.29 to −2.47	0.01	0.0	0.80	
Energy restriction							0.47
Yes	2	−7.00	−20.29 to 6.29	0.30	0.0	0.70	
No	2	−12.78	−21.16 to −4.39	0.003	0.0	0.60	
Study duration							0.72
≥16 wk	2	−10.19	−19.02 to −1.37	0.02	0.0	0.52	
<16 wk	2	−12.84	−24.76 to −0.92	0.03	0.0	0.53	
LDL-C, mg/dL							
Participant's age							0.14
>30 y	2	−13.27	−24.40 to −2.33	0.01	0.0	0.73	
≤30 y	2	−3.61	−10.35 to 3.13	0.29	0.0	0.92	
Energy restriction							0.85
Yes	2	−7.05	−17.07 to 2.97	0.16	0.0	0.40	
No	2	−7.21	−17.57 to 3.15	0.17	35.7	0.21	
Study duration							0.68
≥16 wk	2	−5.51	−12.34 to 1.32	0.11	0.0	0.35	
<16 wk	2	−8.33	−20.36 to 3.70	0.17	21.7	0.28	
HDL-C, mg/dL							
Participant's age							0.02
>30 y	2	−2.03	−7.36 to 3.30	0.45	0.0	0.40	
≤30 y	2	4.13	−3.49 to 11.77	0.28	81.0	0.02	
Energy restriction							0.004
Yes	2	−1.57	−5.76 to 2.77	0.49	0.0	0.38	
No	2	5.32	−1.26 to 11.90	0.11	54.8	0.13	
Study duration							<0.001
≥16 wk	2	2.31	−9.13 to 13.75	0.69	88.1	0.004	
<16 wk	2	0.23	−4.34 to 4.79	0.92	0.0	0.88	
TG, mg/dL							
Participant's age							0.05
>30 y	2	−2.93	−19.15 to 13.28	0.72	0.0	0.75	
≤30 y	2	−24.79	−39.95 to −9.63	0.001	0.0	0.47	

(*Continued*)

TABLE 2 (*Continued*)

Subgrouped by	Number of trials	Effect size	95% CI	*P* value for effect estimates[2]	I^2, %	*P* value for within-subgroup heterogeneity[2]	*P* value for between-subgroup heterogeneity[3]
Energy restriction							0.11
Yes	2	−25.38	−42.75 to −7.98	0.004	0.0	0.37	
No	2	−7.40	−22.33 to 7.52	0.33	6.3	0.30	
Study duration							0.93
≥16 wk	2	−15.31	−36.21 to 5.59	0.15	0.0	0.71	
<16 wk	2	−15.21	−42.08 to 11.67	0.26	76.2	0.04	
Weight, kg							
Participant's age							0.18
>30 y	3	−1.39	−2.48 to −0.30	0.01	0.0	0.97	
≤30 y	4	−0.90	−2.74 to 0.94	0.33	83.1	<0.001	
Energy restriction							0.87
Yes	5	−1.08	−2.33 to 0.18	0.09	78.5	0.001	
No	2	−0.57	−5.44 to 4.30	0.81	0.0	0.98	
Study duration							0.001
≥16 wk	3	0.07	−1.78 to 1.93	0.93	48.3	0.14	
<16 wk	4	−1.62	−2.48 to −0.76	<0.001	67.9	0.005	
WC, cm							
Participant's age							0.18
>30 y	2	−3.63	−9.24 to 1.98	0.20	78.7	0.03	
≤30 y	2	−3.10	−3.47 to −2.72	<0.001	0.0	0.87	
Study duration							
≥16 wk	2	−4.81	−9.03 to −0.60	0.02	33.7	0.21	0.31
<16 wk	2	−2.37	−4.18 to −0.56	0.01	74.9	0.04	
TT, nmol/L							
Participant's age							0.24
>30 y	3	−0.25	−0.36 to −0.14	<0.001	0.0	0.38	
≤30 y	2	−0.12	−0.31 to 0.07	0.21	9.5	0.29	
Energy restriction							0.28
Yes	3	−0.24	−0.34 to −0.13	<0.001	0.0	0.53	
No	2	−0.18	−0.71 to 0.35	0.49	49.5	0.15	
Study duration							0.08
≥16 wk	2	0.02	−0.26 to 0.31	0.87	0.0	0.51	
<16 wk	3	−0.25	−0.35 to −0.14	<0.001	0.0	0.63	
FAI							
Participant's age							0.01
>30 y	2	−1.76	−4.14 to 0.62	0.14	65.8	0.08	
≤30 y	2	−0.09	−0.17 to −0.01	0.03	0.0	0.88	
Energy restriction							0.94
Yes	2	−1.35	−4.12 to 1.41	0.33	88.7	0.003	
No	2	−0.13	−1.20 to 0.93	0.80	0.0	0.66	

[1]FAI, free androgen index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LGI, lower glycemic index; TC, total cholesterol; TG, triglyceride; TT, total testosterone; WC, waist circumference.
[2]Calculated by random-effects models.
[3]Calculated by fixed-effects models.

Lipid profile.

Total cholesterol. LGI diets decreased fasting TC concentrations when compared with HGI diets (WMD: −11.13; 95% CI: −18.23, −4.04 mg/dL; $P = 0.002$; **Supplemental Figure 2**A) as evidenced by pooled data from 4 eligible studies (16, 56, 58, 72). The studies were homogenous ($I^2 = 0.0\%$; $P = 0.82$).

Results of our a priori subgroup analyses revealed TC concentrations were decreased only in LGI dietary interventions where participants were younger (≤30 y; WMD: −10.88; 95% CI: −19.29, −2.47 mg/dL; $P = 0.01$; Table 2) and no prescribed energy restriction was applied (WMD: −12.78; 95% CI: −21.16, −4.39 mg/dL; $P = 0.003$); however, subgroup analyses based on the duration of LGI diets did not have a differential effect, as both shorter (<16 wk; WMD: −12.84; 95% CI: −24.76, −0.92 mg/dL; $P = 0.03$) and longer (≥16 wk; WMD: −10.19; 95% CI: −19.02, −1.37 mg/dL; $P = 0.02$) trials exhibited decreased TC concentrations postintervention (Table 2).

Sensitivity analyses showed the results of our meta-analysis for TC were not affected by the removal of any individual study. No evidence of publication bias was observed ($P = 0.17$, Begg's test, and $P = 0.65$, Egger's test).

LDL cholesterol. LGI diets decreased fasting LDL-cholesterol concentrations when compared with HGI diets (WMD: −6.27; 95% CI: −12.01, −0.53 mg/dL; $P = 0.03$; Supplemental Figure 2B), as evidenced by pooled data of

4 eligible studies (16, 56, 58, 72). The studies were homogenous ($I^2 = 0.0\%$; $P = 0.51$).

Results of our a priori subgroup analyses revealed a significant reduction in LDL cholesterol only in the LGI dietary interventions in older participants (>30 y; WMD: −13.27; 95% CI: −24.20, −2.33 mg/dL; $P = 0.01$; Table 2). The significant effects of the LGI diets on LDL-cholesterol concentrations were not maintained after analyses were subgrouped by energy restriction or study duration (Table 2).

Sensitivity analyses showed the exclusion of studies by Atiomo et al. (72) (WMD: −5.29; 95% CI: −11.53, 0.94 mg/dL; $P = 0.09$) and Gower et al. (58) (WMD: −5.01; 95% CI: −11.13, 1.10 mg/dL; $P = 0.10$) altered the overall effect sizes. Begg's test and Egger's test showed $P = 0.05$ and $P = 0.25$, respectively.

HDL cholesterol. LGI diets were not significantly different from HGI diets for increasing HDL-cholesterol concentrations (WMD: 1.61; 95% CI: −4.05, 7.28 mg/dL; $P = 0.57$; Supplemental Figure 2C), as shown by pooling data from 4 studies (16, 56, 58, 72). Studies were moderately heterogeneous ($I^2 = 73.1\%$; $P = 0.01$).

Subgroup analyses showed participant's age, energy restriction, and study duration explained the heterogeneity, as evidenced by I^2 statistics, albeit the effect estimates were not significant in any of the evaluated subgroups (Table 2).

Results of the sensitivity analyses showed excluding individual studies did not change the overall effect estimate. No evidence of publication bias was observed ($P = 0.49$, Begg's test, and $P = 0.18$, Egger's test).

Triglycerides. Pooled data from 4 eligible trials (16, 56, 58, 72) showed a significant reduction in fasting TG concentrations with LGI diets when compared with HGI diets (WMD: −14.85; 95% CI: −28.75, −0.95 mg/dL; $P = 0.03$; Supplemental Figure 2D). The studies were moderately heterogeneous ($I^2 = 31.0\%$; $P = 0.22$).

The reduction in TG concentrations was evident only in younger participants (≤30 y; WMD: −24.79; 95% CI: −39.95, −9.63 mg/dL; $P = 0.001$) and in trials with energy-restricted protocols (WMD: −25.38; 95% CI: −42.78, −7.98 mg/dL; $P = 0.004$) when compared with subgroups who were older (>30 y) or without energy-restricted protocols (Table 2). The effects of LGI diets on TGs did not remain significant in any of the evaluated subsets after subgrouping studies by the intervention duration (Table 2).

Results of the sensitivity analysis showed excluding studies by Atiomo et al. (72) (WMD: −15.73; 95% CI: −32.84, 1.38 mg/dL; $P = 0.07$), Asemi et al. (56) (WMD: −7.43; 95% CI: −20.95, 6.08 mg/dL; $P = 0.28$), and Kazemi et al. (16) (WMD: −13.97; 95% CI: −33.72, 5.77 mg/dL; $P = 0.16$) from the analyses altered the overall effect estimate. We observed no evidence of publication bias ($P = 1.00$, Begg's test, and $P = 0.96$, Egger's test).

Anthropometrics.

Weight. Pooled data from 7 eligible studies (15, 16, 56, 72–75) showed no significant effects of LGI diets on body weight compared with HGI diets (WMD: –1.04; 95% CI: –2.19, 0.10 kg; $P = 0.07$; **Supplemental Figure 3**A). The studies were moderately heterogeneous ($I^2 = 67.9\%$; $P = 0.005$).

Subgroup analysis showed that participant's age, energy restriction, and study duration explained the heterogeneity (Table 2); decreases in body weight were evident in LGI diets with older participants (>30 y; WMD: −1.39; 95% CI: −2.48, −0.30 kg; $P = 0.01$) and studies with a shorter intervention period (<16 wk; WMD: −1.62; 95% CI: −2.48, −0.76 kg; $P<0.001$) when compared with younger participants or longer interventions (Table 2). By contrast, the effects of the LGI diet on weight was not significant in subgroup analyses based on energy restriction (Table 2).

Excluding the Turner-McGrievy et al. study (15) from the analyses altered the overall effect size (WMD: −1.47; 95% CI: −2.08, −0.87 kg; $P < 0.001$). We observed no evidence of publication bias ($P = 0.65$, Begg's test, and $P = 0.88$, Egger's test).

Waist circumference. LGI diets decreased WC when compared with HGI diets (WMD: −2.81; 95% CI: −4.40, −1.23 cm; Supplemental Figure 3B) using pooled data from 4 studies (16, 71–73). The studies were moderately heterogeneous ($I^2 = 53.9\%$; $P = 0.08$).

Results of the subgroup analysis showed participant's age and study duration explained heterogeneity. Decreased WC in LGI diets was observed in younger participants (≤30 yr; WMD: −3.10; 95% CI: −3.47, −2.72 cm; $P <$ 0.001) in contrast to older participants (Table 2). When the meta-analysis was subgrouped by the study duration, the significant effects of LGI diets on WC were observed in both subsets (Table 2). We were unable to conduct subgroup analyses based on energy restriction given the small number ($n = 1$) of studies (16) without energy restriction.

The overall meta-analysis effect estimates were sensitive to the Asemi et al. (71) study (WMD: −3.06; 95% CI: −6.40, 0.27 cm; $P = 0.07$). We observed no evidence of publication bias ($P = 0.49$, Begg's test, and $P = 0.93$, Egger's test).

Androgen status.

Total testosterone. LGI diets decreased fasting TT concentrations compared with HGI diets (WMD: −0.21; 95% CI: −0.32, −0.09 nmol/L; $P < 0.001$; **Supplemental Figure 4**A), as evaluated by pooled data from 5 eligible studies (57, 58, 72–74). The heterogeneity was low ($I^2 = 8.6\%$; $P = 0.36$) among the studies.

Result of our a priori subgroup analyses revealed decreased TT concentrations were pronounced only in the LGI diets where participants were older (>30 y; WMD: −0.25; 95% CI: −0.36, −0.14 nmol/L; $P < 0.001$), energy restriction was prescribed (WMD: −0.24; 95% CI: −0.34, −0.13 nmol/L; $P<0.001$), and in shorter trials (<16 wk; WMD: −0.25; 95% CI: −0.35, −0.14 nmol/L; $P < 0.001$; Table 2).

Sensitivity analyses showed excluding studies by Azadi-Yazdi et al. (73) (WMD: −0.13; 95% CI: −0.32, 0.05 nmol/L; $P = 0.16$) and Foroozanfard et al. (74) (WMD: −0.17; 95% CI: −0.38, 0.02 nmol/L; $P = 0.08$) altered the overall effect estimates. We observed no evidence of publication bias ($P = 0.32$, Begg's test, and $P = 0.53$, Egger's test).

Free androgen index. Analyses of pooled data from 4 eligible studies (57, 58, 73, 74) showed that LGI diets did not significantly lower FAI compared with HGI diets (WMD: −0.63; 95% CI: −1.66, 0.40; $P = 0.23$; Supplemental Figure 4B). The studies were moderately heterogeneous ($I^2 = 66.9\%$; $P = 0.03$). Participant's age explained the heterogeneity in the subgroup analyses. Decreases in FAI in the LGI diet were observed in younger participants (≤30 y; WMD: −0.09; 95% CI: −0.17, −0.01; $P = 0.03$) in contrast to older participants (Table 2). The subgroup analysis by energy restriction showed that the effect estimates were not significant in both subsets (Table 2).

We were unable to conduct subgroup analyses based on study duration as only 1 study had an intervention period of ≥16 wk (16). The sensitivity analyses showed that excluding the Azadi-Yazdi et al. (73) study resulted in a significant reduction of FAI in LGI diets compared with HGI diets (WMD: −0.09; 5% CI: −0.17, −0.08; $P = 0.03$). We observed no evidence of publication bias ($P = 0.17$, Begg's test, and $P = 0.37$, Egger's test).

Discussion

The present systematic review and meta-analysis of 10 RCTs that included 403 women who were predominantly overweight or obese and living with PCOS is the first to show LGI diets in comparison with HGI diets improve *1*) glucoregulatory status as assessed by decreased HOMA-IR and fasting insulin; *2*) lipid profile, as evidenced by decreased TC, LDL cholesterol, and TGs; *3*) abdominal adiposity, as evidenced by decreased WC; and, *4*) hyperandrogenism, as assessed by decreased TT. However, LGI diets had no significant effects over the HGI diets on fasting glucose, HDL cholesterol, body weight, or FAI. Only 2 ($n = 2$) studies were designed to investigate the impacts of LGL diets on PCOS health outcomes; therefore, meta-analyses were not possible, and the impacts of the LGL diet remain to be elucidated by future work.

Our observations add a novel dimension to current evidence about the favorable effects of modifying dietary composition by incorporating LGI diets to mitigate cardiometabolic and reproductive aberrations in women with PCOS. Further, our findings reiterate and extend those of previous systematic reviews and meta-analyses about the benefits of LGI diets on decreasing HOMA-IR (81), insulin (82, 83), TC (32, 34, 35), LDL cholesterol (32, 34, 35), and TGs (81) in non-PCOS individuals with comparable metabolic impairments to PCOS, including type 2 diabetes, dyslipidemia, metabolic syndrome, and obesity. Also, our observations corroborate previous systematic reviews and meta-analyses that showed no effects of LGI diets on HDL cholesterol in individuals with diabetes (32, 35). In contrast, we did not observe decreased fasting glucose (29) following the LGI diets. We attributed the discrepancies in fasting glucose reports to high (92.9%) heterogeneity among RCTs, albeit our subgroup analysis revealed decreased fasting glucose in LGI diets with shorter (<16 wk) duration of intervention, similar to those of fasting insulin. We acknowledge these observations are less anticipated since longer interventions are generally expected to exert more favorable effects on glucoregulatory status (61). We attribute a lack of difference in fasting glucose and insulin concentrations between the intervention and control groups who participated in trials with longer intervention periods to higher attrition rates and subsequently lower statistical power of these trials to capture any true differences. Also, decreased compliance of participants in longer interventions may contribute to these observations, consistent with previous reports (17, 84), notwithstanding we remain uncertain due to our incomplete knowledge of dietary adherence in individual RCTs. Changes in insulin concentrations in response to interventions are faster in women with PCOS when compared with glucose concentrations (7, 41, 42), which could explain significant reductions in both HOMA-IR and fasting insulin in response to LGI diets in the current work. Evaluating other markers, including glycated hemoglobin could have better reflected changes in glucoregulatory status in the long term.

The lack of effect of LGI diets on body weight in our meta-analysis does not align with previous systematic reviews and meta-analyses (32, 36). We attributed the lack of difference in weight to comparable prescribed energy contents of the diets in both intervention and control arms across all but 1 trial (15); specifically, unlike the HGI diet, the LGI diet in the trial by Turner-McGrievy et al. (15) was not energy-restricted; however, all other RCTs consistently included or excluded energy restriction across their LGI and HGI diets (Table 1). Our sensitivity analysis showed that excluding the trial by Turner-McGrievy et al. (15) significantly decreased pooled effect estimate of the weight (–1.47 kg) in favor of the LGI diet; however, subgroup analyses of all other trials based on the presence or lack of energy restriction did not reveal any effect of LGI diet on weight. Nevertheless, we cannot preclude the role of energy restriction in the overall effect estimates of other evaluated markers as our subgroup analyses revealed significant reductions of HOMA-IR, TGs, and TT where LGI diets were combined with energy restriction. Our meta-analysis indicated a reduction in testosterone in response to LGI diets in women with PCOS. We were unable to identify a systematic review and meta-analysis about the relation between dietary glycemic indices and androgen status, likely due to the lack of research about this critically important, yet largely overlooked area. However, we and others have shown decreased androgen concentrations secondary to modulations in insulin signaling and function and associated metabolic regulation in women with PCOS (57, 85–88) through mechanisms identified in Figure 1.

The biological mechanisms through which LGI diets could affect cardiometabolic and reproductive complications associated with PCOS are not fully elucidated. In general, previous reports attributed the benefits of LGI diets to their complex carbohydrate profile and high dietary fiber content, particularly soluble fiber; lower saturated fat and increased mono- and polyunsaturated fat content; plant protein in place of animal protein; low energy intake independent of calorie restriction; and a favorable micronutrient composition (24, 28, 89–92). All of these components have been individually shown to improve a wide range of cardiometabolic and associated reproductive abnormalities in PCOS (16, 19, 93, 94) and non-PCOS clinical populations (25, 85, 92, 95–100), and their respective mechanisms have been elaborated in greater detail in previous reviews (24, 38, 91, 101–106).

We observed no evidence of substantial publication bias in the evaluated outcomes, as evidenced by the Begg's and Egger's test results. However, our observations had limitations inherent to the small number and sample sizes of eligible studies that yielded large SDs for many of the evaluated outcomes, overlapping CIs, and a variable degree of heterogeneity. A primary limitation was a lack of a unique/universal definition for LGI/LGL diets, which is not uncommon in studies of this type, as corroborated in previous systematic reviews and meta-analyses (32, 36, 89, 107). Future research requires consensus on the definition of LGI/LGL (108) and subsequent modification of the nutrient composition of diets to prevent and manage PCOS health complications. We observed instability in the significance of the pooled effect estimates with the removal of single trials during sensitivity analyses. Specifically, sensitivity analyses showed the loss of significant differences between groups in some measures (HOMA-IR, fasting insulin, LDL cholesterol, TGs, and TT) and gaining significance for others (decreased body weight and FAI) following LGI diets. The control arms identified in the present work lacked minimal or no intervention. Therefore, we are limited in our ability to detect any potential placebo effects or isolated impacts of LGI/LGL diets on evaluated outcomes. A placebo or "no intervention" control is difficult to implement in women with PCOS because there are ethical considerations in failing to provide this patient population with a standard of care to manage their condition upon PCOS diagnosis. Further, it is difficult to apply a successful placebo/control group and maintain blinding in trials with whole-diet alterations (e.g., LGI/LGL diets) wherein multiple dietary components change, particularly in the long term (109). Future research should carefully consider strategies to address these barriers, including matching the intervention and placebo arms in all dietary aspects except for the active component being investigated, where possible (109, 110). Further, all included RCTs were in women with overweight or obesity, reflecting the common clinical presentation of women with PCOS; therefore, our observations may be skewed toward increased BMI classes. We considered the possibility of performing additional a priori subgroup analyses to account for potential impacts of diagnostic criteria used to identify PCOS: baseline BMI classes, dietary macronutrient composition (i.e., carbohydrate, fat, protein, and fiber), additional interventions to diet (e.g., metformin use), and type of biochemical assays used to measure TT (e.g., LC-MS). Our subgroup analyses based on PCOS diagnostic status yielded comparable results to energy restriction presented in the current work given that similar RCTs were subgrouped in both categories. However, the subgroup analyses were not possible for *1*) baseline BMI given the small number ($n = 1$) of studies that included overweight women (56), *2*) dietary macronutrient composition given the lack of sufficient reports and/or the paucity of studies (<2) in each subgroup, *3*) metformin use due to inconsistent reports on the medications, or *4*) biochemical assay since none of the evaluated studies reported the use of LC-MS. Importantly, only 50% (5/10) (16, 56, 57, 71, 73, 74, 77) of all included trials in the current work controlled for macronutrient composition (carbohydrate, fat, protein) between their intervention and control groups, whereas others lacked control (54, 58, 75, 76) or reporting (15, 72) of macronutrient composition data (Table 1). As such, questions remain to be addressed in future research regarding whether the observed benefits truly stem from modified GI levels per se or are mediated and/or confounded by altered dietary macronutrient composition. A high attrition rate was reported in some of the evaluated trials (7, 9, 10, 18) and has been identified as a challenging limitation in the lifestyle modification of women with PCOS by us and others (7, 9, 10, 13, 14, 16, 18, 19). In the trials evaluated, none reported serious adverse events (SAEs) in response to LGI or LGL diets, which may indicate the overall safety of consuming LGI/LGL diets. However, this observation may be biased by the incomplete or less consistent reports of individual trials about SAEs. In addition, our incomplete knowledge about the adherence of individual RCTs to intention-to-treat protocols as recommended by the CONSORT (111, 112) contributes to our uncertainty and caution in the interpretation of findings; the lack of these reports is often the case in PCOS trials involving lifestyle interventions and likely contributes to confounded interpretations. The degree of adherence to intervention protocol was reported in only 1 trial (16, 57) included in the present review; therefore, limiting our ability to evaluate whether the observations were skewed toward those who were able to adhere to the diets. The lack of adherence reports is especially important in longer interventions wherein compliance to LGI and/or LGL diets is likely more difficult when compared with shorter interventions, possibly contributing to observed heterogeneity in reported outcomes.

In conclusion, evidence exists that an LGI diet is associated with improved cardiometabolic and reproductive profiles in women with PCOS; however, the overall effects of an LGL diet requires further elucidation. Sources of uncertainty include small sample sizes of individual RCTs and variability in heterogeneity, attrition rate, compliance, measurements employed, and attempts to achieve weight loss across the trials, making it difficult to isolate the impact of LGI diet on PCOS outcomes. Before LGI diets are universally

recommended by healthcare providers, research is required that extends beyond intermediate biomarkers that are typically assessed (e.g., body weight or insulin resistance) and assesses more patient-important and clinically pressing yet controversial PCOS complications, including diabetes and cardiovascular disease risk, ovulatory cyclicity, and infertility.

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