Review

Lifestyle Modification Programs in Polycystic Ovary Syndrome: Systematic Review and Meta-Analysis

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Context: Polycystic ovary syndrome (PCOS) is a prevalent disorder that affects women of childbearing age and may be related to obesity and insulin resistance.

Objective: The purpose of this systematic review was to appraise the evidence of the impact of lifestyle modification (LSM) interventions on outcomes of women with PCOS.

Data Sources: Sources included Ovid Medline, OVID Embase, OVID Cochrane Library, Web of Science, Scopus, PsycINFO, and CINAHL (up to January 2011).

Study Selection: We included randomized controlled trials that enrolled woman of any age with PCOS who received LSM and compared them against women who received no intervention, minimal intervention, or metformin.

Data Extraction: Two authors performed the data extraction independently.

Data Synthesis: We included 9 trials enrolling 583 women with a high loss to follow-up rate, lack of blinding, and short follow-up. Compared with minimal intervention, LSM significantly reduced fasting blood glucose (weighted mean difference, −2.3 mg/dL; 95% confidence interval, −4.5 to −0.1, $I^2 = 72\%$, $P = .04$) and fasting blood insulin (weighted mean difference, −2.1 μU/mL, 95% confidence interval, −3.3 to −1.0, $I^2 = 0\%$, $P < .001$). Changes in body mass index were associated with changes in fasting blood glucose ($P < .001$). Metformin was not significantly better than LSM in improving blood glucose or insulin levels. We found no significant effect of LSM on pregnancy rate, and the effect on hirsutism was unclear.

Conclusions: The available evidence suggests that LSM reduces fasting blood glucose and insulin levels in women with PCOS. Metformin has similar effects. Translation of these short-term effects to patient-important outcomes, beyond diabetes prevention, remains uncertain. **(*J Clin Endocrinol Metab* 98: 4655–4663, 2013)**

Polycystic ovary syndrome (PCOS) is a prevalent disorder that affects approximately 10% of women of childbearing age (1, 2) with classic features of anovulatory infertility, menstrual dysfunction, and hirsutism (3). Other important manifestations include metabolic abnormalities, including insulin resistance and dyslipidemia, low-grade inflammation, an increased risk of type 2 diabetes, and cardiometabolic risk particularly in the presence of obesity (4–8).

Approximately 50% of the affected women are overweight or obese, and some studies demonstrate greater visceral fat tissue than that of body mass index (BMI)–matched healthy control women (9, 10). Obesity greatly affects the severity of PCOS and might have an important role in the development of hyperandrogenism and chronic anovulation (11). Increased amounts of adipose tissue are associated with numerous abnormalities of sex steroid metabolism such as increased androgen production and suppression of sex hormone–binding globulin. Obese patients with PCOS have more severe cardiovascular and metabolic risk factors than their lean counterparts (12).

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Abbreviations: BMI, body mass index; FBG, fasting blood glucose; FBI, fasting blood insulin; FGS, Ferriman-Gallwey score; LSM, lifestyle modification; MI, minimal intervention; OR, odds ratio; PCOS, polycystic ovary syndrome; RCT, randomized controlled trial; WMD, weighted mean difference.

Obesity, abdominal obesity, and weight gain in teenage and adult women can be used as predictors of the future presence of hirsutism and menstrual irregularities in PCOS (13).

Given the association of insulin resistance with increased cardiometabolic risk, its reduction is one of the primary goals in treating obesity and PCOS (14). In most cases, this can be achieved with modest weight reduction (15–17). Lifestyle modification (LSM) programs, comprising diet and/or physical activity, are recommended for high-risk patients (prediabetic) to delay the onset of adult type 2 diabetes (18, 19), one of the most serious complications of PCOS. In addition, overweight and obese women with PCOS may benefit from LSM through adiposity reduction (20), improved ovulatory function (21), and a reduction in overall cardiovascular risk (22). Whether LSM may improve some aspects of the phenotype in normal-weight women with PCOS is still unclear. However, sustained weight loss achieved after bariatric surgery (23) or long-term dietary intervention (24) has been found to significantly improve the phenotype in most women with PCOS.

Previous observational studies showed that LSM can be associated with clinical improvement in PCOS. Kiddy et al (15) demonstrated that moderate weight loss during long-term calorie restriction is associated with marked clinical improvement in menstrual function and fertility. Clark et al (16) demonstrated in a retrospective study that weight loss is associated with improvement in ovulation, pregnancy outcome, self-esteem, and endocrine parameters in women who are infertile and overweight.

The Endocrine Society formed a task force of experts to develop clinical practice guidelines to aid practicing clinicians in the provision of care to women with PCOS. Consistent with the Institute of Medicine guidance (25), The Endocrine Society commissioned the conduct of systematic reviews to support the development of key recommendations. In this systematic review and meta-analysis, we aim to appraise and summarize the evidence about the benefits associated with LSM in women with PCOS.

Materials and Methods

Search and analyses methods, eligibility criteria, and the outcomes of interest were specified in advance in a protocol, developed by the task force and study investigators. Outcomes of interest were chosen based on importance to patients and necessity for decision making. Patient-important outcomes were hirsutism (measured by the modified Ferriman-Gallwey score [FGS]), fertility, amenorrhea, and acne. Metabolic outcomes such as fasting blood glucose (FBG) and insulin (FBI) were also included.

Eligibility criteria

We included randomized controlled trials (RCTs) that enrolled woman of any age with PCOS who received LSM, broadly comprising modifications of diet and/or physical activity, and compared them against women who had the same diagnosis but received metformin, the most commonly used agent in PCOS (26, 27) or minimal intervention (MI), which could be a control or placebo intervention.

Search methods

An expert reference librarian (P.J.E.), following the protocol, designed and conducted an electronic search strategy (Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). We searched electronic databases to identify relevant studies (Ovid Medline, OVID Embase, OVID Cochrane Library, Web of Science, Scopus, PsycINFO, and CINAHL) through January 2011. To identify additional candidate studies, we reviewed the reference lists of the eligible primary studies, narrative reviews, and systematic reviews, and we queried the expert members of the commissioning task force.

Selection of studies

Two reviewers working independently considered the potential eligibility of each of the abstracts and titles that result from executing the search strategy. Eligible studies were reviewed in full-text versions (all available versions of each study). There were no disagreements between the reviewers in the full text screening.

Data extraction and management

Using a standardized, piloted, and web-based data extraction form and working in duplicates, we abstracted the following descriptive data from each study: full descriptions of participants enrolled (principal baseline characteristics such as age, childbearing, weight, and BMI), the interventions they received (type and frequency), the control interventions, the monitoring for efficacy of the follow-up and adherence to the treatment, the measure of outcome (specifically defined as an event or measure and time frame for the ascertainment of this outcome) and the source of funding. We extracted the outcomes of interest at the longest point of complete follow-up.

Knowledge and Evaluation Research Unit (J.P.D., G.P., R.J.M., A.W., P.E., A.B., V.M.M., M.H.M.), Division of Preventive, Occupational and Aerospace Medicine (M.H.M.), Division of Endocrinology, Diabetes, Metabolism, Nutrition (V.M.M.), and Division of General Internal Medicine (A.W.), Mayo Clinic, Rochester, Minnesota 55905; Unidad de Conocimiento y Evidencia (J.P.D., G.P. V.M.M.), Lima, Peru 32; Department of Internal Medicine (A.H.), University of North Dakota, Fargo, North Dakota 58102; Division of Endocrinology (R.P.), Department of Clinical Medicine, Sant'Orsola-Malpighi Hospital, University Alma Mater Studiorum of Bologna, 40126 Bologna, Italy; University of Minnesota Medical School (R.J.M.), Minneapolis, Minnesota 55455; Division of Endocrinology and Metabolism (V.S.), Louisiana State University Health Sciences Center, Shreveport, Louisiana 70112; Department of Obstetrics and Gynecology (K.H.), Division of Reproductive Endocrinology, University of Rochester Medical Center, Rochester, New York 14627; Pharmacy Practice (O.J.P.), Western University of Health Sciences, Pomona, California 91766; Department of Medicine (M.B.E.), Texas Tech University Health Science Center at Amarillo, Amarillo, Texas 79106; Department of Pediatrics (G.P.), Children's Hospital of Michigan, Wayne State University School of Medicine/Detroit Medical Center, Detroit, Michigan 48201; and Department of Internal Medicine (J.P.D.), Henry Ford Hospital, Detroit, Michigan 48202

Author contact

When data were not available from the published articles, repeated efforts were made to contact the authors. We decided a priori to attempt a maximum of 2 times per each author (through e-mail), with 2 weeks between each attempt. When the author's e-mail address was not available, the contacts were made by mail.

Assessment of risk of bias in included studies

To assess the methodological quality of the included RCTs, we used the Cochrane risk of bias assessment tool to evaluate randomization performance and methods, allocation concealment, baseline imbalances, extent of blinding (patients, caregivers, data collectors, outcome assessors, and data analysts), rate of loss to follow-up, and monitoring of adherence.

Meta-analysis

For dichotomous outcomes we estimated the odds ratio (OR), and for continuous outcomes we estimated the weighted mean difference (WMD). The I^2 statistic was used to measure inconsistency in results across studies not attributable to chance (28). To pool data across studies, we tested random-effects and fixed-effects models and present results for both. When the I^2 statistic is 0 (ie, there is no heterogeneity), the 2 models converge, and data are presented only for 1 model. The random-effects model offers the advantage of incorporating within-study and between-study variances, whereas the fixed-effects model provides more reliable estimates of between-study variance when the number of included studies is small. Our analyses were performed using Comprehensive Meta-Analysis (version 2.2; BioStat Inc.).

Assessment of publication bias

Evaluation of publication bias was not feasible because of heterogeneity and the small number of included studies (29).

Subgroup analysis, meta-regression, and sensitivity analysis

We determined a priori hypotheses (limited to a small number to avoid chance findings) to explore subgroup interactions and give a potential explanation for heterogeneity. Subgroup analyses were based on (1) patients: baseline BMI (<30 vs >30 kg/m^2); (2) interventions: physical exercise vs diet vs combined strategies; (3) study quality (good to moderate vs fair to poor); and (4) achieved weight reduction vs no weight reduction achieved. We conducted a test of interaction (30) to evaluate the significance of subgroup analyses and potential correlation between subgroups and the pooled effect size. We also performed a meta-regression to assess the correlation between BMI reduction (independent variable) and metabolic parameters (dependent variable). We tested every outcome in sensitivity analysis to determine the extent to which the choice of meta-analytic model (fixed effect vs random effects) affects the inferences of each result.

Results

Search results and study description

A literature search identified 745 articles of which 9 RCTs in 10 publications were eligible (Figure 1). The meta-analysis included 610 women; their mean age was 27 years (range, 18–35 years). The average length of the follow-up was 5 months (range, 1.5–11 months). Five RCTs enrolled obese patients, and 4 RCTs enrolled overweight patients. The interventions evaluated in the trials were hypocaloric diet alone in 1 RCT, physical exercise alone in 3 RCTs (1 not included

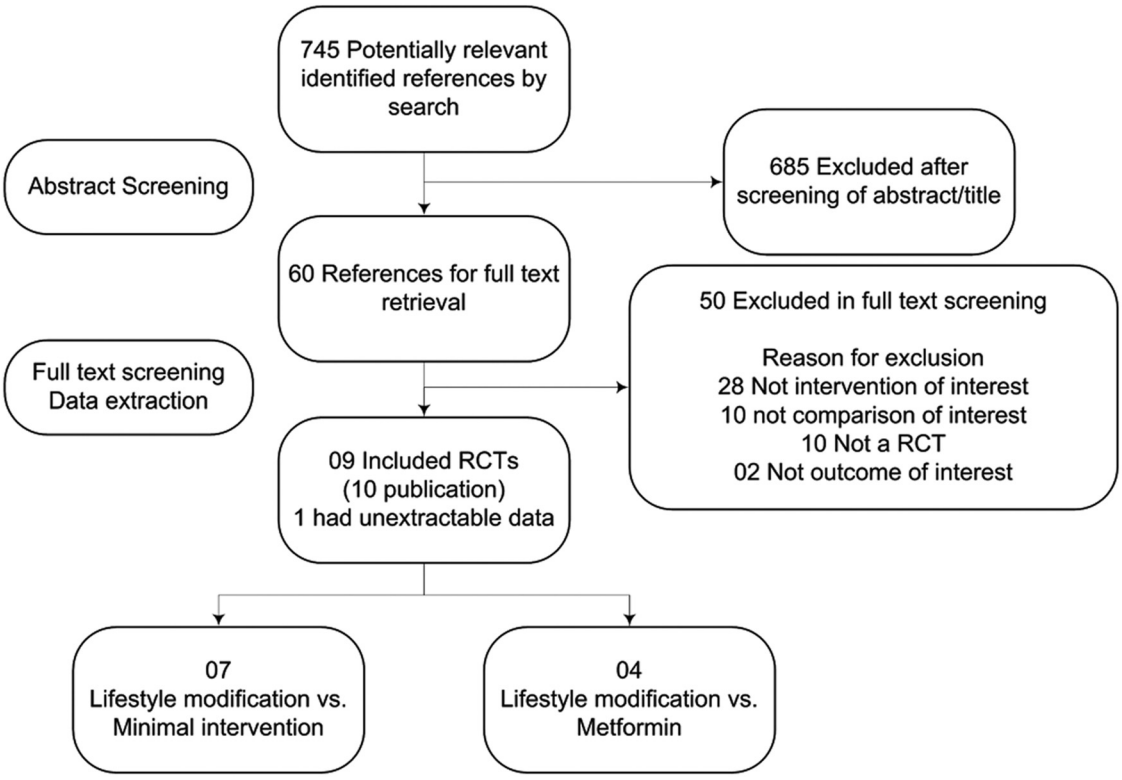

Figure 1. Flow chart.

in the meta-analysis), and a combined LSM approach (hypocaloric diet plus physical exercise) in 5 RCTs. Trials were published between 1994 and 2011, leading to some variation in the diagnostic criteria of PCOS. There was important between-study inconsistency in the diagnostic criteria of PCOS, disease severity (ie, infertile women with evident clinical presentation vs fertile subclinical presentations), patient BMI and LSM regimens used (ie, different hypocaloric diets and aerobic vs resistance physical exercise). Table 1 describes the characteristics of included trials.

Author contact

We attempted to contact by e-mail authors of 4 studies (31–34) to clarify certain characteristics from their trials and successfully received answers regarding 2 trials (31, 34).

Risk of bias

All of the included RCTs had adequate randomization methods, and 6 RCTs preserved randomization by implementing concealed allocation. Two RCTs blinded out-

Table 1. Description of Included Studies

Name and Year	Age, y	Follow-Up, mo	No.	Groups	BMI	Subject Characteristics	Funding	Main Conclusions
Brown et al, 2009 (32)[a]	18–50	6	11	LSM	38	Exercise: patients were assigned to a moderate to intensive exercise program for 5 − 6 mo; the load work per subject was 228 min/wk	NFP	Moderate-intensity exercise without significant weight loss improved several components of the lipoprotein profiles of women with PCOS
				Control	31	No intervention		
Guzick et al, 1994 (33)	32	5	12	LSM	38	Combined: low-calorie dietary intake (1000–1200 kcal/d) and aerobic exercise (walking 2 miles/d, 5 days/wk) for 3 mo	NFP	Weight loss in obese, hyperandrogenic, anovulatory women appears to reduce insulin and non-SHBG T concentrations despite the absence of a change in gonadotropin secretion and may lead to resumption of ovulation
				Control		No intervention		
Hoeger et al, 2004 (34)	28	12	27	LSM	39	Combined: diet (500–1000 kcal/d) and exercise (150 min/wk for 12 mo)	NFP	Weight reduction might play the most significant role in restoration of ovulation in obese women with PCOS
				Metformin		Metformin: 1700 mg/d/12 mo		
				Control		No intervention		
Hoeger et al, 2008 (31)	18	6	32	LSM	>25	Combined: diet, exercise, and behavioral tactics for 6 mo; each patient was assigned in a closed group format for intervention	NFP	Both lifestyle modification and oral contraceptives significantly reduce androgens and increase SHBG in obese adolescents with PCOS; metformin, in combination with lifestyle modification and oral contraceptives, reduces central adiposity, reduces total testosterone, and increases HDL, but does not enhance overall weight reduction
				Metformin		Metformin: 1700 mg/d for 6 mo		
				Control		Placebo for 6 mo		
Karimzadeh and Javedani, 2010 (49)	27	6	255	LS M	27	Combined: hypocaloric diet (500 cal of deficit) and 120 min of exercise per day, 3−5 d/wk for 6 mo	NR	Lifestyle modification improves the lipid profile in PCOS patients
				Metformin		Metformin: 1500 mg/d		
Palomba et al, 2010 (36)	18–35	1.5	64	LSM	32	Combined: hypocaloric diet plus exercise 3 times/wk for 1.5 mo	NR	In overweight and obese clomiphene citrate–resistant PCOS patients, a 6-wk intervention of structured exercise training and a hypocaloric diet was effective in increasing the probability of ovulation
				Control		No interventions		
Qublan et al, 2007 (50)	31	3	46	LSM	32	Diet: 1200–1400 kcal/d for 3 mo	NR	Amelioration of hyperinsulinemia and hyperandrogenemia with dietary intervention or metformin treatment improves significantly the clinical features and reproductive function in overweight PCOS women
				Metformin		Metformin: 1700 mg/d for 3 mo		
Stener-Victorin et al, 2009 (51, 52)	30	4	84	LSM	27	Exercise: aerobic exercise (30–45 min, 3 d/wks with 1 d/wk of reinforcement) for 4 mo	Includes for profit funding	Low-frequency electroacupuncture and physical exercise lower high sympathetic nerve activity improve menstrual frequency and decrease the levels of several sex steroids at week 16 and at the 16-wk follow-up compared with no intervention in women with PCOS
				Control		Any active interventions; only information about diet and exercise		
Vigorito et al, 2007 (53)	21.8	3	90	LSM	29	Exercise. 30 min of bicycle exercise, 3 times/wk for 3 mo	NFP	After 3 mo, a structured exercise training program improves peak oxygen consumption, reduces BMI and C-reactive protein, and improves insulin sensitivity indexes
				Control		No exercise		

Abbreviations: LSM, lifestyle modifications; NFP, not for profit; NR, not reported; SHBG, sex hormone–binding globulin. [a] Not included in the meta-analysis.

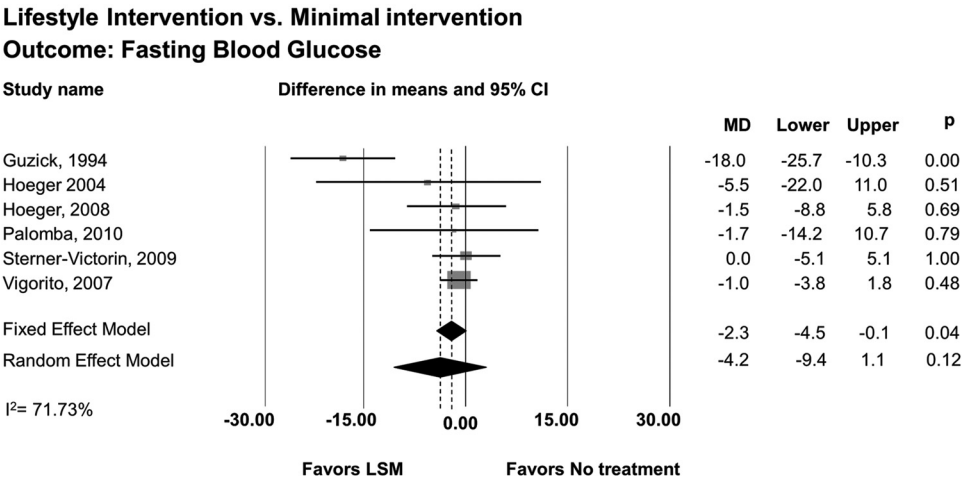

Figure 2. Lifestyle intervention vs minimal intervention outcome: FBG. MD, median.

come assessors, and 1 RCT blinded the data analyst; none of them blinded caregivers. Six of the 8 RCTs included in the meta-analysis reported attrition during the follow-up, with a mean of 16% (range, 9–76%); 3 RCTs did not have any loss to follow-up. Loss to follow-up was greater in the LSM groups, increasing the risk of bias. The overall risk of bias was considered moderate to high. Supplemental Table 2 describes the quality of the included trials.

Outcomes of interest

Compared with MI, LSM reduced FBG (fixed effect: WMD, −2.3 mg/dL, 95% CI, −4.5 to −0.1, $P = .04$, $I^2 = 72\%$) (Figure 2) and FBI (fixed effect: WMD, −2.1 μIU/mL, 95% CI, −3.3 to −1.0, $P < .001$, $I^2 = 0\%$) (Figure 3). The effect of LSM on FGS was only significant under the fixed effect (Supplemental Figure 1). Compared with metformin, LSM was not different in its ability to reduce FBG (fixed effect: WMD, 0.00, 95% CI −2.4 to 2.5, $P = .97$, $I^2 = 15.3\%$) (Supplemental Figure 2), FBI (fixed effect: WMD, 0.0, 95% CI, −1.9 to 1.8, $P = .98$, $I^2 = 0\%$) (Supplemental Figure 3), hirsutism score (reported in 1 RCT: WMD, −0.8, 95% CI, −3.5 to 1.9, $P = .56$) (Supplemental Figure 4) or pregnancy rate (reported in 1 RCT: OR, 1.5, 95% CI, 0.7 to 3.3, $P = .35$) (Supplemental Figure 5). None of the included studies reported the effect of treatment on acne or other fertility-related outcome.

The study by Brown et al (32) was not included in the meta-analyses because it reported outcomes as median percent change; thus, results could not be combined with other trials. This study showed no significant differences between the exercise group and the control group in FBG (median percent change: exercise group = 4.75%, control group = −0.54%) or FBI (median percent change: exercise group = −4.88%, control group = 7.79%). More participants were lost to follow-up in the LSM arm than in the control arm (62% vs 32%).

Subgroup analysis, meta-regression, and sensitivity analysis

We could not perform 2 of the planned subgroup analyses: (1) weight reduction subgroup because all the

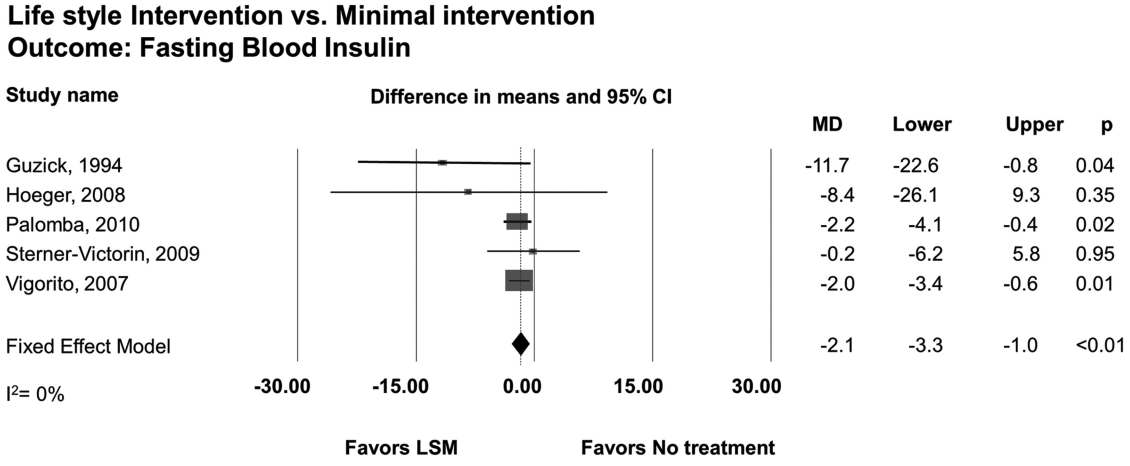

Figure 3. Lifestyle intervention vs minimal intervention outcome: FBI. MD, median.

included studies achieved some weight reduction and (2) study quality subgroup because only 1 study had a different overall risk of bias than the others. The other 2 subgroup analyses performed did not identify any significant interactions. In a meta-regression model of LSM vs MI, we found a direct correlation between the change in BMI and FBG changes (slope = 3.34, 95% CI, 1.74 to 4.94, $P < .001$) (Supplemental Figure 6); with regard to FBI, the meta-regression showed no significant trend (slope = 2.09, 95% CI, −0.094 to 4.28, $P = .06$) (Supplemental Figure 7). We did not find an interaction with hirsutism. When we used a random-effects model to combine the data of LSM vs MI in FBG, we found the same tendency of decreasing this metabolic parameter but without a statistical significance difference (random effect: WMD, −4.2, 95% CI, −9.4 to 1.1, $P = .12$) (Figure 2). Sensitivity analysis of the outcome of hirsutism showed that the results are very susceptible to change based on the correlation coefficients of before and after values used in analysis and analysis model (random vs fixed).

Discussion

Main findings

We conducted a systematic review and meta-analysis to determine the efficacy of LSM on PCOS. Evidence from RCTs at moderate to high risk of bias shows a significant, but small, effect on glucose and insulin blood levels. In this sense, the use of physical exercise and/or hypocaloric dieting seems to be efficacious in overweight or obese women with PCOS. In these women, we also found a significant direct correlation between the weight reduction and the improvement in metabolic parameters that could be attributed to decreased insulin resistance or to other factors. The effects of metformin were no different from the effects of LSM. The available literature does not provide long-term follow-up to ascertain the benefits on other outcomes such as prevention of diabetes or obesity, fertility, or hirsutism; the data from these important patient and clinician outcomes would allow calculation of the number needed to treat associated with LSM programs. However, they does not allow evaluation of the independent effect of LSM after accounting for weight loss. Concordantly, studies were too brief to assess the impact of LSM on the incidence of diabetes or cardiovascular disease.

Comparison with other reviews

Our findings in terms of the effect of LSM on FBI are consistent with those of a previously published Cochrane Database systematic review (35). However, the effect on FBG was not statistically significant in that review. In the current meta-analysis, one additional RCT (36) was added to the analysis, making the effect of LSM on FBG significant. Furthermore, the Cochrane systematic review demonstrated a small reduction in FGS score, whereas we found this analysis unreliable. The statistical significance was only demonstrated using the fixed-effects model (used in the Cochrane review). In addition, the method of analysis was different between the 2 reviews (here, we compared the change from baseline to the end of the trial between study arms, whereas in the Cochrane review, they compared postintervention values between the two arms). We also found that the analysis is sensitive to the choice of pre/postintervention correlation coefficient used. Therefore, this analysis is not robust, and the estimated effect on FGS score is not reliable. Furthermore and aside from statistical significance, the observed change in FGS score in both reviews is trivial and unlikely to be clinically important.

The effect of LSM observed in this report is also consistent with that observed in other populations, such as patients with impaired fasting glucose (37).

Limitations and strengths

The quality of the evidence presented in this review is low because of the high rates of loss to follow-up, short trial duration, heterogeneity, and imprecision (small sample size and wide confidence intervals). The included subjects were overweight, limiting inference in nonoverweight women with PCOS. In addition, the definition of a lifestyle intervention includes diet, physical exercise, and behavioral interventions; however, most of the included studies did not contain such a comprehensive program and have mostly investigated the effect of exercise. Considering that LSM is likely to act in a cumulative dose-dependent fashion (38) and the brevity of the trials, it is probable that currently available evidence underestimates the impact of LSM.

The strength of this review relates to the comprehensive nature of the literature search and the measures undertaken to reduce the effect of bias and random error: predefined protocol-driven work, duplicate review, and author contact.

Implications for practice and research

Despite the limitations of the existing evidence, LSM programs should be recommended as first-line treatment and as a part of any management plan for women with PCOS, given the limited risk and overall likely, albeit modest, benefit with such an intervention. Indirect evidence regarding the benefits of LSM can also be derived from

non-PCOS settings, such as individuals with type 2 diabetes (37, 39) and obesity (40, 41). This is particularly important, considering the minimal harm and overall low cost of such interventions and the additional cardiovascular and metabolic benefits associated with LSM (42). Because of the short-term follow-up of subjects, it is not clear whether the LSM is maintained by the patients. Most obese individuals regain some or all of their lost weight over time (43, 44); thus, the benefits of LSM on PCOS may not be continually conferred in the long-term. Many of the reviewed studies used structured and supervised diet and exercise programs, which were not continued after the trial period. To transfer the benefits of an LSM intervention to the patients' usual daily activities, special attention must be given to the sustainability of healthy behaviors after initial interventions are complete. This may also be true for adherence to metformin over time. Overweight and obese women with PCOS may require long-term treatment and monitoring of LSM by their health care providers. The National Institutes of Health clinical guidelines (45) and the Scottish Intercollegiate Guidelines Network (SIGN) guidelines for management of obesity (46) for lasting treatment of overweight and obesity recommend designing attainable and sustainable long-term goals for LSM (emphasize healthy eating and increased physical activity and reduce sedentary behavior) with continual monitoring and frequent assessment and feedback from a health care provider. Determinants of long-term weight loss maintenance for women with PCOS warrant further study.

Further research is needed to clarify the effects of LSM in lean women and teenagers and also the degree of dependence between LSM effects and weight reduction. The accompanying clinical practice guidelines from The Endocrine Society will provide practical recommendations for the treatment of PCOS (47). Further trials with longer follow-up duration, larger sample size, different comparison than metformin (ie, contraceptive pills or ovulatory inductors), and clear diagnostic criteria that evaluate patient-important outcomes (48) are needed.

Conclusions

This systematic review and meta-analysis demonstrates that LSM programs decrease the levels of fasting glucose and insulin, suggesting that these programs will be beneficial in overweight or obese women with PCOS. Changes in BMI were associated with changes in FBG. Clinicians prescribing LSM interventions must consider the patient's capacity to sustain diet and exercise adherence and weight maintenance over time for the clinical benefits on PCOS to continue. Longer and larger trials at low risk of bias are needed to draw stronger conclusions about the effects of LSM on outcomes more important to women with PCOS and not only surrogates. It is likely that the current evidence is underestimating the real effects of these interventions.

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References

1. **Asunción M, Calvo RM, San Millán JL, Sancho J, Avila S, Escobar-Morreale HF.** A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. *J Clin Endocrinol Metab*. 2000;85:2434–2438.
2. **Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R.** Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. *J Clin Endocrinol Metab*. 1998;83:3078–3082.
3. **Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO.** The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab*. 2004;89:2745–2749.
4. **Balen A.** Polycystic ovary syndrome and cancer. *Hum Reprod Update*. 2001;7:522–525.
5. **Fearnley EJ, Marquart L, Spurdle AB, Weinstein P, Webb PM.** Polycystic ovary syndrome increases the risk of endometrial cancer in women aged less than 50 years: an Australian case-control study. *Cancer Causes Control*. 2010;21:2303–2308.
6. **Ehrmann DA.** Polycystic ovary syndrome. *N Engl J Med*. 2005;352:1223–1236.
7. **Dunaif A, Segal KR, Futterweit W, Dobrjansky A.** Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes*. 1989;38:1165–1174.
8. **Toprak S, Yönem A, Cakir B, et al.** Insulin resistance in nonobese patients with polycystic ovary syndrome. *Horm Res*. 2001;55:65–70.
9. **Kiddy DS, Sharp PS, White DM, et al.** Differences in clinical and endocrine features between obese and non-obese subjects with poly-

cystic ovary syndrome: an analysis of 263 consecutive cases. *Clin Endocrinol (Oxf)*. 1990;32:213–220.
10. **Yildirim B, Sabir N, Kaleli B.** Relation of intra-abdominal fat distribution to metabolic disorders in nonobese patients with polycystic ovary syndrome. *Fertil Steril*. 2003;79:1358–1364.
11. **Yildiz BO, Knochenhauer ES, Azziz R.** Impact of obesity on the risk for polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2008;93:162–168.
12. **Cattrall FR, Healy DL.** Long-term metabolic, cardiovascular and neoplastic risks with polycystic ovary syndrome. *Best Pract Res Clin Obstet Gynaecol*. 2004;18:803–812.
13. **Moran LJ, Brinkworth G, Noakes M, Norman RJ.** Effects of lifestyle modification in polycystic ovarian syndrome. *Reprod Biomed Online*. 2006;12:569–578.
14. **Azziz R, Carmina E, Dewailly D, et al.** Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *J Clin Endocrinol Metab*. 2006;91:4237–4245.
15. **Kiddy DS, Hamilton-Fairley D, Bush A, et al.** Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)*. 1992;36:105–111.
16. **Clark AM, Ledger W, Galletly C, et al.** Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. *Hum Reprod*. 1995;10:2705–2712.
17. **Duncan GE, Perri MG, Theriaque DW, Hutson AD, Eckel RH, Stacpoole PW.** Exercise training, without weight loss, increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary adults. *Diabetes Care*. 2003;26:557–562.
18. **Gillies CL, Abrams KR, Lambert PC, et al.** Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. *BMJ*. 2007;334:299.
19. **Colberg SR, Albright AL, Blissmer BJ, et al.** Exercise and type 2 diabetes: American College of Sports Medicine and the American Diabetes Association: joint position statement. Exercise and type 2 diabetes. *Med Sci Sports Exerc*. 2010;42:2282–2303.
20. **Lee S, Kuk JL, Davidson LE, et al.** Exercise without weight loss is an effective strategy for obesity reduction in obese individuals with and without type 2 diabetes. *J Appl Physiol*. 2005;99:1220–1225.
21. **Moran LJ, Pasquali R, Teede HJ, Hoeger KM, Norman RJ.** Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. *Fertil Steril*. 2009;92:1966–1982.
22. **Bianchi C, Miccoli R, Penno G, Del Prato S.** Primary prevention of cardiovascular disease in people with dysglycemia. *Diabetes Care*. 2008;31(Suppl 2):S208–S214.
23. **Escobar-Morreale HF, Botella-Carretero JI, Alvarez-Blasco F, Sancho J, San Millán JL.** The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. *J Clin Endocrinol Metab*. 2005;90:6364–6369.
24. **Pasquali R, Gambineri A, Cavazza C, et al.** Heterogeneity in the responsiveness to long-term lifestyle intervention and predictability in obese women with polycystic ovary syndrome. *Eur J Endocrinol*. 2011;164:53–60.
25. **Institute of Medicine.** *Clinical Practice Guidelines We Can Trust In*. Washington, DC: National Academies Press; 2011:1–300.
26. **Palomba S, Pasquali R, Orio F Jr, Nestler JE.** Clomiphene citrate, metformin or both as first-step approach in treating anovulatory infertility in patients with polycystic ovary syndrome (PCOS): a systematic review of head-to-head randomized controlled studies and meta-analysis. *Clin Endocrinol (Oxf)*. 2009;70:311–321.
27. **Vause TD, Cheung AP, Sierra S, et al.** Ovulation induction in polycystic ovary syndrome: no. 242, May 2010. *Int J Gynaecol Obstet*. 2010;111:95–100.
28. **Higgins JP, Thompson SG, Deeks JJ, Altman DG.** Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
29. **Lau J, Ioannidis JP, Terrin N, Schmid CH, Olkin I.** The case of the misleading funnel plot. *BMJ*. 2006;333:597–600.
30. **Altman DG, Bland JM.** Interaction revisited: the difference between two estimates. *BMJ*. 2003;326:219.
31. **Hoeger K, Davidson K, Kochman L, Cherry T, Kopin L, Guzick DS.** The impact of metformin, oral contraceptives, and lifestyle modification on polycystic ovary syndrome in obese adolescent women in two randomized, placebo-controlled clinical trials. *J Clin Endocrinol Metab*. 2008;93:4299–4306.
32. **Brown AJ, Setji TL, Sanders LL, et al.** Effects of exercise on lipoprotein particles in women with polycystic ovary syndrome. *Med Sci Sports Exerc*. 2009;41:497–504.
33. **Guzick DS, Wing R, Smith D, Berga SL, Winters SJ.** Endocrine consequences of weight loss in obese, hyperandrogenic, anovulatory women. *Fertil Steril*. 1994;61:598–604.
34. **Hoeger KM, Kochman L, Wixom N, Craig K, Miller RK, Guzick DS.** A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: a pilot study. *Fertil Steril*. 2004;82:421–429.
35. **Moran LJ, Hutchison SK, Norman RJ, Teede HJ.** Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database Syst Rev*. 2011:CD007506.
36. **Palomba S, Falbo A, Giallauria F, et al.** Six weeks of structured exercise training and hypocaloric diet increases the probability of ovulation after clomiphene citrate in overweight and obese patients with polycystic ovary syndrome: a randomized controlled trial. *Hum Reprod*. 2010;25:2783–2791.
37. **Yamaoka K, Tango T.** Efficacy of lifestyle education to prevent type 2 diabetes: a meta-analysis of randomized controlled trials. *Diabetes Care*. 2005;28:2780–2786.
38. **Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB.** Changes in diet and lifestyle and long-term weight gain in women and men. *N Engl J Med*. 2011;364:2392–2404.
39. **Esposito K, Kastorini CM, Panagiotakos DB, Giugliano D.** Prevention of type 2 diabetes by dietary patterns: a systematic review of prospective studies and meta-analysis. *Metab Syndr Relat Disord*. 2010;8:471–476.
40. **Franz MJ, VanWormer JJ, Crain AL, et al.** Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. *J Am Diet Assoc*. 2007;107:1755–1767.
41. **Curioni CC, Lourenco PM.** Long-term weight loss after diet and exercise: a systematic review. *Int J Obes (Lond)*. 2005;29:1168–1174.
42. **Kesaniemi YK, Danforth E Jr, Jensen MD, Kopelman PG, Lefèbvre P, Reeder BA.** Dose-response issues concerning physical activity and health: an evidence-based symposium. *Med Sci Sports Exerc*. 2001;33:S351–S358.
43. **Anderson JW, Konz EC, Frederich RC, Wood CL.** Long-term weight-loss maintenance: a meta-analysis of US studies. *Am J Clin Nutr*. 2001;74:579–584.
44. **Galani C, Schneider H.** Prevention and treatment of obesity with lifestyle interventions: review and meta-analysis. *Int J Public Health*. 2007;52:348–359.
45. **National Institutes of Health.** Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults—the Evidence Report. *Obes Res*. 1998;6(suppl 2):51S–209S
46. **Scottish Intercollegiate Guidelines Network.** *Management of Obesity. a National Clinical Guideline*. Edinburgh, Scotland: Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2010. SIGN Publication No. 115.
47. **Legro RS, Arslanian SA, Ehrmann DA, et al.** Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2013;98:4565–4592.
48. **Gandhi GY, Murad MH, Fujiyoshi A, et al.** Patient-important

outcomes in registered diabetes trials. *JAMA*. 2008;299:2543–2549.
49. **Karimzadeh MA, Javedani M.** An assessment of lifestyle modification versus medical treatment with clomiphene citrate, metformin, and clomiphene citrate-metformin in patients with polycystic ovary syndrome. *Fertil Steril*. 2010;94:216–220.
50. **Qublan HS, Yannakoula EK, Al-Qudah MA, El-Uri FI.** Dietary intervention versus metformin to improve the reproductive outcome in women with polycystic ovary syndrome. A prospective comparative study. *Saudi Med J*. 2007;28:1694–1699.
51. **Stener-Victorin E, Jedel E, Janson PO, Sverrisdottir YB.** Low-frequency electroacupuncture and physical exercise decrease high muscle sympathetic nerve activity in polycystic ovary syndrome. *Am J Physiol Regul Integr Comp Physiol*. 2009;297:R387–R395.
52. **Jedel E, Labrie F, Odén A, et al.** Impact of electro-acupuncture and physical exercise on hyperandrogenism and oligo/amenorrhea in women with polycystic ovary syndrome: A randomized controlled trial. *Am J Physiol Endocrinol Metab*. 2011;300:E37–E45.
53. **Vigorito C, Giallauria F, Palomba S, et al.** Beneficial effects of a three-month structured exercise training program on cardiopulmonary functional capacity in young women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2007;92:1379–1384.