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REVIEW

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Impact of insulin sensitization on metabolic and fertility outcomes in women with polycystic ovary syndrome and overweight or obesity—A systematic review, meta-analysis, and meta-regression

Suhaniya N. S. Samarasinghe[1] | Eduard Ostarijas[2,3] | Matthew J. Long[4] | Simon Erridge[5] | Sanjay Purkayastha[5] | Georgios K. Dimitriadis[6] | Alexander D. Miras[7]

[1]Department of Metabolism, Digestion and Reproduction, Imperial College London, London, UK

[2]Institute for Translational Medicine, University of Pecs Medical School, Pécs, Hungary

[3]Faculty of Medicine, J. J. Strossmayer University of Osijek, Osijek, Croatia

[4]Department of Gastroenterology, Guy's and St Thomas' NHS Foundation Trust, London, UK

[5]Department of Surgery and Cancer, Imperial College London, London, UK

[6]Department of Endocrinology ASO/EASO COM, King's College Hospital NHS Foundation Trust, London, UK

[7]School of Medicine, Ulster University, Belfast, UK

Correspondence
Dr. Suhaniya Samarasinghe, Department of Metabolism, Digestion and Reproduction, Imperial College London, London W12 0HS, UK.
Email: suhaniya.samarasinghe@nhs.net

Summary

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive-age women. This systematic review, meta-analysis, and meta-regression aims to compare the effect of insulin sensitizer pharmacotherapy on metabolic and reproductive outcomes in women with PCOS and overweight or obesity. We searched online databases MEDLINE via OVID, EMBASE, Clinicaltrials.gov, and EudraCT for trials published from inception to November 13, 2023. Inclusion criteria were double-blind, randomized controlled trials in women diagnosed with PCOS, body mass index (BMI) ≥ 25 kg/m^2, which reported metabolic or reproductive outcomes. The intervention was insulin sensitization pharmacotherapy versus placebo or other agents. The primary outcomes were changes from baseline BMI, fasting blood glucose, and menstrual frequency. Nineteen studies were included in this review. Metformin had the most significant effect on the fasting plasma glucose and body mass index. Insulin sensitizer pharmacotherapy significantly reduced fasting plasma glucose, body mass index, fasting serum insulin, HOMA-IR, sex hormone binding

Abbreviations: BD, twice daily; BMI, body mass index; CI, confidence interval; DHEAS, dehydroepiandrosterone; ESHRE/ASRM, European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine; FPG, fasting plasma glucose; FSH, follicle-stimulating hormone; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LH, luteinizing hormone; NICHD, National Institute of Child Health and Human Development; OD, once daily; PCOS, polycystic ovary syndrome; PO, oral administration; RCT, randomized controlled trial; S/C, subcutaneously; SD, standard deviation; SHBG, sex hormone binding globulin; SMD, standardized mean difference; T2DM, type 2 diabetes mellitus; TDS, three times a day.

globulin, and total testosterone, but the effect size was small. There was a lack of menstrual frequency and live birth data. The results indicate a role for insulin sensitizers in improving the metabolic and, to a lesser degree, reproductive profile in these women. Further research should examine insulin sensitizers' effects on objective measures of fecundity.

KEYWORDS
insulin sensitization, overweight, PCOS

1 | INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder in women of reproductive potential.[1,2] The three key features associated with PCOS are clinical or biochemical androgen excess, oligo/amenorrhoea or ovulatory dysfunction, and imaging demonstrating polycystic ovarian morphology. The Androgen Excess-PCOS society (AE-PCOS) criteria[3] is as follows: hyperandrogenism, which is defined as biochemical (total testosterone ≥55 ng/ml) or clinical (Ferriman–Gallwey score ≥8); irregular menses, which was defined as menses ≤nine times per year; and polycystic appearing ovaries (defined as either ovary having a volume of ≥10 cm^3 on abdominal or transvaginal ultrasound).[4] The 1990 National Institute of Health–National Institute of Child Health and Human Development Conference on PCOS recommended that after excluding other endocrinopathies, the first two should form the diagnostic criteria.[4–6] In 2003, the Rotterdam Consensus extended the diagnostic criteria to state that at least two out of three of the above features are required.[6]

Women with PCOS often display one or more conditions that form part of the metabolic syndrome.[4,7] By 30 years of age, 5%–10% of women with PCOS develop type 2 diabetes mellitus (T2DM) and 30%–40% impaired glucose tolerance.[8] Insulin resistance plays a central role in the pathogenesis of PCOS and is fuelled, at least in part, by the presence of obesity. The obesity rate in this patient population can vary from 50% to 80%, depending on the ethnicity and study population.[9] Compensatory hyperinsulinemia exacerbates hyperandrogenemia by stimulating ovarian androgen production and lowering sex hormone-binding globulin (SHBG) production from the liver.[10]

Lifestyle intervention is usually the initial strategy in women with PCOS and overweight or obesity to improve the metabolic and hormonal profile. A systematic review and meta-analysis of 15 studies with 498 participants concluded that lifestyle intervention may improve free androgen index (FAI), weight, and BMI in PCOS.[7] However, most studies included in the review were of low methodological quality.[7] A significant challenge is adherence to diet and physical activity recommendations in the long term.

Medical intervention with pharmacotherapy is considered when patients have not responded to lifestyle interventions. Numerous clinical trials have examined the use of direct insulin sensitizers in women with PCOS, that is, that have a direct action on insulin sensitivity in the context of minimal or no weight loss. The two most common classes of drugs studied are biguanides (metformin)[11] and thiazolidinediones (e.g., pioglitazone).[12] Three other classes of drugs of interest in the treatment of PCOS that can indirectly increase insulin sensitivity through weight loss are glucagon-like peptide-1 receptor agonist (GLP-1 RA) (e.g., exenatide and liraglutide),[13] glucosidase inhibitors (acarbose), and lipase inhibitors (orlistat).

There are only a few systematic reviews and meta-analyses on the use of insulin sensitizers in women with PCOS and overweight or obesity. These have focused predominantly on metformin, pioglitazone, and, to a lesser extent, GLP-1 RA, with weight loss as the outcome of interest and minimal information on reproductive parameters.[6,7] These meta-analyses included open-label studies, increasing the risk of bias.

In this systematic review, meta-analysis, and meta-regression, we aimed to assess the highest quality evidence available on the impact of insulin sensitizers on key metabolic and reproductive outcomes in women with PCOS and overweight or obesity.

2 | METHODS

2.1 | Search strategy and selection criteria

This systematic review, meta-analysis, and meta-regression was reported per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[14] The protocol is prospectively registered on PROSPERO (CRD42021236556). Eligible randomized controlled trials (RCTs) were identified through a comprehensive search of four databases, including MEDLINE via Ovid and EMBASE, for articles published from inception to November 13, 2023. SS and ML applied the following MeSH terms in the search process: *(polycystic ovary syndrome) AND ((overweight) OR (abdominal obesity)) AND ((biguanides) OR (thiazolidinediones) OR (glucagon-like peptide 1) OR (orlistat) OR (acarbose))* (see Appendix S1 for the full search strategy).

Search terms were applied to each database, and studies were imported into the Covidence[15] systematic review management tool for screening and data extraction. The criteria for study inclusion were human studies in adult females, diagnosis of PCOS, BMI ≥ 25 kg/m^2, RCTs, which were double-blind, and the outcomes of interest were metabolic and reproductive. Diagnosis of PCOS was based on either the 2012 National Institute of Health criteria (2012),[7] European Society of Human Reproduction and Embryology (ESHRE)/American Society for Reproductive Medicine (ASRM) Rotterdam Consensus Criteria

TABLE 1 Characteristics of the studies included in the meta-analysis.

First author (year)	Country	Diagnostic criteria	Sample size for intervention group (*n*)	Intervention	Comparator	Dose	Body mass index (kg/m^2)	Duration (weeks)
Chou et al.[17]	Brazil	NICHD	14	Metformin	Placebo	500 mg TDS, PO	35.60 (4.90)	13
Elkind-Hirsch et al.[18]	USA	NIH	55	Liraglutide	Placebo	3 mg, OD, S/C	41.6 (1.1)	32
Frossing et al.[19]	Denmark	ESHRE/ASRM	48	Liraglutide	Placebo	1.8 mg OD, S/C	33.30 (5.10)	26
Glintborg et al.[20]	Denmark	NICHD	15	Pioglitazone	Placebo	30 mg OD, PO	32.20 (30.70–36.60)	16
Glintborg et al.[21]	Denmark	ESHRE/ASRM	15	Pioglitazone	Placebo	30 mg OD, PO	33.40 (27.30–40.60)	16
Hanjalic-Beck et al.[22]	Germany	NICHD	19 18	Metformin vs. Acarbose	Metformin or acarbose	850 mg, TDS, PO 100 mg, TDS, PO	35.50 (5.62) 33.50 (5.50)	12
Hoeger et al.[23]	USA	NICHD	9	Metformin	Lifestyle modification + metformin, lifestyle modification + placebo, placebo alone	850 mg, BD, PO	37.10 (4.90)	48
Kashani et al.[24]	Iran	ESHRE/ASRM	20	Metformin vs. Pioglitazone	Metformin or pioglitazone	750 mg BD, PO vs. 15 mg BD, PO	32.98 (3.51) 33.15 (3.12)	6
Maciel et al.[25]	Brazil	NICHD	8	Metformin	Placebo	500 mg TDS, PO	37.20 (1.70)	26
Mantzoros et al.[26]	USA	NICHD	24	Troglitazone	Troglitazone 400 mg or 200 mg + placebo	200 mg or 400 mg OD, PO	42.89 (1.23)	13
Moini et al.[27]	Iran	ESHRE/ASRM	50	Orlistat + low energy diet	Low energy diet + orlistat, low energy diet + placebo	120 mg TDS, PO	29.01 (2.09)	13
Nylander et al.[28]	Denmark	ESHRE/ASRM	48	Liraglutide	Placebo	1.8 mg OD, S/C	33.30 (5.10)	26
Pasquali et al.[29]	Italy	NICHD	12	Metformin + low energy diet	Placebo	850 mg BD, PO	39.80 (7.90)	26
Penna et al.[30]	Brazil	NICHD	15	Acarbose	Placebo	150 mg OD, PO	35.87 (2.60)	26
Penna et al.[31]	Brazil	NICHD	15	Acarbose	Placebo	150 mg OD, PO	35.87 (2.60)	26
Rautio et al.[32]	Finland	ESHRE/ASRM	12	Rosiglitazone		4 mg BD, PO	33.10 (1.70)	17
Tang et al.[33]	UK	ESHRE/ASRM	69	Metformin	Placebo	850 mg BD, PO	37.60 (5.00)	26
Trolle et al.[34]	Denmark	NICHD	50	Metformin	Placebo	850 mg BD, PO	35.20 (6.40)	26
Vigerust et al.[35]	Denmark	NICHD	14	Pioglitazone	Placebo	30 mg OD, PO	32.20 (30.70–36.60)	16

Note: BMI is expressed as mean (± SD) or median and interquartile range (IQR). OD = once daily, BD = twice daily, TDS = three times a day, PO = per oral, S/C = subcutaneous.

(2003),[15,16] or Androgen Excess Society Criteria (2006).[16] If a study was not published in English, efforts were made by members of the study team (if fluent in that language) to translate it.

The intervention included insulin sensitization pharmacotherapy exenatide, liraglutide, metformin, orlistat, pioglitazone, rosiglitazone, troglitazone, or acarbose versus placebo or other agents, for example, ovulation induction agents. We elected to include relevant studies of rosiglitazone and troglitazone despite being withdrawn from clinical care to evaluate the impact of this mechanism of action on PCOS. All selected studies included the following information: demographic characteristics, criteria used for diagnosis of PCOS, drug dosages, and duration of treatment. We excluded studies using two or more drugs in combination as it would not be possible to ascertain which medication influenced the primary and secondary outcomes. The primary outcome was a change in baseline BMI, fasting blood glucose, and menstrual frequency. The secondary outcomes were a change from baseline in fasting insulin, HOMA-IR, the plasma concentration of the anti-Mullerian hormone, SHBG, total testosterone, and Ferriman–Gallwey scale for hirsutism. Other outcomes of interest were dehydroepiandrosterone (DHEAS), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and pregnancy as a marker of fertility. The results are presented as standardized mean difference (SMD) with a 95% CI.

2.2 | Data analysis

Two unblinded, independent reviewers (SS and ML) identified and selected the RCTs that met the inclusion criteria (Table 1). The corresponding author was contacted for missing data if necessary for studies that met the inclusion criteria. Disagreements between reviewers were resolved by discussion and a final decision made by the senior author (AM). The two independent investigators (SS and ML) performed a quality appraisal using the Cochrane Collaboration risk of bias (RoB) 2 tool[36] for each full-text article. The RoB tool is composed of five distinct domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain is characterized as "low risk," "some concerns," or "high" risk. SS sought individual patient-level data if the summary estimates were not provided in the desired way.

SS and ML extracted data using a customized spreadsheet which recorded the study author and year of publication, number of study participants, intervention (insulin sensitizer agent) and study outcomes. SS contacted the corresponding author for clarification if data was missing or unclear. In two studies,[37,38] the reported results were inconsistent with data from other studies. They were excluded from the numerical analysis due to a high risk of bias and failure to perform well in influence analysis. EO analyzed the data using the inverse variance method and a mixed-effects (plural) model with a restricted maximum-likelihood (REML) estimator for τ^2. The model assessed within-subgroup studies using the random-effects model to account for variability among studies (as is usually applied in biomedical summary statistics due to heterogeneity), while the between-subgroup level was estimated using a fixed-effects model, treating each subgroup as a fixed, exhaustive category that represents distinct, non-random true effect sizes; such an approach is referred to as mixed-effects plural model[39] SD, if not available for estimation using confidence intervals, were approximated using the average SD of similar studies, as suggested by the Cochrane Handbook for Systematic Reviews of Interventions.[40] The results are SMD with their respective 95% CI. Heterogeneity was assessed and quantified with χ^2 and I^2 tests, respectively, with a cut-off value set at $\alpha = 0.1$.

Egger's test of intercept was used to assess potential publication bias in all outcomes with a minimum of 10 studies, which was confirmed visually with funnel plot asymmetry (Figure 1). A meta-regression analysis using bubble plots also examined study duration as a potential moderator of result significance (Figure 2). All meta-analytical calculations, including forest and bubble plots, were performed using the R statistical software (v4.3.1) and the packages meta (v6.5-0) and dmetar (GitHub commit 87eca88).

3 | RESULTS

The literature search yielded 35 RCTs conducted in women with PCOS and overweight or obesity (Figure 3). After removing duplicates and excluding studies that did not meet our PICO (Patient, Intervention, Comparison, Outcome) or had inconsistent results, 19 studies that met the eligibility criteria were included (Table 1; further information in Appendix S1). All studies contained information regarding the criteria for diagnosing PCOS, sample size, intervention and dosing schedule, baseline BMI, and duration of treatment. There was variability in the length of treatment between studies, but this did not significantly affect the overall results for most outcomes. The results from the quality appraisal are presented in Figure 4.

3.1 | Primary outcomes

3.1.1 | Fasting plasma glucose

Metformin (SMD −0.28; CI −0.50 to −0.06) and liraglutide (SMD −2.00; CI −3.89 to −0.11) significantly reduced fasting plasma glucose (Figure 5). There was low heterogeneity between the metformin studies ($I^2 = 0\%$) but high heterogeneity between liraglutide studies ($I^2 = 96\%$). One RCT on orlistat[27] also showed a significant reduction in BMI. Except for a single study of rosiglitazone, thiazolidinediones did not significantly affect fasting plasma glucose. The overall reduction effect of insulin sensitizers on fasting plasma glucose was statistically significant (SMD −0.35; CI −0.52 to −0.17). In meta-regression analysis, blood glucose levels decreased over time but were not significant ($p = 0.21$).

3.1.2 | BMI

Only metformin significantly reduced BMI (SMD −0.22; CI 0.43 to −0.02; $I^2 = 0\%$), but the overall effect for all studied medication was

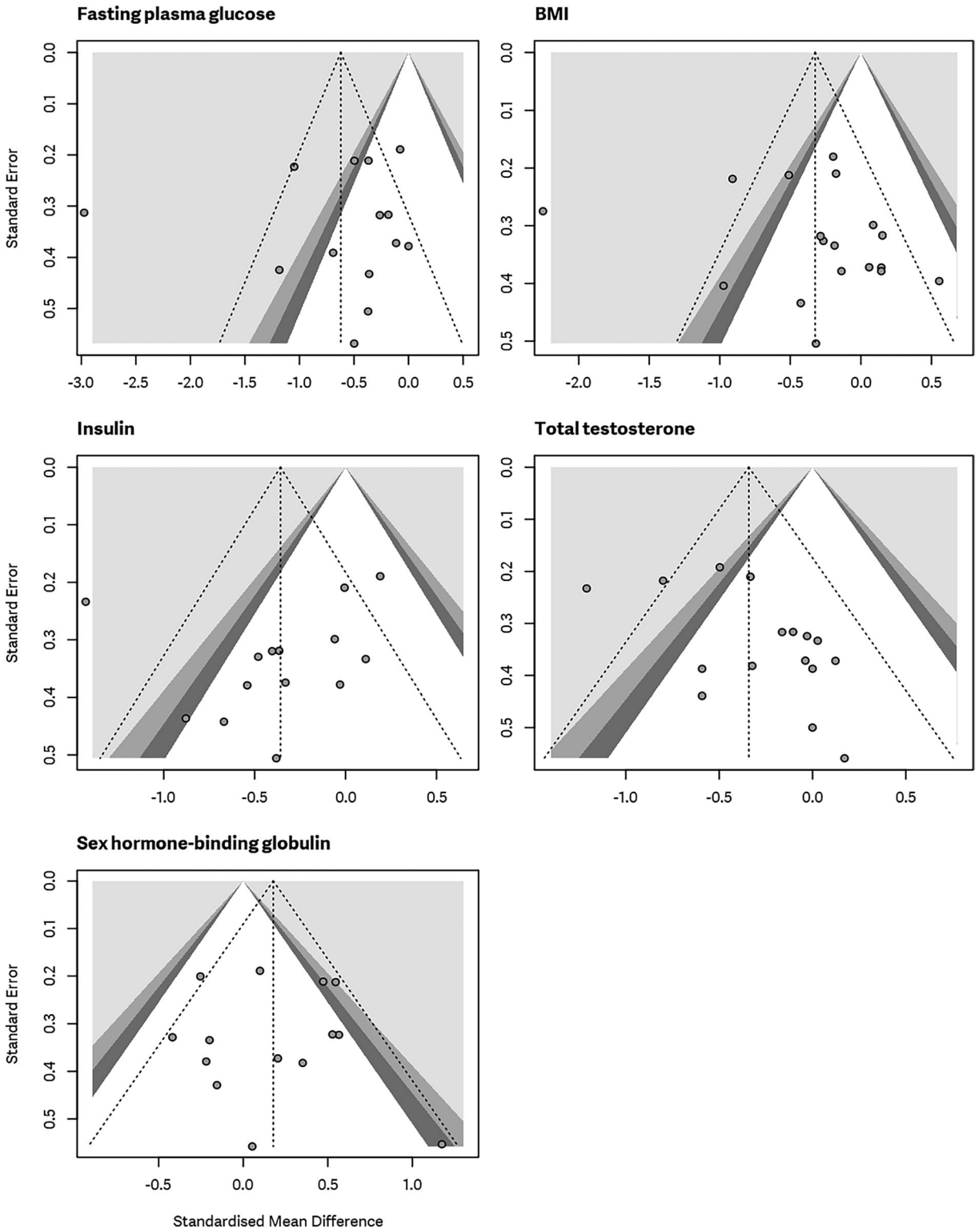


FIGURE 1 Funnel plots were calculated for all outcomes with at least 10 studies.

statistically significant (SMD −0.21; CI −0.37 to −0.06) (Figure 6). There was a tendency for acarbose and liraglutide to cause a reduction in BMI although this was not significant. Thiazolidinediones did not significantly affect BMI but tended to cause an increase. The meta-regression analysis (with study duration as the variable of interest) demonstrated a statistically significant reduction in BMI over time with insulin sensitizer treatment (β per week = −0.0415; CI −0.0759 to −0.0070; $p = 0.018$).

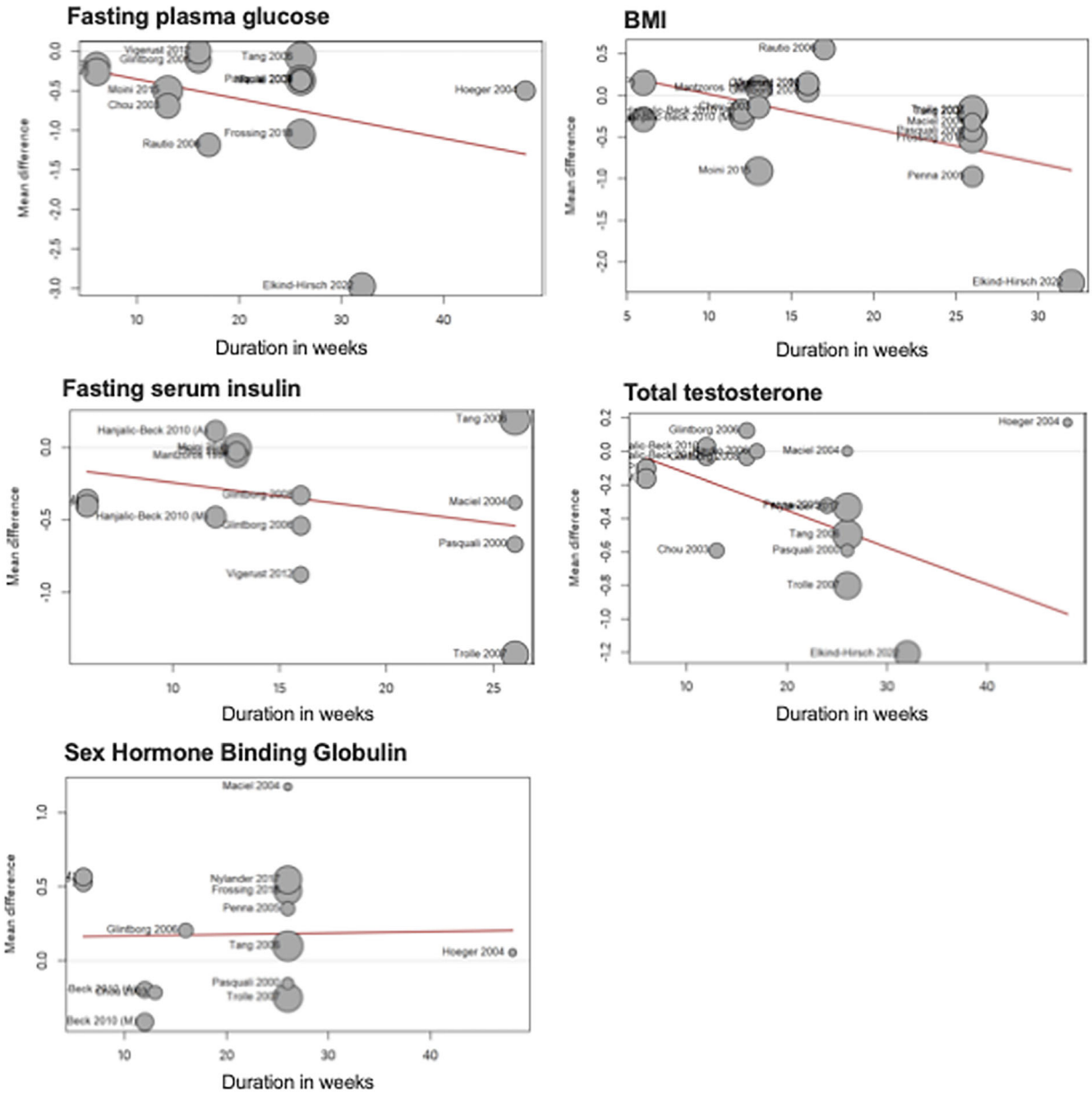


FIGURE 2 Meta-regression analysis was performed for all outcomes where the number of studies was at least 10, with duration of treatment (weeks) as the moderator variable.

3.1.3 | Menstrual frequency

Menstrual frequency was a predefined primary outcome, but there was insufficient data in the literature to perform a meta-analysis.

3.2 | Secondary outcomes

Overall, treatment with an insulin sensitizer reduced fasting insulin levels (SMD −0.25; CI −0.46 to −0.05). Of included subgroups, both metformin (SMD −0.46; CI −0.91 to −0.00; $I^2 = 80\%$) and thiazolidinediones (SMD −0.38; CI −0.69 to −0.07; $I^2 = 0\%$) significantly contributed to the overall result (Figure 7A). The single studies for acarbose[22] and orlistat[27] did not significantly affect fasting insulin. Metformin, orlistat, and thiazolidinediones had no significant effect on HOMA-IR (SMD −0.15; CI −0.39 to 0.10) (Figure 7B). Liraglutide 3 mg significantly reduced HOMA-IR.[18] Overall, use of insulin sensitizers significantly reduces HOMA-IR (SMD −0.37; CI −0.58 to −0.16). No data were available for the other medications studied. Liraglutide significantly increased SHBG (SMD 0.51; CI 0.22 to 0.80); the use of acarbose, metformin, or thiazolidinediones may cause an increase in SHBG (Figure 7C).

Metformin significantly reduced total testosterone (SMD −0.42; CI −0.66 to −0.18) and the total effect of all pooled therapeutic options also showed an overall reduction in testosterone levels (SMD −0.29; CI −0.47 to −0.11) (Figure 7D). The meta-regression analysis

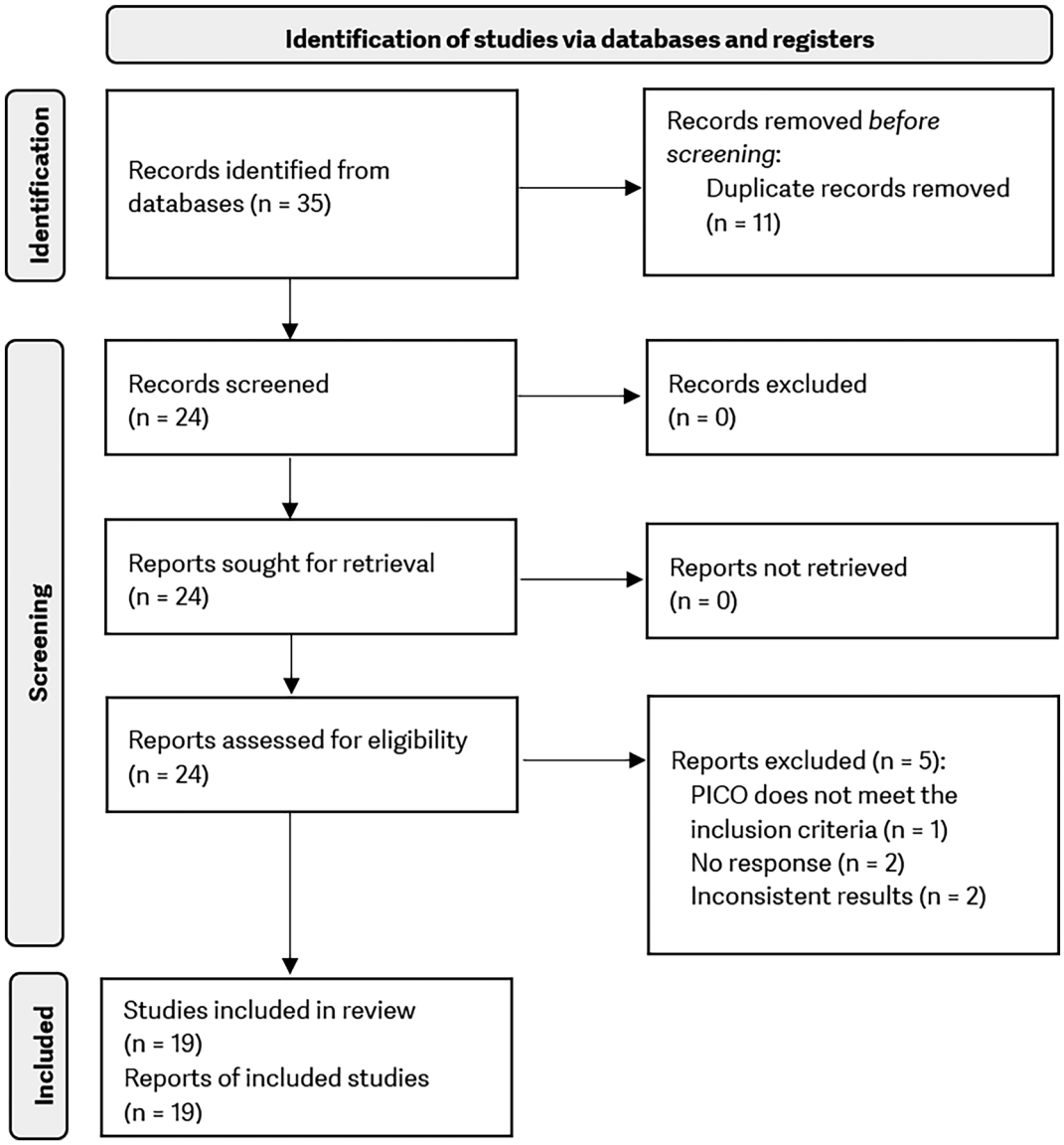


FIGURE 3 Study selection. The PRISMA 2020 flow diagram was adapted from Page et al.[41]

demonstrated that there was a significant reduction in testosterone levels with a longer duration of treatment ($p = 0.02$). In subgroup analysis, acarbose, liraglutide, and thiazolidinediones did not affect total testosterone concentrations significantly. There was no significant reduction in the Ferriman–Gallwey scale hirsutism score with either acarbose, metformin, or thiazolidinediones (Figure 7E). There were no data available for AMH levels.

3.3 | Other clinically relevant outcomes

Acarbose, liraglutide, metformin, and thiazolidinediones did not significantly affect DHEAS (SMD −0.06; CI −0.27 to 0.16) (Figure 8A). Liraglutide 1.8 mg/day[28] significantly reduced LH (SMD −0.55; CI −0.97 to −0.13) (Figure 8B). There was no significant reduction in FSH (SMD 0.02; CI −0.21 to 0.25) after administration of individual insulin sensitizers.

Pregnancy data were not available.

Overall, the use of an insulin sensitizer in women with PCOS and overweight or obesity caused a significant improvement in metabolic outcomes: plasma glucose (SMD −0.35; CI −0.52 to −0.17), BMI (SMD −0.21; CI −0.37 to −0.06), fasting insulin (SMD −0.25; CI −0.46 to −0.05), HOMA-IR (SMD −0.37; CI −0.58 to −0.16), and some elements of the reproductive profile—SHBG (SMD 0.25; CI 0.07 to 0.42) and total testosterone (SMD −0.29; CI −0.47 to −0.11).

4 | DISCUSSION

This systematic review, meta-analysis, and meta-regression for women with PCOS and overweight or obesity found that insulin sensitizer therapy can lead to a significant improvement in metabolic outcomes. There was also a significant improvement in two components

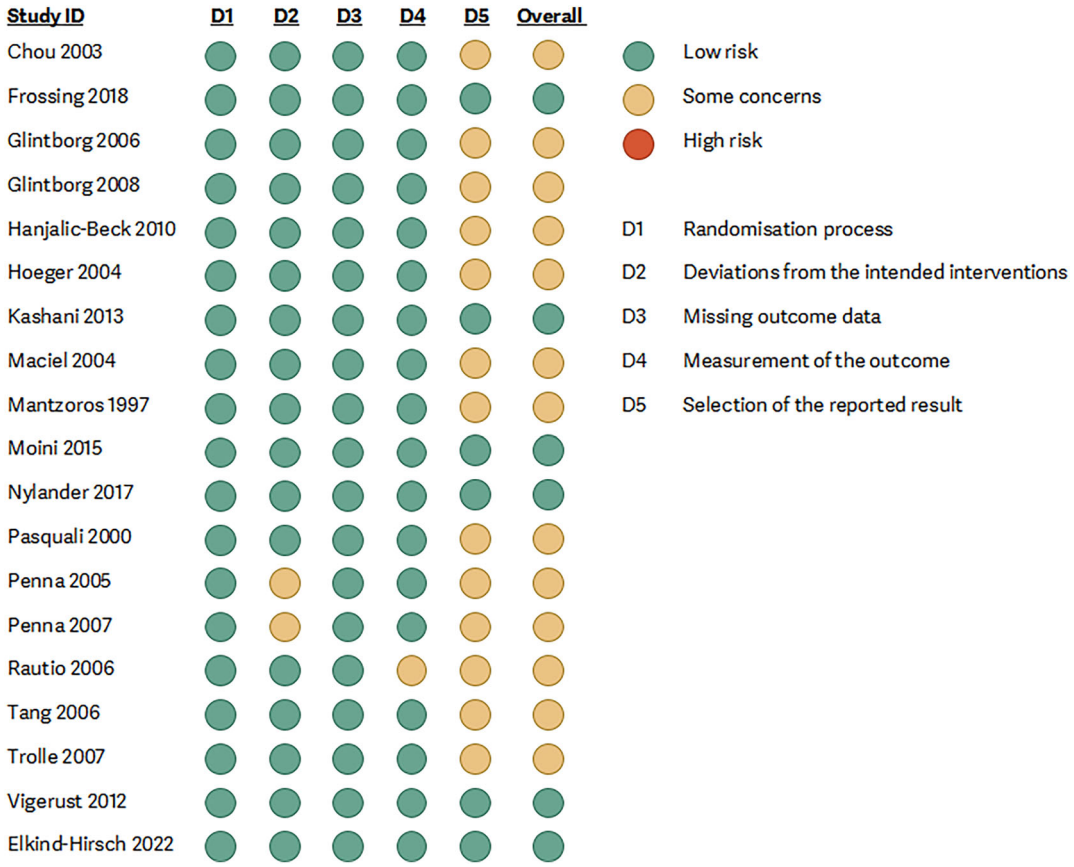


FIGURE 4 Results from the Cochrane RoB 2 tool.[36]

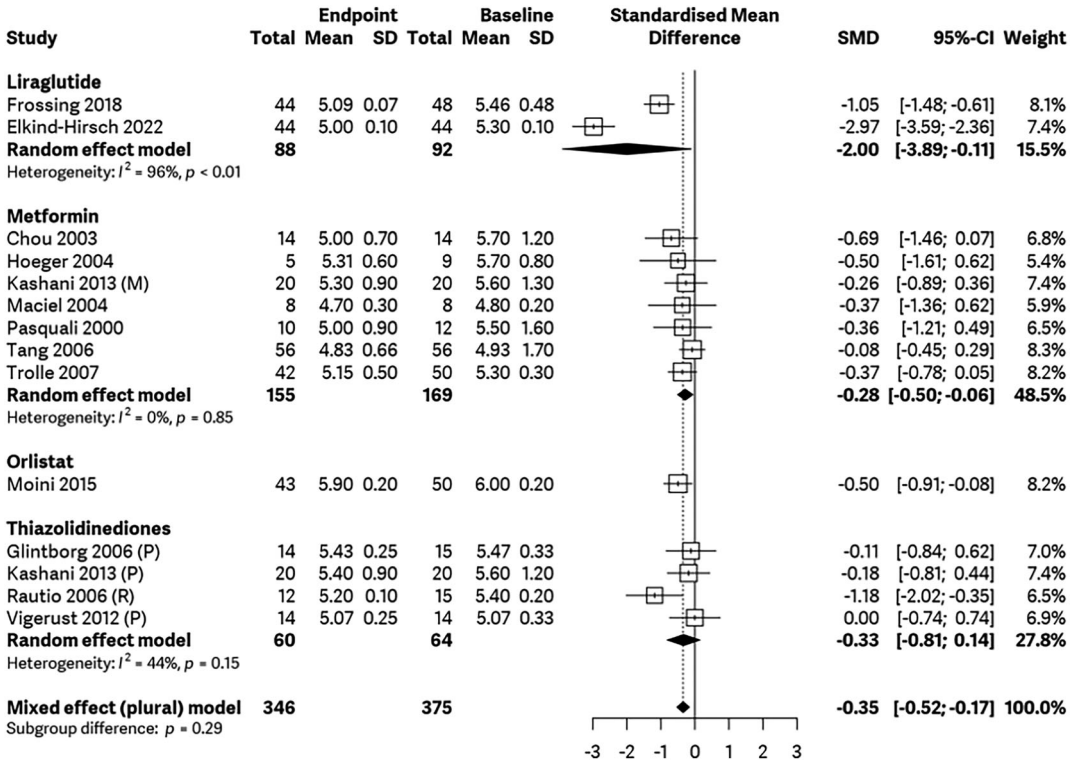


FIGURE 5 Forest plot comparing fasting plasma glucose outcomes between insulin sensitizer therapies and comparators.

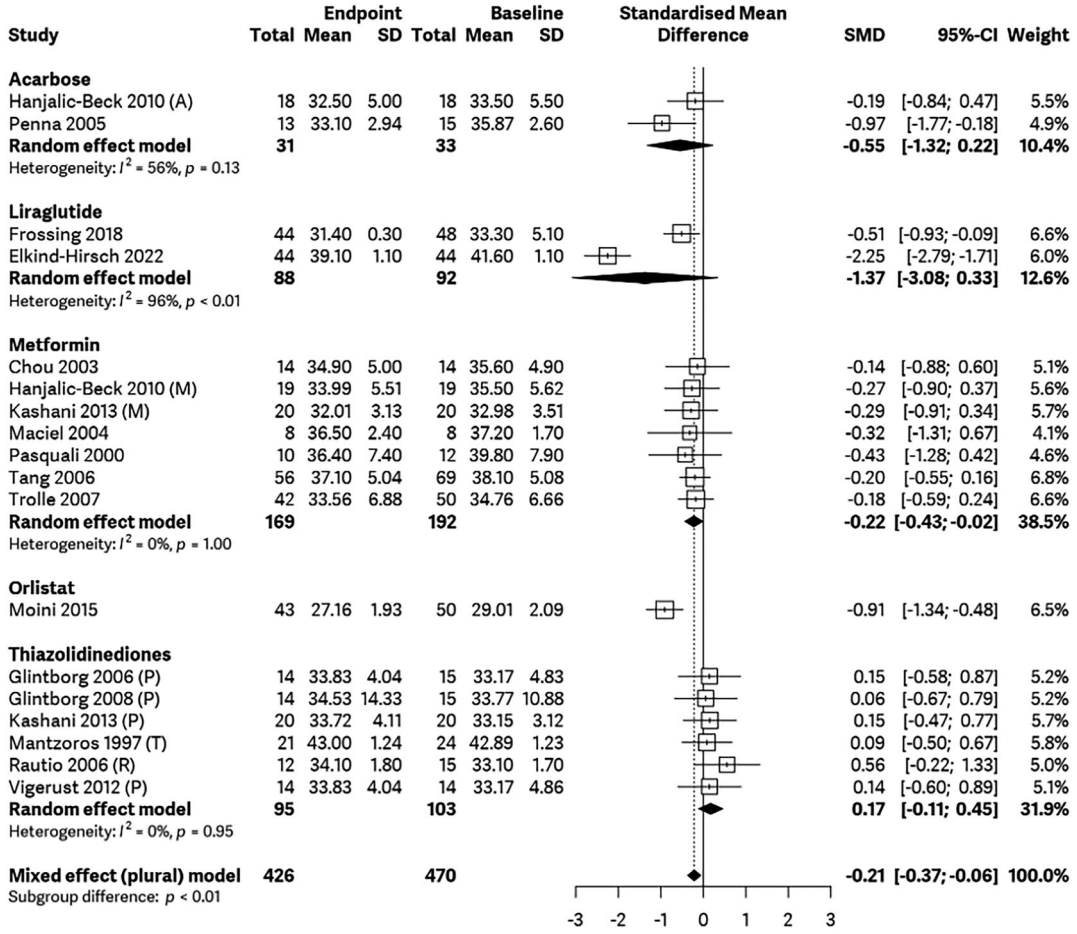


FIGURE 6 Forest plot comparing body mass index (BMI) outcomes between insulin sensitizer therapies and comparators.

of the reproductive profile—total testosterone and SHBG. Metformin was the best-performing insulin sensitizer. Despite statistical significance, the effect size for these outcomes was modest. Duration of treatment had a significant impact on BMI and total testosterone. An unexpected finding was the lack of data for hard reproductive outcomes like menstrual frequency and pregnancy.

The International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome 2023 reviewed studies and meta-analyses assessing metformin and its impact on metabolic and reproductive outcomes and reported that metformin alone should be considered in adults with PCOS and a BMI ≥ 25 kg/m^2.[42] From the RCTs we included, metformin resulted in a significant decrease in BMI, fasting glucose, and insulin, without affecting other metabolic and reproductive outcomes. However, there was significant heterogeneity between studies for fasting insulin and the results, therefore, need to be interpreted with caution. While there was a significant reduction in fasting glucose and insulin, they may not have reduced enough to decrease HOMA-IR significantly.

A network meta-analysis in 2020 assessed 14 trials on 619 women and concluded that combination therapy of metformin and GLP-1 receptor agonists (RA) or metformin and thiazolidinediones was superior to metformin monotherapy in improving hyperandrogenism.[43] Combination therapy with metformin and GLP-1 RA also improved fasting glucose compared to GLP-1 RA alone. The authors found that pioglitazone and rosiglitazone were less effective than metformin in reducing fasting blood glucose, which is in keeping with our results. In contrast with this network meta-analysis, we found that thiazolidinediones cause a significant decrease in fasting insulin. This is in keeping with its mechanism of action of increasing peripheral insulin sensitivity.[44]

Although we found no significant reduction in fasting blood glucose with thiazolidinediones, there was a significant reduction in fasting insulin. This is potentially due to the short duration of treatment in the RCTs included in this meta-analysis. We did not observe a significant increase in BMI with the use of thiazolidinediones again probably potentially due to the short duration of treatment.[45] The use of pioglitazone in clinical trials has yielded mixed results, with some studies observing significant weight gain[46,47] and others, a moderate weight increase.[48,49] Rosiglitazone and troglitazone are no longer used due to their association with a higher risk of cardiovascular events and liver toxicity, respectively. However, we included them in this systematic review and meta-analysis to assess how effective PPAR-γ agonism is as a mechanism of action in women in PCOS.

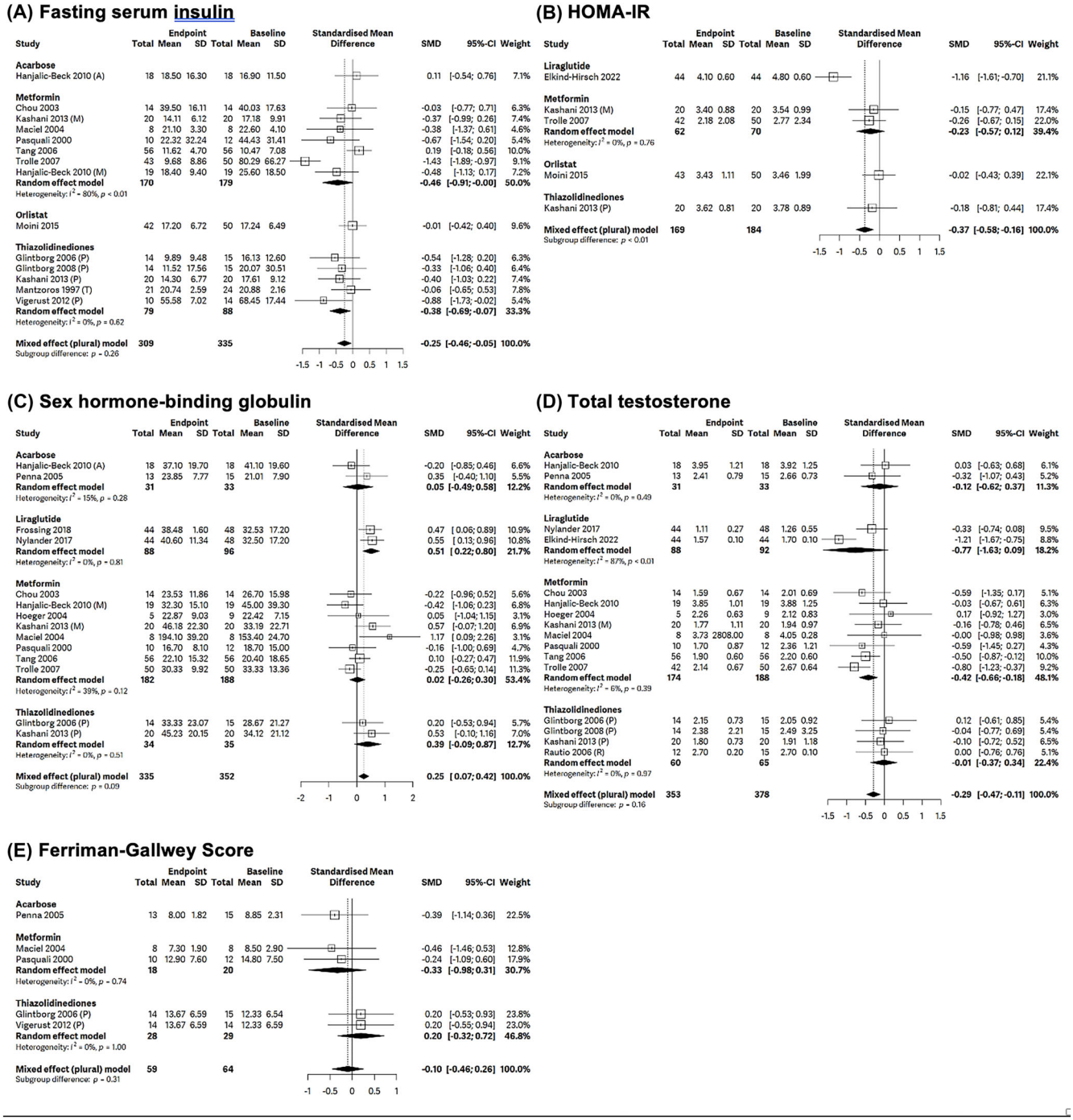
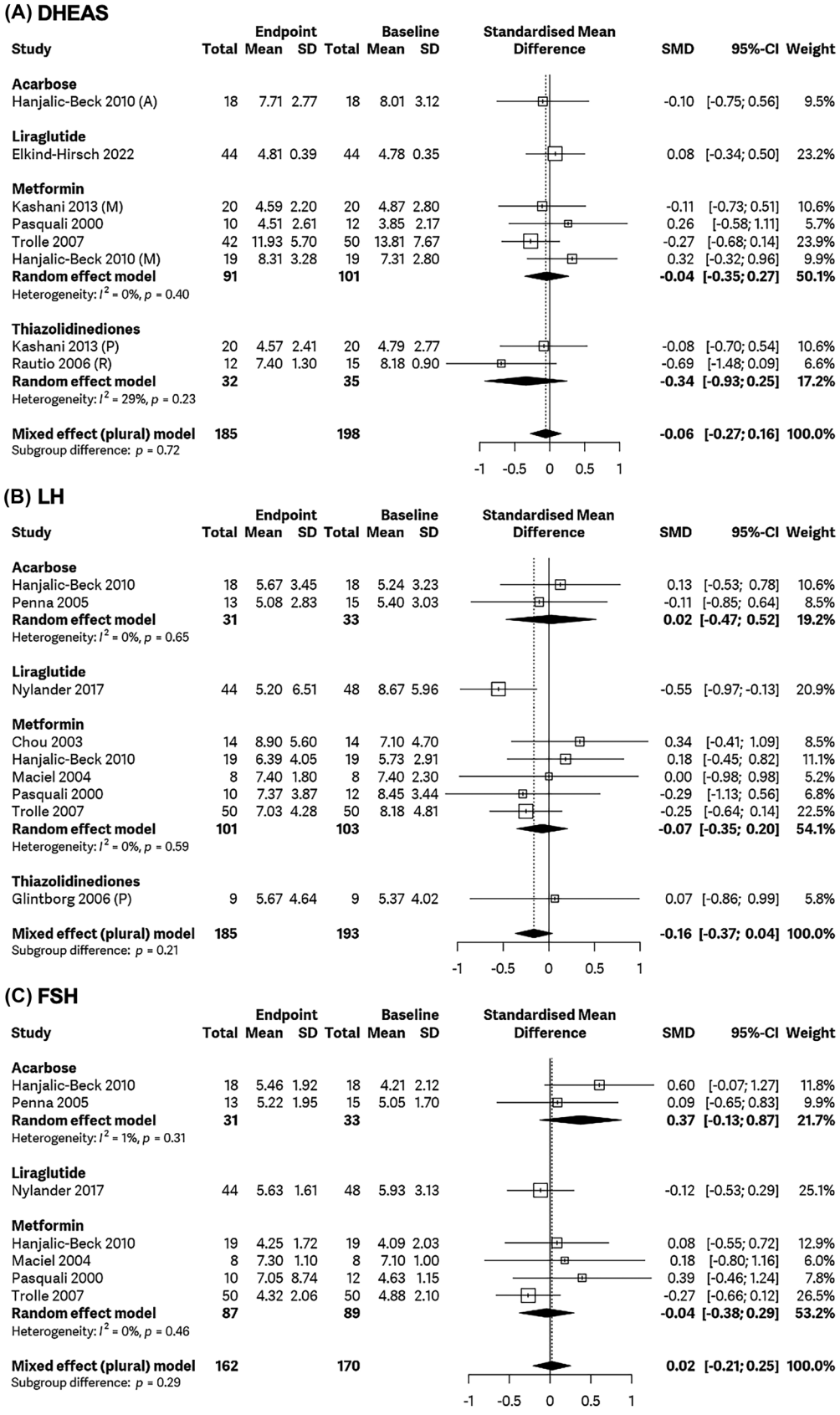


FIGURE 7 (A) Forest plot comparing fasting insulin outcomes between insulin sensitizer therapies and comparators; (B) forest plot comparing HOMA-IR outcomes between insulin sensitizer therapies and comparators; (C) forest plot comparing SHBG outcomes between insulin sensitizer therapies and comparators; (D) forest plot comparing total testosterone outcomes between insulin sensitizer therapies and comparators; (E) forest plot comparing Ferriman–Gallwey scale outcomes between insulin sensitizer therapies and comparators.

Trials of GLP-1 RA therapy in women with PCOS and obesity showed that both liraglutide and exenatide are effective in weight reduction either as monotherapy or in combination with metformin,[45,50,51] which is in keeping with our results. When comparing the effects of exenatide alone or combined with metformin, both monotherapy and combination therapy significantly reduced BMI and HOMA-IR. Monotherapy and combination therapy also increased menstrual frequency, testosterone, and free androgen index.[34] A systematic review and network meta-analysis comparing liraglutide, liraglutide plus metformin alone, metformin plus orlistat in women with PCOS, and overweight or obesity found that liraglutide alone caused the greatest reduction in body weight.[52] Combination therapy with liraglutide and metformin also significantly reduced these two outcomes, albeit less so, potentially due to a lower dose of liraglutide in

FIGURE 8 (A) Forest plot comparing DHEAS outcomes between insulin sensitizer therapies and comparators; (B) forest plot comparing LH outcomes between insulin sensitizer therapies and comparators; (C) forest plot comparing FSH outcomes between insulin sensitizer therapies and comparators.



the combination treatment.[52] The significant increase in SHBG in our meta-analysis with liraglutide is probably due to improved insulin sensitivity with weight loss. We did not find a significant reduction in total testosterone, but free testosterone was not included in this study.

Orlistat causes modest weight loss and has no systemic adverse effects.[32] As we only included double-blind RCTs in this meta-analysis, we provide the results of a single RCT on orlistat, demonstrating a significant reduction in fasting blood glucose and BMI. This finding aligns with previous meta-analyses, which demonstrated that orlistat significantly reduces anthropometric and metabolic outcomes such as BMI and HOMA-IR as well as testosterone[53] in women with PCOS.[52,53] A comparison of orlistat and metformin showed similar positive effects on BMI, insulin resistance, insulin, and testosterone.[53]

Menstrual frequency was a predefined primary outcome, but there was insufficient data in the literature to perform a meta-analysis. An RCT comparing liraglutide 1.8 mg/day to placebo in women with PCOS and overweight (without diabetes) demonstrated that the use of liraglutide resulted in a significant increase in the number of menstrual bleeds measured using bleeding diaries during the study period[28]; there was no significant reduction in anti-Mullerian hormone concentrations.[28] A 2022 study comparing liraglutide 3 mg/day to placebo documented a restoration in menstrual cyclicity (reported menses) in the treatment arm.[18] An RCT comparing metformin to placebo demonstrated a significant increase in menstrual frequency (reported menses) in both groups but no significant differences between groups.[33]

The major strength of this systematic review, meta-analysis, and meta-regression is the large number of studies included. The meta-analysis and meta-regression were performed using only double-blind RCTs to reduce bias and provide more confidence in our findings. Other strengths include performing a meta-regression (Egger's test), using internationally accepted diagnostic criteria for defining PCOS in the study population and low heterogeneity between studies. Previously published meta-analyses on the metabolic and reproductive effects of pharmacotherapy on women with PCOS and overweight or obesity have included nonrandomized studies as well as RCTs and focused on certain types of commonly used pharmacotherapies such as metformin, orlistat, and GLP-1 receptor agonists. This is the first study to include all direct and indirect insulin sensitizer pharmacotherapy.

We included only a small number of studies for GLP-1 RA, orlistat, and acarbose. Although several other trials have studied the use of GLP-1 RA in women with PCOS and overweight or obesity, most were either open-label or single-blind and, therefore, of lower methodological quality. An important limitation was the lack of hard reproductive fecundity measures such as ovulation and pregnancy.

Future RCTs should address both harder reproductive outcomes and test the impact and safety of modern pharmacotherapy for obesity on women with PCOS. A recently published single-blind, randomized, placebo-controlled prospective study comparing the effects of semaglutide to placebo in healthy women with PCOS and obesity demonstrated the positive effects of semaglutide on anthropometric and metabolic outcomes such as BMI, waist circumference, plasma glucose, and serum insulin.[54] Another potential treatment of interest is tirzepatide, a dual glucose-dependent insulinotropic polypeptide and GLP-1 RA approved by the Food and Drug Administration in May 2022 for adults with type 2 diabetes. Results from the SURMOUNT-1 study showed that once-weekly treatment with tirzepatide provided a significant and sustained reduction in body weight.[55]

In conclusion, although lifestyle modification is the recommended first-line treatment for women with PCOS and overweight or obesity, insulin sensitizer pharmacotherapy has added benefit in significantly improving metabolic outcomes and, to a lesser extent, some elements of the reproductive hormonal profile. Further work is needed to assess the use of modern obesity pharmacotherapy on hard outcomes such as menstrual cyclicity and fertility in women with PCOS and overweight or obesity.

AUTHOR CONTRIBUTIONS

Suhaniya N.S. Samarasinghe and Matthew J. Long wrote the study protocol, assessed the eligibility of studies using the inclusion criteria, assessed the risk of bias, and then performed data extraction for relevant studies. Eduard Ostarijas performed the statistical analyses. Suhaniya N.S. Samarasinghe wrote the first draft of the report, which Simon Erridge, Sanjay Purkayastha, Georgios K. Dimitriadis, and Alexander D. Miras revised. All authors gave final approval for this version to be published. Suhaniya N.S. Samarasinghe had the final responsibility to submit the work for publication.

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CONFLICT OF INTEREST STATEMENT

ADM has received honoraria for educational events from Novo Nordisk, Astra Zeneca, Currax, Boehringer Ingelheim, Screen Health, and GI Dynamics. GKD has received honoraria for educational events from Novo Nordisk, Medtronic, and J&J/Ethicon. EO has received an honorarium for an educational event from Krka.

DATA AVAILABILITY STATEMENT

All data requests should be submitted to the corresponding author for consideration.

ORCID

Suhaniya N. S. Samarasinghe https://orcid.org/0000-0001-8111-4218

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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