Impact of pharmacological interventions on anthropometric indices in women with polycystic ovary syndrome: a systematic review and meta-analysis of randomised controlled trials

Running title: pharmacological interventions in PCOS

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Abstract

Context: Polycystic ovary syndrome (PCOS) is a heterogeneous condition affecting women of reproductive age and is associated with increased body weight.

Objective: To review the literature on the effect of different pharmacological interventions on the anthropometric indices in women with PCOS.

Data sources: We searched PubMed, MEDLINE, Scopus, Embase, Cochrane library and the Web of Science in April 2020 with an update in PubMed in March 2021.

Study selection: The study followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)2020**.**

Data extraction: Reviewers extracted data and assessed the risk of bias using the Cochrane risk of bias tool.

Results: 80 RCTs were included in the meta-analysis. *Metformin vs placebo* showed significant reduction in the mean body weight (MD: -3.13 kgs; 95% CI:- 5.33,-0.93, I^2= 5%) and the mean body mass index (BMI) (MD: -0.75 kg/m^2; 95% CI: -1.15, -0.36, I^2= 0%). There was a significant reduction in the mean BMI with *orlistat vs placebo* (MD: -1.33 kg/m^2; 95% CI: -2.16 -0.66, I^2= 0.0%), *acarbose vs metformin* (MD: -1.26 kg/m^2; 95% CI: -2.13, -0.38, I^2= 0%), and *metformin vs pioglitazone* (MD: -0.91 kg/m^2; 95% CI: -1.62, -0.19, I^2= 0%). A significant increase in the mean BMI was also observed in *pioglitazone vs placebo* (MD: +2.59 kg/m^2; 95% CI: 1.78, 3.38, I^2= 0%) and *in rosiglitazone vs metformin* (MD: +0.80 kg/m^2; 95% CI: 0.32, 1.27, I^2= 3%). There was a significant reduction in the mean waist circumference (WC) with *metformin vs placebo* (MD: -1.21 cm; 95% CI: -3.71-1.29, I^2= 0%) while a significant increase in the mean WC with *pioglitazone vs placebo* (MD: +5.45 cm; 95% CI: 2.18, 8.71, I^2= 0%).

Conclusion: Pharmacological interventions including metformin, sitagliptin, pioglitazone, rosiglitazone orlistat and acarbose have significant effects on the anthropometric indices in women with PCOS.

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous and complex endocrine disorder affecting women of reproductive age, with a prevalence ranging from 8% to 13 % [1,2]. PCOS is characterised by both clinical and biochemical evidence of excess androgen levels (manifested as acne and hirsutism), menstrual irregularities and sonographic polycystic ovarian morphology[3]. Metabolic disorders such as insulin resistance (IR) and impaired glucose tolerance are common in women with PCOS, leading to an increased risk of type 2 diabetes mellitus (T2DM)[4]. Moreover, PCOS predisposes to a range of other complications including infertility, increased body weight, increased risk of cardiovascular disease (CVD) and endometrial cancer[5-7].

Increased body weight is a prominent feature of PCOS and around 50% of women with PCOS are either overweight or obese[8]. Obesity exacerbates PCOS features such as excessive hair growth, infertility and pregnancy complications, aggravates IR, which culminates in an increased metabolic risk associated with PCOS[9]. Therapeutic approaches including lifestyle modifications through dietary interventions and physical activity are the cornerstone in the management of PCOS[10]. There are also differing pharmacotherapeutic interventions including insulin sensitisers (metformin and thiazolidinediones) that improve IR and peripheral glucose uptake [11,12]. However, these therapeutic options are primarily licensed to treat other conditions such as T2DM and their effectiveness in PCOS remains unclear in the literature. There are also significant gaps between the available evidence and the evidence-based treatment options[3]. This might often lead to the delay in offering satisfactory treatment options and the clinical inertia around treating PCOS[3]. Therefore, this systematic review and meta-analysis aimed to evaluate and analyse the available evidence on the effectiveness of different therapeutic options used to treat PCOS in improving anthropometric outcomes.

Methods

Protocol and registration

This systematic review and meta-analysis were prospectively registered in the PROSPERO international prospective register of systematic reviews (CRD42020178783) and is reported according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[13].

Eligibility criteria

We included only randomised controlled trials (RCTs). The RCTs included in the systematic review were defined based on the PICO (population, intervention, comparator, and outcome) elements. The inclusion criteria are presented in Table 1. Briefly, only RCTs recruited women of reproductive age (≥ 18 years) diagnosed with PCOS were eligible. RCTs were included regardless of the design (open-labelled, double-blinded, and within-subject crossover) and randomisation methodology. Also, RCTs needed to have reported a comparison of at least one pharmacological agent with placebo or various combinations of pharmacological agents.

Literature search

A systematic and comprehensive literature search was conducted in six biomedical databases: PubMed, EMBASE, MEDLINE, Scopus, Cochrane Library (CENTRAL) and Web of Science, in April 2020 with an update in PubMed in March 2021 (L.Ö).The medical database PubMed was used to develop a preliminary search strategy. Search terms were selected by experts in the field of the subject (T.S & M.A) in close collaboration with a medical librarian specialised in systematic reviews (L.Ö). All terms were searched in a combination of title, abstract and Medical Subject Headings (MeSH) for the best possible literature retrieval. A filter for English language was applied. The search string developed in PubMed were later used to search in all selected electronic databases. A separate search for grey,

unpublished literature and clinical trials was performed in March 2021 including Open Grey Clinical Trials.gov and in the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT). The full search strategy including results, notes and search technical specifications for all databases and grey sources is available as a supplementary material.

All records found in the literature search were uploaded to Covidence software(www.covidence.org)[14] for blinded screening. Full-text review and data extraction were performed after automatic removal of the duplicate records in the software. Selected references were then uploaded to the EndNote software for reference management[15]. Finally, the reference lists of all included studies as well as systematic reviews and meta-analyses found in the literature search were screened by hand for additional undetected studies (M.A & N.S). Cabell's Predatory Report [16] was used to verify that none of the selected studies were published in potential predatory journals.

Study selection

Two reviewers (M.A, & N.S) conducted the initial screening by independently assessing titles and abstracts for eligibility considering the inclusion/exclusion criteria. Full text assessment of the potentially eligible studies was undertaken blindly by both reviewers. Any disagreements between reviewers about the inclusion were resolved by consensus (M.A, N.S) using covidence blinded conflict resolving function (www.covidence.org)[14].Non-pharmacological interventions and observational studies were excluded. Where duplicate publications for the same study were identified, the most recent version of the study was selected. The process of study identification and selection was performed independently by two reviewers. The study selection process is presented in Figure 1 following the PRISMA guidelines[13].

Data extraction

Two independent reviewers (M.A and N.S) extracted information on the country of the RCTs, name of the author, year of publications, design of the intervention, type of the interventions and comparators,

number of participants and baseline characteristics of the participants, duration of the RCTs, and the measured anthropometric outcomes reported including body weight, body mass index (BMI), waist circumference (WC), and waist to hip ratio (WHR).

Risk of bias assessment in the included studies

The Cochrane collaboration's tool for assessing risk of bias (RoB) was used as recommended by Higgins et al[17]. Six domains including (selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias) were assessed. Two independent reviewers (M.A and N.S) assessed the RoB for each study, and a third reviewer (S.T) mediated any conflict between reviewers. The recommendations from the Cochrane handbook[18] were followed and any RoB was graded as either 'high RoB', 'low RoB', or 'unclear RoB' Figure 1, supplementary materials. The proportion of studies regarded as either with 'high RoB', 'low RoB', or 'unclear RoB' for each specific RoB domain was calculated and reported Figure 1, supplementary materials.

GRADE scoring

The strength of the evidence for each desired outcome (body weight, BMI, WC, and WHR) was assessed using recommendations from the Grading of Recommendations, Assessments, Development and Evaluation (GRADE) system[19]. GRADEpro GDT software was used to grade the quality of each outcome and to produce "Summary of findings Table" Table 1, supplementary materials**.**

Data analysis and evidence synthesis

When quantitative data on the impact of the intervention (mean value) on a specific outcome from at least two independent trials were available, the pooled effect estimates (mean difference) and its 95% confidence intervals (95% CI) were quantified using the random-effects model as recommended by the *Cochrane handbook*[18] .To conduct the meta-analysis for the continues outcomes, we assumed data were normally distributed. Extremely skewed data or data reported as range were excluded from the

meta-analysis. Means and standard deviation (SD) for both pre and post-intervention values and changes from baseline scores were combined for the meta-analysis. For data presented as standard error (SE),CIs, *p*-values, and *t* values, the RevMan calculator was used when necessary to convert them into means and SD. Mean difference (MD) was used when same continuous data presented using the same scales across the trials. Where units of measurements were varied, scales were converted to the most common measures. For trials with more than one intervention arm, data from all arms were combined using the method recommended in the *Cochrane Handbook* [18]. Post-intervention scores and data from crossover trials were used from the last point the trials were reported.

Assessment of heterogeneity

Heterogeneity for each result of the outcomes across the trials was assessed using the squared (I^2) statistics. A statistically significant heterogeneity (observed I^2 *%)* was determined by visually examined forest plots for no substantial or little overlapping of the confidence intervals (CIs) of the results across the studied. For substantial heterogeneity, the source was investigated by removing the study that represented the largest effect from the analysis and the I^2 was re-evaluated. If heterogeneity was still not resolved, assessment of the population groups for similarities in the baseline characteristics and subgroup analyses were performed.

Subgroup analysis

Where data from more than two trials were present, subgroup analysis was conducted. Subgroup analysis was performed on the characteristics of the interventions including dosages/mg, frequency of administration (one/day [QD], twice/ day [BID] and trice/day [tds]), and duration of the interventions (weeks/months). Outcome data were divided by subgroups, and the subtotal summary of results were presented and reported quantitatively.

Trial data were pooled, and meta-analysis was performed using the Review Manager software (RevMan 5.4, The Cochrane collaboration).

Results

In total, 6,326 records were identified, of which 3,186 studies were screened for eligibility based on titles and abstracts after removing duplicates. A total of 814 full-text articles were retrieved for detailed assessment for eligibility, of which 80 RCTs were found eligible and included in this study (Figure 1). No additional, eligible studies were identified in the hand screening of the included papers.

characteristics of the included RCTs

The 80 RCTs were published between 2000 and 2020 and included (4,028 participants both PCOS and control) that met the inclusion criteria and were included in the meta-analysis. Forty-two trials[20-61] diagnosed PCOS based on the Rotterdam 2003 criteria[62], ten trials[35,63-72] used the National Institute of Health 1990 (NIH, NICHD) criteria, one trial[73] used the Androgen Excess Society 2006 (AES) criteria[74],and no diagnostic criteria were specified for the reminder of the trials (Table 2).

Interventions and comparisons details

Twenty-one RCTs (26.3%) assessed the effect of metformin compared with placebo[20,26,31,36,37,39,42,46,47,50,54,57,59,75-83]. Six RCTs (7.5%) compared metformin with pioglitazone[23,53,61,84-86]. Two RCTs (2.5%) evaluated liraglutide compared with metformin[69,87]. Five RCTs (6.3%) examined pioglitazone compared with placebo[21,63,88-90]. Nine RCTs (11.3%) compared rosiglitazone with metformin[22,33,38,41,44,58,91-93]. Three RCTs (3.8 %) examined liraglutide compared to liraglutide added to metformin[34,35,71].Three RCTs (3.8%) compared orlistat with metformin[23,30,94]. Two RCTs (2.5%) compared sitagliptin added to metformin with metformin alone[28,95]. Two RCTs (2.5%) evaluated sitagliptin with placebo[24,29]. Three RCTs (3.8 %) assessed exenatide compared to metformin[27,43,60]. Two RCTs (2.5%,) compared orlistat with placebo[25,45]. Two RCTs (2.5%) compared acarbose versus placebo[96,97].Three RCTs (3.8%) compared acarbose to metformin[51,67,72]. Two RCTs (2.5%) compared saxagliptin alone and with metformin plus saxagliptin [55,65]. Two RCTs (2.5%) compared metformin with simvastatin[68,98]. Two RCTs (2.5%) compared metformin with NAC[32,49]. Two RCTs (2.5%) examined

atorvastatin with placebo[99]. Three RCTs (3.8%) compared spironolactone and placebo[48,64,66]. Five RCTs (6.3%) assessed rosiglitazone with placebo[40,73,100-102](Table 2).

Outcomes measured

All RCTs assessed the outcomes at baseline and post-intervention at various follow up times**.** Thirty-one trials[22,26,30,31,34,35,38,40-43,46,53,54,56,59,60,69,71,73,77,81,84-87,94,100,103] reported on changes in body weight. Seventy-nine RCTs reported on changes in BMI as the primary outcome [20-55,57-61,63-73,77-92,95-99,101,102].Twenty-three RCTs reported on changes in WC[31,34,35,41,46,53-56,58,63,65,69-71,78,84,87,90,91]. Thirty- four RCTs reported on changes in WHR [20,31,39-43,46,50,54,58,60,63,73,76,78,82,84-86,88,89,102] (Table 2).

Risk of bias assessment

Risk of bias (RoB) for the included RCTs and the overall RoB are illustrated in Figure 1, supplementary materials. Twenty-six RCTs were judged to have low RoB with regard to selection bias for using appropriate methods to generate their sequences for randomisation and allocation concealment [20,27,28,32,36-38,40,46,50,57,64,65,67,68,72,78,80,83,85,86,95-97]. One trial [63] was judged to have a high risk of selection bias. Five trials were categorised as having an unclear RoB across all six assessed RoB domains due to insufficient information [47,49,53,59,90]. Due to the nature of the trials (open-label), thirty-five trials were judged to have a high risk of performance bias[20,22,23,25,27-31,33-35,41,43,44,55,60,61,64-66,69-71,76,85-87,94]. The remainder of the trials were judged to have an unclear risk of performance bias due to a lack of a clear statement about whether the outcome assessors were blinded to the participants allocation and interventions. One trial was judged to have a high risk of reporting bias due to selective data reporting [76].

Effect of interventions on anthropometric outcomes

Results of the pharmaceutical medications compared with placebo presented in Figures 2-3 and compared with other medications are shown in Table 3.

Body weight

Metformin versus placebo

In four RCTs, metformin 1500 mg once a day (QD) significantly reduced the mean body weight (mean difference (MD): -8.47 kgs; 95% CI: -13.50-3.98). In two RCTs compared placebo, metformin 850 mg twice a day (BID) was associated with no significant change in the mean body weight (MD: -2.84 kgs; 95% CI: -10.15 - 4.46 kgs). In four RCTs, metformin 2000 mg QD was associated with no significant change in the mean body weight (MD: -1.6 kgs; 95% CI: -4.08-0.84). Overall, regardless of the administered dosage, metformin was associated with a significant reduction in the mean body weight (MD: -3.13 kgs; 95% CI: - 5.33, -0.93, I^2= 5%) compared with placebo. (Figure 2-A) (moderate grade evidence, Table 1, supplementary materials).

Metformin versus orlistat

In three RCTs, Metformin 1500 mg QD for three months compared with orlistat 120 mg three times a day (TDS) significantly reduced the mean body weight (MD: -3.28 kgs; 95% CI: -7.29-0.74, I^2= 58%) (Table 3); very-low grade evidence, Table 1, supplementary materials).

Metformin versus Rosiglitazone

Three RCTs compared metformin with rosiglitazone showed a significant increase in the mean body weight (MD: +1.95 kgs; 95% CI: 0.03-3.87, I^2= *3%*) with rosiglitazone. This significant increase to the mean body weight was mainly driven by the RCTs that administered 1500 mg/day of metformin compared to 4 mg/day of rosiglitazone for six months (MD: +3.19 kg; 95% CI; 0.65-5.73) (Table 3) (very low-grade evidence, Table 1, supplementary materials).

The meta-analysis showed that there was no difference in the mean body weight when rosiglitazone was compared with placebo (Figure 2-B). Similarly, no significant change in the mean body weight was

seen when metformin alone or in combination with liraglutide was compared with other medications (liraglutide, pioglitazone, and exenatide) (Table 3).

Body Mass Index

Metformin versus placebo

In four RCTs, metformin 850 mg BID for six months was associated with no significant change in the mean BMI (MD: -0.94 kg/m^2; 95% CI: -2.31- 0.47, I^2= 0%) compared with placebo. The pooled effect estimates from 11 RCTs showed that metformin 1500 QD for three months was associated with a significant reduction in the mean BMI (MD: -0.80 kg/m^2; 95% CI: -1.30, -0.31, I^2= 0%). The pooled effect estimates from two RCTs showed that metformin 1500 mg QD for six months associated with no significant change in the mean BMI (MD: +0.34 kg/m^2; 95% CI: -1.01- 1.68, I^2= 0%). Individual studies showed no significant change in the mean BMI to metformin 1700 mg QD for 12 months (MD: -0.20 kg/m^2; 95% CI: -1.67-1.27), to metformin 1000 mg QD for 6 months (MD: -1.20 kg/m^2; 95% CI: -4.09-1.69), and to metformin 850 mg BID for 36 months (MD: -0.80 kg/m^2; 95% CI: -2.14-0.54) compared to placebo. Whereas metformin 1500 mg QD for seven weeks was associated with a significant reduction in the mean BMI (MD: -3.0 kg/m^2; 95% CI: -5.11, -0.89). Overall, regardless of the dosage, duration, and frequency per day, the pooled effect estimates from 21 RCTs included 1,280 (662 in the intervention arm, 618 in the placebo arm) women with PCOS showed that metformin was associated with a significant reduction in the mean BMI (MD: -0.75 kg/m^2; 95% CI: -1.15, -0.36, I^2= 0%) (Figure 3-A) (moderate grade evidence, Table 1, supplementary materials).

Orlistat versus placebo

Orlistat 120 mg tds for six months in one RCT and for three months in another RCT significantly reduced the mean BMI (MD: -1.33 kg/m^2; 95% CI: -2.16 -0.66, I^2= 0.0%) compared with placebo. (Figure 2-A, supplementary materials) (very low-grade evidence, Table 1, supplementary materials).

Acarbose versus Metformin

In one RCT acarbose 100 mg QD for three months was associated with a significant reduction in the mean BMI, while in two RCTs acarbose 300 mg QD for three months was associated with no significant change in the mean BMI. However, in the three RCTs, regardless of the dosage, frequency, and duration, acarbose showed a significant reduction in the mean BMI (MD: -1.26 kg/m²; 95% CI: -2.13, -0.38, I^2= *0%*) (Table 3) (low grade evidence, Table 1, supplementary materials).

Pioglitazone versus placebo

The pooled effect estimate showed that there was a significant increase in the mean BMI between women received pioglitazone 45mg QD (MD: +3.33 kg/m²; 95% CI: 1.60- 5.06), and pioglitazone 30 mg QD (MD: +2.38 kg/m²; 95% CI; 1.48-3.28). However, regardless of the dosage, frequency, and duration, the mean BMI increased (MD: +2.59 kg/m²; 95% CI: 1.78-3.38, I^2= 0%) in 56 women who received pioglitazone compared to 58 women who received placebo. (Figure 2-B) (low grade evidence, Table 1, supplementary materials).

Metformin versus Pioglitazone

Metformin 850 mg BID for six months, in two RCTs showed a significant reduction in the mean BMI by (MD: -1.07 kg/m²), whereas metformin 1500 mg QD for 3 months in four RCTs, showed no significant change in the mean BMI compared to women in the pioglitazone group. Overall, metformin at various dosages significantly reduced the mean BMI (MD: -0.91 kg/m²; 95% CI: -1.62-0.19) (Table 3) (very low grade evidence, Table 1, supplementary materials).

Metformin and Sitagliptin versus Metformin alone

In two RCTs, when Sitagliptin 100 mg added to metformin at different doses, a significant reduction in the mean BMI (MD: -3.94 kg/m²; 95% CI: -7.81-0.08, I^2= 0%) was observed (Table 3) (very low grade evidence, Table 1, supplementary materials).

Exenatide versus metformin

In three RCTs, exenatide 10 ug showed a significant reduction in the mean BMI (MD: -0.85 kg/m²; 95% CI: -1.61-0.08, I^2= 0%). when compared with Metformin 1000 mg QD. (Table 3) (very low grade evidence, Table 1, supplementary materials).

Rosiglitazone versus Metformin

Compared with rosiglitazone 4 mg QD, metformin 850 mg BID, metformin 1500 mg QD, metformin 1000 mg QD and metformin 2000 mg QD were associated with no significant change in the BMI. Overall effect, regardless of the dosage, frequency, and duration, in 10 RCTs that included 262 women with PCOS in the metformin arm compared with 258 women with PCOS in the rosiglitazone arm, rosiglitazone was associated with a significant increase in the mean BMI (MD: +0.80 kg/m²; 95% CI: 0.32-1.27, I^2= 3.0%) (Table 3) (moderate grade evidence, Table 1, supplementary materials).

The meta-analysis showed that there was no difference in the mean BMI when rosiglitazone, sitagliptin, atorvastatin and acarbose were compared with placebo (Figure 2-C,D,E and F). Similarly, no significant change in the mean BMI was seen when metformin alone or in combination with liraglutide was compared with other medications (liraglutide, orlistat, spironolactone, saxagliptin, simvastatin, and NAC (Table 3).

Waist Circumference

Pioglitazone versus placebo

The pooled estimate showed that there was a significant increase in the mean WC when women received pioglitazone 45 mg QD for six months (MD: +6.60 cm; 95% CI: 2.78- 10.42), pioglitazone 30 mg QD for 6 months (MD: +2.70 cm; 95% CI: -6.94-12.34) and pioglitazone 30 mg QD for 4 months (MD: +2.0 cm; 95% CI: -6.33- 10.33). However, regardless of the dosage, frequency, and duration, the mean WC was significantly increased (MD: +5.45 cm; 95% CI: 2.18- 8.71, I^2= 0%) in 37 women who

received pioglitazone compared to 40 women who received placebo (Figure 3-A, supplementary materials) (very low grade evidence, Table 1, supplementary materials).

Metformin versus placebo

In one RCT, metformin 2000 mg QD was associated with no significant change in the mean WC (MD: + 0.80 cm; 95% CI: -4.32-5.92) while in four RCTs, metformin 1500 mg QD for three months significantly reduced the mean WC (MD: -1.84 cm; 95% CI: -4.71-1.03) when compared with placebo. However, regardless of the dosage metformin insignificantly reduced the mean WC (MD: -1.21 cm; 95% CI: -3.71-1.29, I^2= 0%). (Figure3-B,supplementary materials) (moderate grade evidence, Table 1, supplementary materials).

The meta-analysis showed that there was no difference in the mean WC when metformin alone or in combination with liraglutide was compared with pioglitazone, liraglutide, rosiglitazone and saxagliptin (Table 3).

Waist to Hip Ratio

Rosiglitazone vs placebo

The meta-analysis showed that there was a significant reduction in the mean WHR when rosiglitazone was compared with placebo (MD: -0.08; 95%CI: -0.11-0.04, I^2= 0%) (Figure 4-A, supplementary materials) (very low-grade evidence, Table 1, supplementary materials).

No difference in the mean WHR when metformin, pioglitazone, and orlistat were compared with placebo (Figure 4- B, C and D, supplementary materials). Similarly, no difference in the mean WHR was also observed when metformin was compared with pioglitazone, exenatide, rosiglitazone, spironolactone, and saxagliptin (Table 3).

Discussion

This systematic review summarises the up-to-date evidence supporting the pharmacological interventions used in the management of PCOS. To our knowledge, this is the first comprehensive systematic review to report the effects of different pharmacological interventions on the anthropometric outcomes of women with PCOS. When metformin was administered at various therapeutic doses, there was a statistically significant reduction in the mean body weight, BMI and WC compared with placebo. Such effects were also observed when metformin was compared with sitagliptin and acarbose. On the other hand, pioglitazone and rosiglitazone were associated with a significant increase in the mean body weight, WC and BMI.

Anthropometric outcomes

Regarding the effect on body weight and BMI, significant beneficial changes were found with metformin versus placebo. Subgroup analyses also indicated that significant reductions in body weight and BMI were noted with differing doses of metformin administered for short or long durations. These findings are in line with the results from previous systematic reviews in which metformin was with lifestyle modification or placebo [104,105]. The most recent meta-analysis[105] reported a large reduction in BMI (WMD = -1.25 kg/m², 95% CI: -1.60, -0.91, $p < 0.00001$) following treatment with metformin. Another meta-analysis[104] also reported a significant reduction in BMI (MD) -0.73 kg/m²,95% CI: -1.14, -0.32, P = 0.0005) with metformin compared with lifestyle or placebo. Therefore, the results reported here are in accord with others that metformin as monotherapy can significantly reduce weight and BMI in women with PCOS. In the present review, it was shown that metformin could also reduce BMI when compared with pioglitazone, an observation that is consistent with a previous meta-analysis in which BMI was increased with pioglitazone treatment to a large extent compared with metformin[12]. Similarly, another systematic review compared the effect of pioglitazone versus metformin in PCOS and showed a decreased effect with pioglitazone than with metformin in reducing BMI[106]. We also found a significant reduction in body weight with metformin administered at various doses compared

with rosiglitazone; however, there was no difference between metformin compared with either liraglutide or exenatide.

Another observation was a significant reduction in BMI with orlistat compared with placebo, which is in line with the findings of other groups [107,108].Nevertheless, no reduction in BMI was seen for orlistat compared with metformin. Finally, a significant reduction of BMI was found with sitagliptin added to metformin versus metformin alone. Currently, due to the cardiovascular risk and other adverse effects associated with thiazolidinediones and the troublesome gastrointestinal adverse effects of orlistat, these medications are of limited use.

Results in the current study are in accord with many clinical trials of varying designs that have evaluated the effects of differing pharmacological interventions on the body composition in patients with T2DM. In an observational study of 51 newly diagnosed patients with T2DM, metformin 1g/day for duration of 6 months was associated with a significant improvement in body composition when compared with placebo[109]. A recent systematic review and meta-analysis evaluating the efficacy of differing pharmacological interventions on adults with T2DM showed that body weight was either significantly reduced or maintained in treatment with metformin and DPP-4 inhibitors[110]. Another meta-analysis of 15 RCTs evaluating the effects of pioglitazone on the glycaemic indices, lipid profiles, BMI and body weight in T2DM reported a significant increase in body weight and BMI (WMD 1.755, 95% CI 0.674 to 2.837 and 1.145, 95% CI 0.389 to 1.901, respectively)[111]. In an RCT of 676 newly diagnosed patients with T2DM (343 in acarbose group and 333 in metformin group) that examined the effect of metformin and acarbose on WHR, it was reported that a significant reduction in WHR in both groups occurred after 25 weeks (acarbose: -0.015, 95% CI: -0.018 to -0.012, $P < 0.001$; metformin: -0.013, 95%CI: -0.016 to -0.010, $P < 0.001$)[112].

This study followed a comprehensive and systematic search of relevant databases and grey sources that only included RCTs. To minimise the risk of bias, all observational studies and non-randomised clinical trials were excluded.

To the authors' knowledge, this study is the most comprehensive and up-to-date systematic review and meta-analysis on the impact of pharmacological interventions on anthropometric parameters in women with PCOS.

However, there are some limitations that must be considered for this systematic review. We applied a language filter and only RCTs reported in English language were included; hence several trials in foreign languages may not have been retrieved. Assessing such trials requires sophisticated translation, which is challenging and might also affect the methodology of this review. Furthermore, only fully published trials were eligible to be included in the review. The majority of the trials were of small sample size and the statistical power used to calculate sample size and to detect the significant differences between the groups was not fully reported. All the trials were of short duration and reported baseline and immediate post-intervention data. Therefore, the long-term effects of different pharmacological interventions in women with PCOS is not clear.

Conclusion

Metformin, alone or in combination with other medications and irrespective of the dosage and duration of therapy can significantly reduce mean body weight, BMI and WC in women with PCOS. Orlistat also significantly reduced mean BMI compared with placebo. On the other hand, both rosiglitazone and pioglitazone, alone or in combination with other medications were associated with significant increases in mean body weight, BMI and WC.

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Data availability

The datasets generated and analysed for this review are available upon reasonable request to the authors.

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Conflict of interest

None to declare.

Ethical approval

Not needed as no patients were involved.

Authors contributions

M.A; designed the review, assessed the quality, extracted, collected, and analysed the data, written, revised, and edited the final manuscript. N.S; assessed the quality, extracted, and collected the data, and revised and edited the final manuscript. H.D; revised and edited the final manuscript. L. Ö; developed and conducted the database searches and revised and edited the final manuscript. R.H.A; contributed to the meta-analysis and participated in the critical discussion and revised and edited the final manuscript. S.A; participated in the critical discussion and revised the final draft of the manuscript. T.S; acted as mediator for the assessment of the quality of the evidence, supervised the study, participated in the critical discussion, revised, and edited the final manuscript.

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Table 1: The inclusion criteria for the included studies in this systematic review

Inclusion criteria

1. Study design: randomised controlled trials including (randomised open-label trials, double-blind controlled trials, crossover randomised trials, parallel randomised trials).
2. Population: adult females aged 18 and over with a diagnosis of PCOS based on a robust diagnostic criterion.
3. Comparator: reported pharmacological interventions compared to placebo or other pharmacological agents.
4. Outcomes: reported outcomes such as BMI, body weight, waist circumference and waist to hip ratio.

Exclusion criteria

1) Study design: case studies, cross-sectional studies and animal studies.
2) Patients population: adolescents females, postmenopausal women, and women without PCOS.

Comparators: non-pharmacological interventions, pharmacological interventions versus dietary interventions, pharmacological interventions versus physical activities or surgery.

Figure 1: PRISMA flow diagram

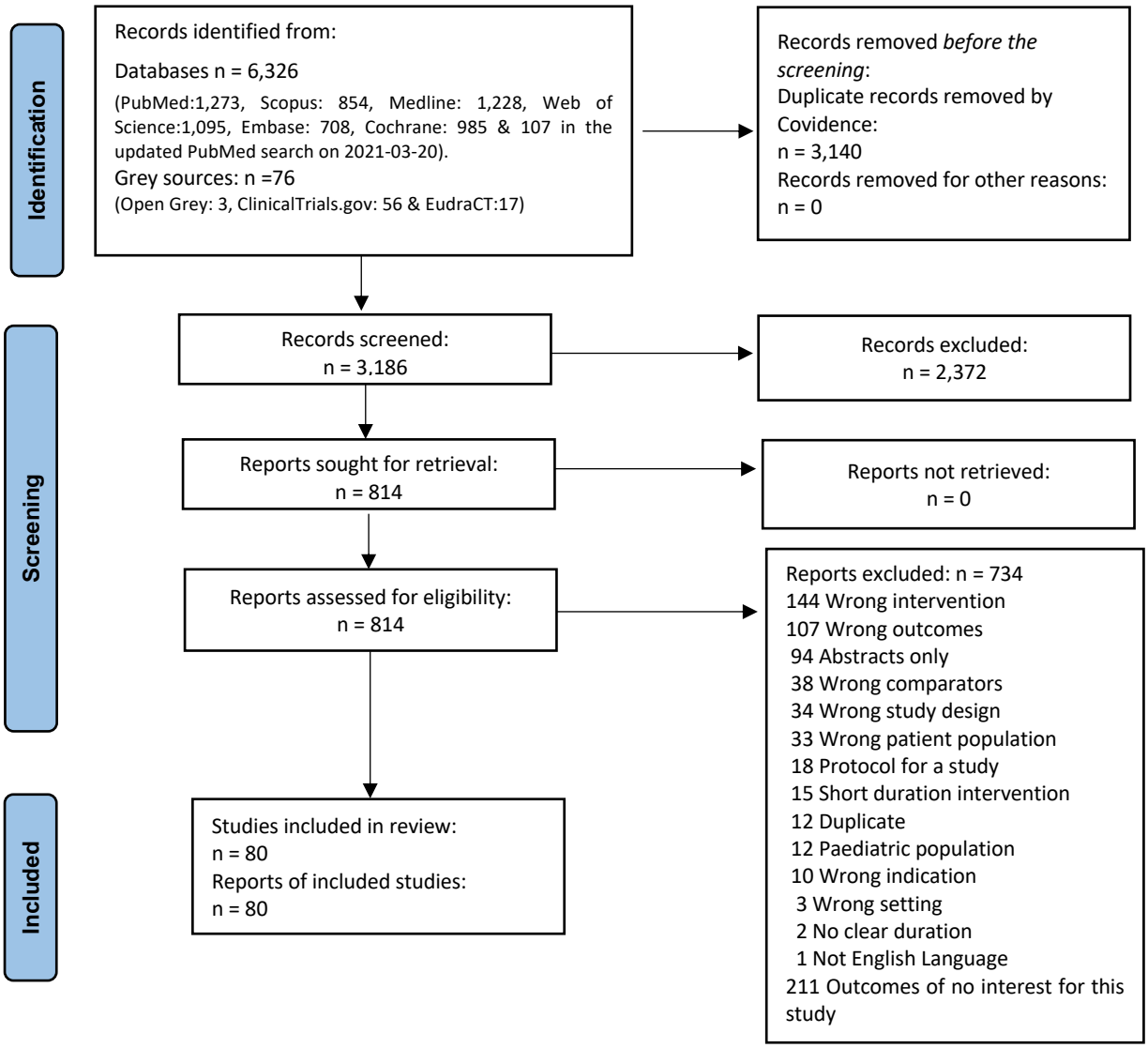


Table 2: Characteristics of the included RCTs

Author	Study design	Country	PCOS diagnostic Criteria	Participants characteristics (PCOS)	Interventions	Durations	Outcomes
Amiri et al [20]	RCT	Iran	Rotterdam	Age:25.6±4.02 BMI: 28.9±5	Metf, Flu, Metf+ Flu, Placebo	6 months	BMI, WHR, WC, FBG,LDL,HDL, TG FAI.
J.Ahmad et al[93]	RCT	India	NIH	Age: 22.81± 4.52 BMI: 27.66 ±5.44	Rosig, Metf	12 months	WHR, BMI
Aroda et al [63]	RCT	USA	NIH	Age: 27.87 ±0.87 BMI: 36.29 ±1.34	Piog, Placebo	6 months	Weight, BMI, WHR, WC, FBG,FI
Ashraf Ganie et al[64]	RCT	India	NIH	Age: 22.9 ±5.3 BMI: 26.8±4.0	Spironolactone vs Met	3 months	BMI,FBG,FI, WHR
Batista et al[73]	RCT	Brazil	AES-2006	Age: 24.5±4.33 BMI: 27.89±6.10	Rosig, placebo	12 weeks	FBG.FI,HOMA-IR
Brettenthaler et al[21]	RCT	Switzerland	Rotterdam	Age: 30.2± 1.4 BMI: 29.4± 1.7	Piog, placebo	3 months	BMI,WHR,FBG, FI, HOMA-IR
Cataldo et al [100]	RCT	USA	NICHD	Age: 29.3 ± 1.5 BMI: 37.2 ± 2.1	Rosig 2mg, 4mg, 8 mg	12 weeks	BMI, WHR, Wt
Cheng et al[75]	RCT	Australia	Rotterdam	Age: 26 ± 4 BMI:24.2±5.3	Metf, placebo	6 months	Wt, BMI, WC, WHR, LDL,HDL, TG,TC,HOMA-IR, HOMA-B
Chou et al[76]	RCT	Brazil	N/A	Age:24±5 BMI:35.6±4.9	Metf, placebo	3 months	BMI,WHR,FBG, FI, TG,TC,HDL, LDL
Cetinkalp et al[22]	RCT	Turkey	Rotterdam	Age: N/A BMA:25.82±6.12	Met, Rosigl , ECA	4 months	FBG,FI, Wt, BMI, HOMA-IR, TC, TG,HDL,LDL
Cho et al[23]	RCT	UK	Rotterdam	Age: 26·4 ± 1·5 BMI: 36·0 ± 1·2	Metf, Orlistat, Piog	12 weeks	BMI, HOMA-IR
Ciotta et al[96]	RCT	Italy	N/A	Age:20.5±0.6 BMI:22.7±0.34	Acarbose, Placebo	3 months	BMI, PRL
Dereli et al[101]	RCT	Turkey	NICHD	Age: 31.4 ± 0.9 BMI: 24.2 ± 1.3	Rosig 2mg, 4 mg	8 months	BMI, WHR
Diamanti-Kandarakis et al[25]	RCT	Greece	Rotterdam	Age: 27·52 ± 5·77 BMI: 35·43 ± 5·3	Orli, placebo	6 months	BMI,WHR, HOMA
Devin et al[24]	RCT-cross over	USA	Rotterdam	Age:N/A BMI:N/A	Sitag, placebo	4 weeks	BMI,WHR,WC, LDL.HDL, TC
Elkind-Hirsch et al[27]	RCT	USA	Rotterdam	Age: 28.2 ± 1.1 BMI: 39.9 ±1.5	Exen, Metf,Exen+Metf	24 weeks	Wt, BMI, CRP, TG, TC,HDL,LDL
Elkind-Hirsch et al[65]	RCT	USA	NIH	Age: 29.9± 7 BMA: 42.1 ±7.3	Sax, Metf, Sax+Metf	16 weeks	FBG,FI, HDL,TG, LDL,HOMA-IR
Eisenhardt et al[26]	RCT	Germany	Rotterdam	Age: 27.0 BMI: 28.9	Metf,Placebo	12 weeks	FBG.FI,HOMA-IR
Ferjan et al[28]	RCT	Slovenia	Rotterdam	Age: 34.3 ± 6.8 BMI: 36.3 ±5.2	Metf, Metf+Sitag	12 weeks	Wt,BMI,WC TC,TG,LDL, HDL, HOMA-IR
Ferjan et al[29]	RCT	Slovenia	Rotterdam	Age: 35.0 ± 7.2 BMI: 36.9 ± 5.5	Sitag, Placebo	12 weeks	HOMA-IR, BMI, HOMA-B, FBG

Table2 continued….

Glintborg et al[90]	RCT	USA	N/A	Age: 32 BMI: N/A	Piog, Placebo	16 weeks	FI, HOMA-IR
Glintborg et al[88]	RCT	USA	N/A	Age: 32 BMI: 32.2	Piog,Plcebo	16 weeks	BMI,WHR, WC, FI
Glintborg et al[89]	RCT	Denmark	N/A	Age: N/A BMI: 33·1	Piog, placebo	16 weeks	BMI, CRP, LDL
Gambineri et al[77]	RCT	Italy	N/A	Age: 27·1 ± 3·6 BMI: 37·6 ± 4·1	Plac, metfo, flut, metf + flut	6 months	FBG,FI, Wt, BMI, HOMA-IR
Ghandi et al[30]	RCT	Iran	Rotterdam	Age: 27±4.92 BMI: 34.88±4.90	Orlistat, Metf	3 months	BMI,WC, TC, TG
Ganie et al[66]	RCT	USA	NIH	Age: 22.6 ±5.0 BMI: 26.5 ±5.6	Spironolactone, Metf	6 months	WHR,BMI,FBG,FI
Hanjalic-Beck et al[67]	RCT	Germany	NIH	Age:N/A BMI:N/A	Metf, Acarbose	12 weeks	BMI,FBG,FI
Heidari et al[31]	RCT	USA	Rotterdam	Age: 32.47.5 BMI: 37.19.1	Metf, placebo	3 months	BMI,WC,WHR, Weight
Jayagopal et al[94]	RCT	UK	N/A	Age: 27 ±0.9 BMI: 36.7 ±3.3	Orlistat, Metf	3 months	FBG, FI, TC,TG, HDL
Javanmanesh et al[32]	RCT	Iran	Rotterdam	Age: 29.75 ± 4.90 BMI: 29.05 ± 2.80	Metf, NAC	24 weeks	BMI, FBG,FI, LDL, TC,TG, HDL ,HOMA-IR
Jensterle et al[87]	RCT	Slovenia	NIH	Age: 27.6±7.2 BMI: 39.5±6.2	Metf, Lira	12 weeks	BMI,WC, TC,TG,LDL,HDL
Jensterle et al[69]	RCT	Slovenia	Rotterdam	Age: 30.7 ± 7.9 BMI: 38.6 ± 6.0	Metf,Lira, Rofl	12 weeks	Wt,BMI,WC,FI, FBG, HOMA-IR
Jensterle et al[34]	RCT	Slovenia	Rotterdam	Age: 33.1 ± 6.1 BMI: 37.2±4.5	Met+Lira, Lira	12 weeks	BMI, Wt, WC, FBG,FI, HOMA-IR
Jensterle et al[35]	RCT	Slovenia	Rotterdam	Age: 34.4 ± 6.5 BMI: 39.0 ± 4.9	Met+Lira,Lira	12 weeks	Wt,BMI, WC, FI,FBG,
Jensterle Sever et al[71]	RCT	Slovenia	NIH	Age: 31.3±7.1 BMI: 37.1±4.6	Lira,Metf, Lira+Metf	12 weeks	FBG,BMI,WC,FI,TC,TG,HDL,LDL
Jensterle et al[33]	RCT	Slovenia	NIH	Age: 23.5±0.7 BMI: 20.9±0.73	Metf,Rosi	6 months	FBG,FI,BMI, HOMA-IR
Jensterle et al[70]	RCT	Slovenia	NIH	Age: 23.1±3.7 BMI: 29.6 ±6.9	Metf, Rosi	6 months	WC,BMI, FI,FBG,TC, TG, LDL,HDL,HOMA-IR
Kilicdag et al[38]	RCT	Turkey	Rotterdam	Age: 24.13 ±1.42 BMI: 26.17 ± 1.44	Metf, Rosi	3 months	BMI, FI,FBG,TC, TG, HOMA-IR
Kocak et al[39]	RCT	Turkey	Rotterdam	Age: 26.2 ±3.7 BMI: 31.91± 5.38	Metf, Placebo	2 months	BMI, FI,FBG,WHR
Karimzadeh et al[36]	RCT	Iran	Rotterdam	Age: 28.81±3.18 BMI: 29.49 ± 4.7	Metf, placebo	3months	BMI, FI,FBG,TC, TG, HDL,LDL

Table2 continued….

Kazerooni et al[37]	RCT	Iran	Rotterdam	Age: 25.6± 4.32 BMI: 28.52± 1.61	Metf, simva,placebo	12 weeks	BMI, FI,FBG,TC, TG, HDL,LDL
Lam et al[40]	RCT	China	RoTterdam	Age:N/A BMI:N/A	Rosi, placebo	12 months	WC,BMI, FI,FBG,TC, TG, LDL,HDL,HOMA-IR
Li et al[41]	RCT	China	Rotterdam	Age: 25.95± 4.36 BMI: 27.54 ±2.21	Rosi, metformin	6 months	WC,BMI, FI,FBG,TC, TG, WHR, LDL,HDL
Lingaiah et al[42]	RCT	Finland	Rotterdam	Age: 27.6 ±4.0 BMI: 26.5 ±6.0	Metf, placebo	3 months	BMI, FI,FBG, WC ,WHR
Liu et al[43]	RCT	China	Rotterdam	Age: 27.69 ± 3.80 BMI: 28.29 ± 1.86	Metf, Exena	24 weeks	WC,BMI, FI,FBG,TC, TG, WHR, LDL,HDL HOMA-IR
Lord et al[78]	RCT	UK	N/A	Age: 27.76 ±4.89 BMI: 33.74± 6.74	Metf, placebo	3 months	WC,BMI, FI,FBG,TC, TG, WHR, LDL,HDL HOMA-IR
Legro et al[91]	RCT	USA	N/A	Age: 28.0 ±4.0 BMI: 40.0 ±10.1	Metf,Rosi	3 months	WC,BMI, FI,FBG, WHR
Morin-Papunen et al[46]	RCT	Finland	Rotterdam	Age: 28.4 ± 3.9 BMI: 27.1 ±6.3	Metf,placebo	3months	Wt, WC,BMI,WHR
Morteza Taghavi et al[47]	RCT	Iran	Rotterdam	Age:N/A BMI:N/A	Metf, placebo	6 months	BMI
Mohiyiddeen et al[44]	RCT	UK	Rotterdam	Age: 29.0 ±1.0 BMI: 29.7 ±1.0	Metf,Rosig	3 months	WC,BMI, FI,FBG,TC, TG, WHR, LDL,HDL
Moini et al[45]	RCT	Iran	Rotterdam	Age: 27.42 ± 3.31 BMI: 29.01 ± 2.09	Orlistat, placebo	3 months	BMI, FI,FBG,TC, TG, Wt, LDL,HDL
Muneyyirci-Delale et al[48]	RCT	USA	Rotterdam	Age:N/A BMI:NA	Metf, spironolactone	12 weeks	BMI,TC, TG,
Mehrabian et al[68]	RCT	Iran	NIH	Age: 29.18±8.28 BMI: 29.83±4.1	Metf, flut, simva	6 months	WC,CRP,BMI,FBG,TG,HDL
Navali et al[98]	RCT	Iran	N/A	Age:26.43±4.67 BMI:27.71±0.73	Metf, Simva	3 months	BMI, FI,FBG,TC, TG, WHR, LDL,HDL
Nemati et al[49]	RCT	Iran	Rotterdam	Age:N/A BMI: 36.3± 8.4	Metf, NAC	12 weeks	BMI,FBG,FI
Ng et al[79]	RCT	China	N/A	Age:30.5 BMI:N/A	Metf, placebo	3 months	BMI,FBG,FI,TC,TG
Naka et al[84]	RCT	Greece	N/A	Age: 23.3± 4.9 BMI: 28.7± 5.5	Metf,Piogl	6 months	WC,BMI, FI,FBG,TC, TG, WHR, LDL,HDL
Ortega-González et al[85]	RCT	Mexico	N/A	Age: 28.8 ±0.9 BMI: 32.2 ±1.0	Metf, Piogl	6 months	Wt, BMI,WHR
Palomba et al[80]	RCT	Italy	N/A	Age: 24.3 ± 3.1 BMI: 22.2 ±2.0	Metf, Placebo	24 months	BMI,LDL
Paredes Palma et al[95]	RCT	Mixeco	N/A	Age:N/A BMI: N/A	Metf, Sitag	N/A	BMI, HOMA-IR
Penna et al[97]	RCT	Brazil	N/A	Age: 26.69 ±1.46 BMI: 35.8± 2.60	Acarbose, Placebo	6 months	BMI

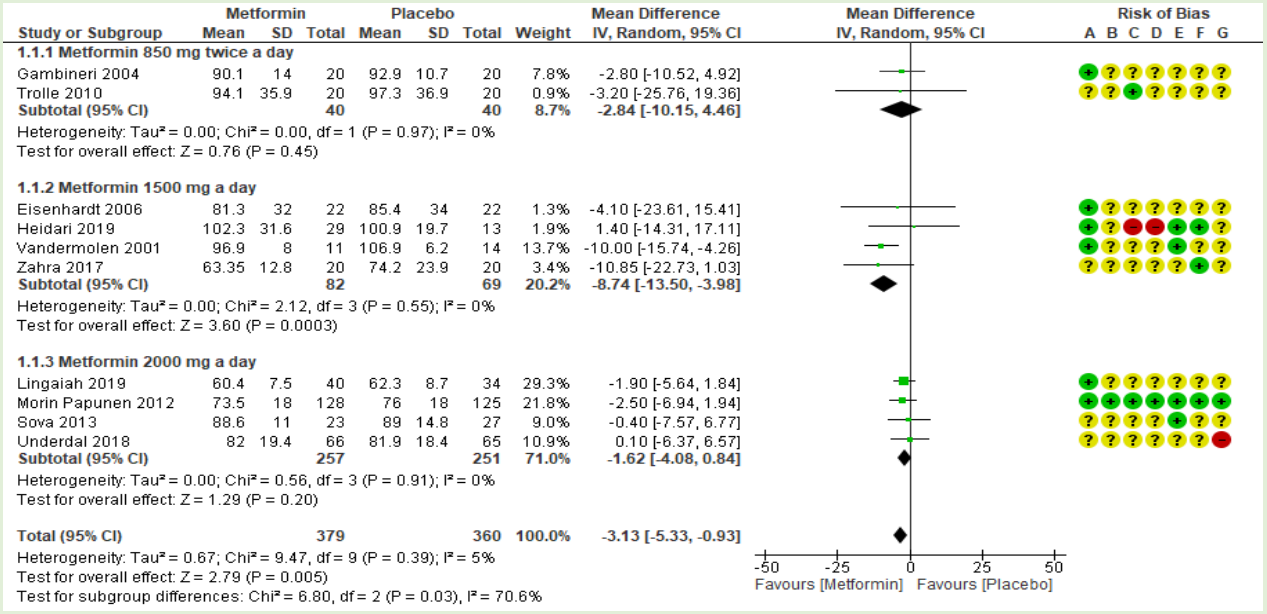
Table2 continued….

Puurunen et al[99]	RCT	Finland	N/A	Age: 40.5 ±5.9 BMI: 30.4 ±8.6	Atorva, placebo	6 months	BMI, WHR,LDL, HDL
Rautio et al[102]	RCT	Finland	N/A	Age: 29.1 ± 1.2 BMI: 33.1 ± 1.7	Rosig, placebo	4 months	BMI, WHR, Wt
Romualdi et al[50]	RCT	Italy	Rotterdam	Age: 24.7 ±4.4 BMI: 22.2 ±2.2	Metf, placebo	6 months	BMI,WHR,LDL,HDL,TC
Rezai et al[51]	RCT	Iran	Rotterdam	Age: 26.3±4 BMI: 26.9 ± 1.8	Metf, Acarbose	3 months	BMI,FBG,HDL,TG,TC.LDL
Steiner et al[92]	RCT	Germany	NIH	Age: 22.9±4.5 BMI: 27.4±6.0	Metf, Rosig	6months	BMI,HOMA-IR, FBG,FI
Sova et al[54]	RCT	Finland	Rotterdam	Age: : 27.7 ±4.0 BMI: 27.5 ±6.2	Metf, placebo	3 months	Wt,WC,WHR,BMI,FBG,FI
Shahebrahimi et al[53]	RCT	Iran	Rotterdam	Age: 27.5 ± 3.68 BMI: 27.71±4.36	Metf, piog	3 months	Wt,BMI,WC, FBG, LDL,HDL,TG
Sohrevardi et al[86]	RCT	Iran	Rotterdam	Age:N/A BMI: 27.5±3.6	Metf,piog, Metf+Piog	3 months	Wt,BMI,WHR,HOMA-IR, FBG, FI
Sathyapalan et al[52]	RCT	UK	Rotterdam	Age: 27.7± 1.4 BMI: 33.20 ±1.4	Atorvas, placebo	12 weeks	Wt,BMI,WC,WHR,HOMA-IR, FBG,FI LDL,TC,TG,HDL
Sönmez et al[72]	RCT	Turkey	NIH	Age: 26.13 ±5.08 BMI: 27 ±2.2	Metf, Acarbose	3 months	BMI,Wt, FBG,FI
Tao et al[55]	RCT	China	Rotterdam	Age: 30 ± 5 BMI: 27.2	Saxag, Metf	24 weeks	Wt, BMI,WC,WHR, LDL,HDL,TG, HOMA-IR
Trolle et al[103]	RCT	Denmark	N/A	Age: 31 BMI:32	Metf, placebo	6 months	Wt,WHR,FBG,FI,HOMA-IR, LDL,HDL
Underdal et al[56]	RCT	Denmark	Rotterdam	Age: 29.5 ±3.9 BMI: 28.7± 6.9	Metf, placebo	NA	Wt,BMI,WC,WHR
Vanky et al[57]	RCT	Norway	Rotterdam	Age: 28.9 ±4.8 BMI: 30.6 ± 7.3	Metf, placebo	36 weeks	BMI, DHEAS
Vandermolen et al[81]	RCT	USA	N/A	Age: 29 6 ±1.2 BMI: 37.6 ± 4.3	Metf, Placebo	7 weeks	Wt,BMI, FBG,FI
Yarali et al[82]	RCT	Turkey	N/A	Age:29.7±5.6 BMI:28.6±4	Metf, placebo	6 weeks	WHR,BMI,FBG,FI
Yilmaz et al[58]	RCT	Turkey	Rotterdam	Age: 24.67+4.60 BMI: 27.12+6.18	Metf, Rosig	24 weeks	FBG,FI,BMI,WHR
Zahra et al[59]	RCT	Pakistan	Rotterdam	Age: 25.8 ± 6.1 BMI: 26.7 ± 6.5	Metf, placebo	3 months	Wt,BMI,FBG,FI,HOMA-IR
Zheng et al[60]	RCT	China	Rotterdam	Age: 27.70 ± 3.41 BMI: 28.27 ± 4.85	Exena, Metf	12 weeks	Wt,BMI,WHR,FBG,FI,HDL,LDL, TG, TC
Ziaee et al[61]	RCT	Iran	Rotterdam	Age: 25.28±4.38 BMI: 26.13 ±3.03	Metf, piog	12 weeks	BMI,HOMA-IR,HDL,LDL,TG,TC

RCT: randomised clinical trial, **N/A**: not available, **BMI**: body mass index, **Wt:** weight, **WHR:** waist hip ratio, **WC**: waist circumference, **FBG**: fasting blood glucose, **FI**: fasting insulin, **HDL**: high density liporotein**, LDL:** Low density lipoprotein, **TG:** triglycerides, **TC**: total cholesterol,**HOMA-IR:** homeostatic model of insulin resistance**,NIH**: national institute for health, **NICHD**:national inistitute of child health and development. **Metf:**metformin, **Saxa:** saxagliptin,**Piog**: pioglitazone, **Rosig**: rosiglitazone,**Atrova:** atorvastatin, **Simva**:simvastatin, **WHO:** world health organisation,**CRP:**C-reactive protein,**Lira**:liraglutide, **USA:** united state of America,**UK**: united kingdom.

Figure 2 : Forest plot of meta-analysis for the effect of various medications on the body weight (kg) compared with placebo

A) Metformin vs Placebo



B) Rosiglitazone vs placebo

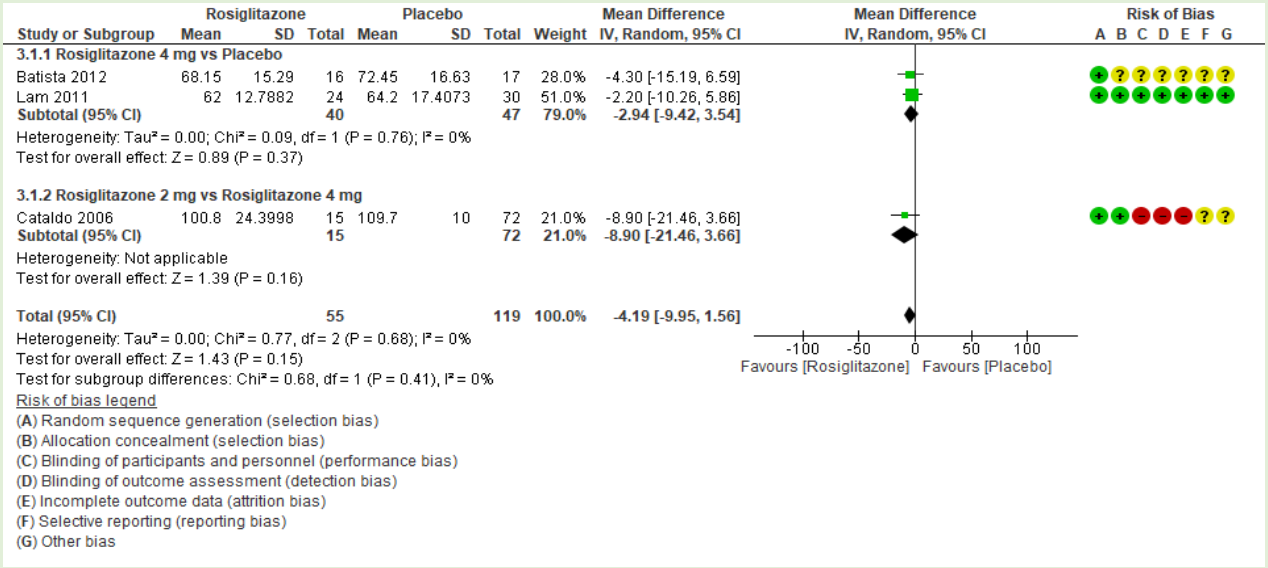


Figure 3: Forest plot of meta-analysis for the effect of various medications on the BMI (kg/m²) compared with placebo

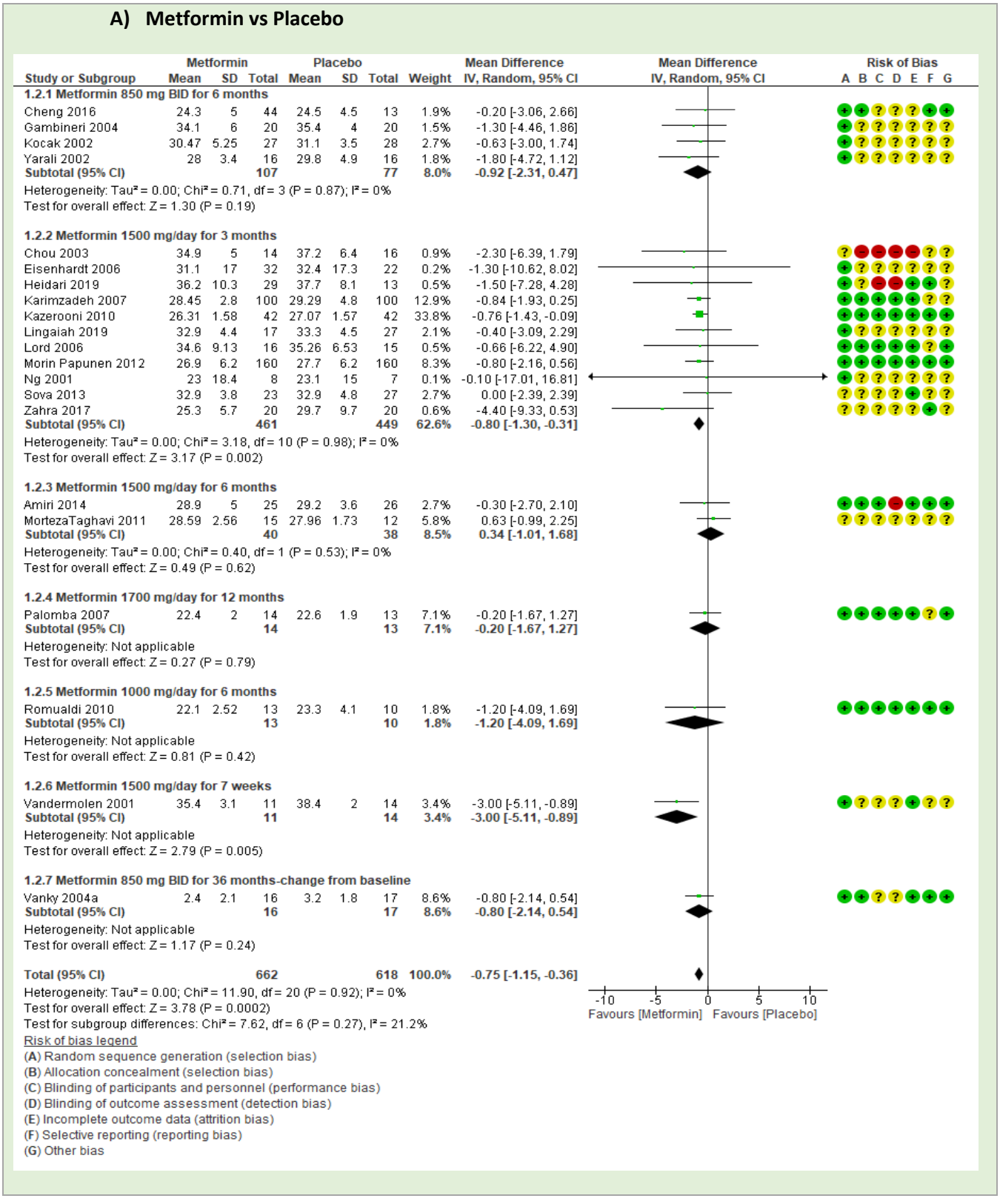


Table 3: summary pooled effect estimates of various medications on body weight, BMI, WC, and WHR in women with PCOS

Intervention	Comparison	No of women in the intervention arm	No of women in the control arm	No of RCTs	Pooled effect estimates	95% CI	I^2 (%)	I^2 (*p* value)	Overall effect (*p*-value*)
Outcome: mean body weight in kilograms (Kg)									
Rosiglitazone vs metformin									
Rosiglitazone 4 mg QD	Metformin 850 mg BID for 3 months	15	15	1	0.35	-2.58-3.28	-	-	-
Rosiglitazone 4 mg QD	Metformin 1500 mg QD for 6 months	67	68	1	3.19	0.65-5.73	-	-	-
Rosiglitazone 4 mg QD	Metformin 2000 mg QD for 4 months	14	33	1	1.83	-6.62-10.28	-	-	-
Overall: Rosiglitazone versus Metformin		96	116	3	1.95	0.03-3.87	3.0	0.36	0.05
Metformin vs pioglitazone									
Metformin 850 mg BID for 6 months	Pioglitazone 45 mg QD	33	31	2	-1.66	-3.19-0.59	0.0	0.56	
Metformin 1500 mg QD for 3 months	Pioglitazone 45 mg QD	50	51	2	-1.45	-6.40-3.51	0.0	0.90	
Overall: Metformin versus Pioglitazone		83	82	4	-1.62	-3.67-0.43	0.0	0.95	0.12
Liraglutide vs metformin									
Liraglutide 1.2 mg QD for 12 weeks	Metformin 1000 mg QD for 12 weeks	42	27	2	2.17	-10.66-14.99	51	0.15	0.74
Liraglutide 1.2 mg QD for 12 weeks	Liraglutide 1.2 mg QD with Metformin 1000 mg QD for 12 weeks	46	47	3	3.30	-2.95-9.54	0.0	0.59	0.30
Metformin vs orlistat									
Metformin 1500 mg QD for 3 months	Orlistat 120 mg tds	60	61	3	-3.28	-7.29-0.74	58	0.09	0.11
Exenatide vs metformin									
Exenatide 10 µg BID	Metformin 1000 mg BID for 12 weeks	109	112	2	0.22	-2.01-2.44	0.0	0.51	0.85
Outcome: mean BMI in kg/m²									
Metformin vs pioglitazone									
Metformin 850 mg BID for 6 months	Pioglitazone	33	31	2	-1.07	-2.02-0.12	0.0	0.80	-

Metformin 1500 mg QD for 3 months	Pioglitazone	86	86	4	-0.69	-1.78-0.41	0.0	0.55	-
Overall: Metformin versus Pioglitazone		119	117	6	-0.91	-1.62-0.19	0.0	0.78	0.01
Rosiglitazone vs metformin									
Rosiglitazone 4 mg QD	Metformin 850 mg BID	154	133	6	0.22	-1.33-1.77	0.0	0.73	-
Rosiglitazone 4 mg QD	Metformin 1000 mg QD	18	17	1	1.38	0.76-2.0	-	-	-
Rosiglitazone 4 mg QD	Metformin 1500 mg QD	67	69	1	0.33	-0.37-1.03	-	-	-
Rosiglitazone 4 mg QD	Metformin 2000 mg QD	23	39	2	-0.32	-2.78-2.14	0.0	0.82	-
Overall: Rosiglitazone versus Metformin		262	358	10	0.80	0.32-1.27	3.0	0.41	0.001
Sitagliptin + metformin vs metformin									
Sitagliptin 100 mg QD with Metformin 850 mg BID	Metformin 850 mg BID	5	5	1	-2.00	-10.87-6.87	-	-	-
Sitagliptin 100 mg QD with Metformin 1000 mg BID	Metformin 1000 mg BID	12	12	1	-4.40	-8.69-0.11	-	-	-
Overall: Sitagliptin plus Metformin versus Metformin		17	17	2	-3.94	-7.81-0.08	0.0	0.63	0.05
Exenatide vs metformin									
Exenatide 10 µg BID	Metformin 1000 mg BID for 12 weeks	31	32	1	-1.15	-3.47-1.17	-	-	-
Exenatide 10 µg BID	Metformin 1000 mg BID for 24 weeks	92	94	2	-0.68	-1.88-0.52	51	0.15	-
Overall: Exenatide versus Metformin		123	126	3	-0.85	-1.61-0.08	6	0.35	0.03
Acarbose vs metformin									
Acarbose 100 mg QD for 3 months	Metformin	30	30	1	-1.30	-2.40-0.20	-	-	-
Acarbose 300 mg QD for 3 months	Metformin	44	42	2	-1.18	-2.63-0.27	0.0	0.56	-
Overall: Acarbose versus Metformin		74	72	3	-1.26	-2.13-0.38	0.0	0.84	0.005
Liraglutide vs metformin									

Liraglutide 1.2 mg QD	Metformin 1000 mg BID for 12 weeks	42	21	2	3.09	-1.11-7.29	4.0	0.31	0.23
Liraglutide 1.2 mg QD for 12 weeks	Liraglutide 1.2 mg QD with Metformin 1000 mg QD for 12 weeks	46	47	3	0.74	-1.27-2.74	0.0	0.53	0.47
Orlistat vs metformin									
Orlistat 120 mg tds	Metformin 1500 mg QD for 3 months	55	55	2	0.04	-4.18-4.26	93	0.0002	0.87
Spironolactone vs metformin									
Spironolactone 50 mg QD	Metformin 1500 mg QD for 12 weeks	12	24	1	0.47	-1.02-1.97	-	-	-
Spironolactone 50 mg QD	Metformin 1000 mg QD for 6 months	85	153	2	0.04	-0.88-0.96	0.0	0.89	-
Overall: Spironolactone versus Metformin		97	177	3	0.16	-0.62-0.94	0.0	0.88	0.69
Saxagliptin vs metformin									
Saxagliptin 5 mg QD	Metformin 2000 mg QD for 24 weeks	21	21	1	1.36	-1.39-4.11	-	-	-
Saxagliptin 5 mg QD	Metformin 2000 mg QD for 16 weeks	11	12	1	0.00	-7.44-7.44	-	-	-
Overall: Saxagliptin versus Metformin		32	33	2	1.20	-1.38-3.78	0.0	0.74	0.36
Metformin vs simvastatin									
Metformin 1000 mg QD	Simvastatin 20 mg QD for 6 months	34	34	1	-0.21	-2.15-1.73	-	-	-
Metformin 1500 mg QD	Simvastatin 20 mg QD for 3 months	100	100	1	-0.08	-1.46-1.30	-	-	-
Overall: Metformin versus Simvastatin		134	134	2	-0.12	-1.25-1.00	0.0	0.91	0.83
Metformin vs NAC									
Metformin 1500 mg QD	NAC 1800 mg QD for 12 weeks	54	54	1	-4.10	-6.63-1.57	-	-	-
Metformin 1500 mg QD	NAC 600 mg tds for 24 weeks	48	46	1	1.25	0.04-2.46	-	-	-

Overall: Metformin versus NAC		102	100	2	-1.30	-6.54-3.93	93	0.0002	0.63
Outcome: mean waist circumference in cm									
Metformin vs pioglitazone									
Metformin 1500 mg QD	Pioglitazone 30 mg QD for 3 months	28	28	1	-0.45	-5.42-4.52	-	-	-
Metformin 850 mg BID	Pioglitazone 30 mg QD for 6 months	15	14	1	0.30	-8.94-9.54	-	-	-
Overall: Metformin versus Pioglitazone		43	42	2	-0.28	-4.66-4.10	0.0	0.98	0.90
Liraglutide vs metformin									
Liraglutide 1.2 mg QD for 12 weeks	Metformin 1000 mg BID for 12 weeks	28	27	2	-3.66	-14.84-7.52	49	0.16	0.52
Liraglutide 1.2 mg QD for 12 weeks	Liraglutide 1.2 mg QD with Metformin 1000 mg QD for 12 weeks	46	47	3	3.34	-2.61-9.29	0.0	0.94	0.27
Rosiglitazone vs metformin									
Rosiglitazone 4 mg QD	Metformin 1500 mg QD	67	67	1	-0.04	-2.43-2.35	-	-	-
Rosiglitazone 4 mg QD	Metformin 850 mg BID	58	56	1	-0.68	-6.07-4.70	-	-	-
Rosiglitazone 4 mg QD	Metformin 2000 mg QD	6	99	1	0.80	-6.30-7.90	-	-	-
Overall: Rosiglitazone versus Metformin		131	222	3	-0.06	-2.15-2.03	0.0	0.98	0.95
Saxagliptin vs metformin									
Saxagliptin 5 mg QD	Metformin 2000 mg QD for 12 weeks	21	21	1	2.80	-0.29-5.89	-	-	-
Saxagliptin 5 mg QD	Metformin 2000 mg QD for 16 weeks	11	12	1	-3.00	-14.98-8.98	-	-	-
Overall: Saxagliptin versus Metformin		32	33	2	2.44	-0.55-5.43	0.0	0.36	0.11
Outcome: mean WHR									

Exenatide vs metformin									
Exenatide 10 µg BID	Metformin 1000 mg BID for 24 weeks	78	80	1	-0.02	-0.04-0.00	-	-	-
Exenatide 10 µg BID	Metformin 1000 mg BID for 12 weeks	31	32	1	-0.01	-0.05-0.03	-	-	-
Overall: Exenatide versus Metformin		109	112	2	-0.02	-0.04-0.00	0.0	0.67	0.56
Spironolactone vs metformin									
Spironolactone 50 mg QD	Metformin 1000 mg QD for 6 months	85	153	2	0.03	0.01-0.05	0.0	0.33	0.96
Metformin vs pioglitazone									
Metformin 1500 mg QD for 3 months	Pioglitazone 30 mg for 3 months	22	23	1	0.02	-0.01-0.05	-	-	-
Metformin 850 mg BID for 6 months	Pioglitazone 30 mg for 3 months	33	31	2	0.01	-0.03-0.05	0.0	0.96	-
Overall: Metformin versus Pioglitazone		55	54	3	0.02	-0.00-0.04	0.0	0.93	0.12
Rosiglitazone vs metformin									
Rosiglitazone 4 mg QD	Metformin 1500 mg QD	67	68	1	0.01	-0.01-0.03	-	-	-
Rosiglitazone 4 mg QD	Metformin 850 mg BID	45	43	1	0.00	-0.03-0.03	-	-	-
Overall: Rosiglitazone versus Metformin		112	111	2	0.01	-0.01-0.02	0.0	0.59	0.38
Saxagliptin vs metformin									
Saxagliptin 5 mg QD	Metformin 2000 mg QD for 16 weeks	11	11	1	-0.06	-0.48-0.36	-	-	-
Saxagliptin 5 mg QD	Metformin 2000 mg QD for 24 weeks	21	21	1	0.03	-0.01-0.07	-	-	-
Overall: Saxagliptin versus Metformin		32	32	2	0.03	-0.01-0.07	0.0	0.67	0.15
Saxagliptin vs saxagliptin+ metformin									
Saxagliptin 5 mg QD	Saxagliptin 5 mg QD with Metformin 2000	21	21	1	0.03	-0.01-0.07	-	-	-

	mg QD for 24 weeks								
Saxagliptin 5 mg QD	Saxagliptin 5 mg QD with Metformin 2000 mg QD for 16 weeks	12	11	1	-0.01	-0.07-0.05	-	-	-
Overall: Saxagliptin versus Saxagliptin with Metformin		33	32	2	0.02	-0.02-0.05	9	0.30	0.34

***RCT**: randomised control trials, **I^2:** heterogeneity, *The overall effect was significant at < 0.05, **CI:** confidence interval, **QD**: once a day, **BID:** Twice a day, **BMI:** body mass index, **WC:** waist circumference, **WHR:** waist to hip ration.*