Impact of pharmacological Interventions on insulin resistance 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 complex endocrine condition affecting women of reproductive age. It is characterised by insulin resistance and is a major risk factor for type 2 diabetes mellitus (T2DM).

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

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

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

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

Data synthesis: In 58 RCTs there were significant reductions in the fasting blood glucose (FBG) with metformin vs placebo (standardised mean difference (SMD): -0.23; 95% CI: -0.40, -0.06, I^2 = 0%, low grade evidence), and acarbose vs metformin (MD: -10.50 mg/dL; 95% CI: -15.76, -5.24, I^2 = 0%, low grade evidence). Significant reductions in fasting insulin (FI) with pioglitazone vs placebo (SMD: -0.55; 95% CI: -1.03, -0.07, I^2= 37%, p = 0.02, very low-grade evidence). A significant reduction in HOMA-IR was seen with exenatide vs metformin (MD: -0.34; 95% CI: -0.65, -0.03, I^2= 0%, low grade evidence). No effect on HOMA-B was observed.

Conclusion: Pharmacological interventions including metformin, acarbose, pioglitazone, and exenatide have significant effects on FBG, FI, HOMA-IR but not on HOMA-B.

Introduction

Polycystic ovary syndrome (PCOS) is a complex disease that affects women of reproductive age with a prevalence of up to 13 % [1,2]. It has been estimated that 50-70% of women with PCOS exhibit metabolic abnormalities, including insulin resistance, abnormal glucose tolerance and an increased risk of type 2 diabetes mellitus (T2DM)[3]. Insulin resistance is considered a result of a defect in insulin action, including insulin-mediated glucose transport and its signalling pathway[4]. However, further evidence suggests a bidirectional link between hyperinsulinemia and androgen production, with high insulin stimulating the ovarian androgen production[5]. Acanthosis nigricans is a velvety or brownish-black skin lesion commonly seen around the neck, and it is a common sign of insulin resistance. The majority of obese and lean women with PCOS have shown to have clinical evidence of acanthosis nigricans[6]. Moreover, hyperinsulinemia increases the risk of T2DM, and over 11% of overweight/obese women with PCOS develop diabetes[7]. The liver has a major role in the regulation of glucose and lipid metabolism and the hepatic insulin effect thought to be the main driver of the insulin resistance. In the postprandial state, the reduction in the glucagon hormone and the increase of insulin level enhances the hepatic glucose consumption, reduces hepatic glucose production and store excess glucose as lipids and glycogen[8]. In disease states such as PCOS, obesity and diabetes the insulin effect of regulating the hepatic metabolism will be affected leading to excess glucose and lipid production commonly referred to as the hepatic insulin resistance[9]. Insulin regulates lipid metabolism by regulating the secretion of the triacylglycerol via the very-low density lipoprotein cholesterol (VLDL-C)[10]. Women with PCOS have abnormal lipoprotein profile characterised by high level of triglycerides, evaluated low-density lipoprotein cholesterol (LDL-C) and reduced high-density lipoprotein cholesterol (HDL-C) which is a risk for cardiovascular disease (CVD)[11]. Hyperinsulinemic glucose clamp is the standard method to determine the insulin sensitivity in which concomitant glucose and insulin are infused then followed by measuring the insulin and glucose levels. Otherwise, the homeostasis

model assessment (HOMA) is used as alternative to determine insulin resistance (IR) and the pancreatic β-cell function[12].

Therapeutic approaches for PCOS are varied in their targets and effects and include both pharmacological and non-pharmacological interventions. Metformin, a widely used insulin sensitising agent, has been associated with a significant benefit in relation to glucose metabolism and metabolic syndrome[13]. At molecular level, metformin activates AMP-activate protein kinase (AMPK) which acts to restore the compromised energy balance by switching on the catabolic pathway, enhancing insulin sensitivity and reducing the hepatic glucose production[14]. A similar effect was also evident with thiazolidinediones (TZDs) such as pioglitazone and rosiglitazone[15]. They alter the gene transcription influencing glucose and lipid metabolism and improve insulin resistance by activating the proliferator-activate receptor gamma (PPAR-gamma)[16]. Statins have place in the management of PCOS because of their abilities to reduce total cholesterol, triglycerides as well as the low-density lipoprotein cholesterol (LDL-C)[17]. Recently, N-acetylcysteine (NAC) a mucolytic agents with insulin-sensitising properties has been used as supporting agent in the management of PCOS particularly in clomiphene resistance situation[18].However, the relative effectiveness of these therapeutic options remains elusive, with a significant gap in the available evidence; therefore, this review aimed to evaluate and analyse the available evidence for the effectiveness of various pharmacological options for the treatment of insulin resistance in PCOS.

Methods

Protocol and registration

The protocol for the review was prospectively registered on PROSPERO (CRD42020178783) and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[19].

This systematic review and meta-analysis is part of a major study that aims to understand the impact of various pharmacological therapies on different health outcomes in women with PCOS, including anthropometric outcomes, insulin resistance, and lipid profile. The first systematic review and meta-analysis study providing findings on the anthropometric outcomes has already been completed and submitted to a peer-reviewed journal. The present study provides findings on the impact of various pharmacological therapies and regimes on insulin resistance in women with PCOS.

Eligibility criteria

Only randomised controlled trials (RCTs) were included in the systematic review. RCTs were defined based on the PICO (population, intervention, comparator, and outcome). Eligibility criteria are presented in Table 1. In brief, only RCTs that recruited women aged ≥ 18 years and diagnosed with PCOS were eligible. RCTs that reported a comparison of at least one pharmacological agent with another pharmacological agent, a combination of pharmacological agents or a placebo were considered eligible to be included regardless of the design (open-labelled, double-blinded, parallel and crossover) and methodology.

Literature search

A systematic search for literature was conducted in six biomedical databases; PubMed, EMBASE, MEDLINE, Scopus, Cochrane Central Library and Web of Science in April 2020 and was updated in March 2021 (L.Ö). Search terms were selected by experts in the field of the subject (TS & MA) in close collaboration with a medical librarian specialised in systematic reviews (L.Ö). The search strategy was systematically developed in PubMed with the support of the MeSH (L.Ö). All search terms were searched in a combination of title, abstract and Medical Subject Headings (MeSH) to retrieve the best possible results. A filter for the English language was applied. All publication types and publication years were included in the search. The search strategy developed in PubMed were later repeated in

all selected electronic databases and open access (Open Grey, ClinicalTrial.gov and Open thesis repository, EU clinical trial registry). The full search strategy, including results, notes, and search technical specifications for all information sourced, is available in the supplementary material. All records found in the literature search was uploaded to Covidence (www.covidence.org) [20] for automatic de-duplication and blinded screening. Full-text review and data extraction was subsequently performed. Selected references were then uploaded to the software EndNote for reference management[21]. The reference list of the final selected studies, as well as systematic reviews and meta-analyses located in the literature search, were also screened for additional undetected studies (MA & NS). Cabell's Predatory Report[22] was informed to verify the academic status of papers from open access journals included in the result.

Study selection

Titles and abstracts of the retrieved citations were screened and assessed for eligibility against the inclusion/exclusion criteria by two independent reviewers (M.A and N.S). The full-text assessment was undertaken and evaluated with the agreement of both reviewers. Any disagreements between reviewers about the inclusion were resolved by consensus, discussion or consultation with a third reviewer (T.S). Non-pharmacological interventions and observational studies were excluded. Where duplicate publications for the same study on the same patients utilising the same intervention and measuring the same outcomes were identified, the most recent version of the study was selected—the study selection process presented in Figure 1 following the PRISMA guidelines[19].

Data extraction

From studies that were deemed eligible, two independent reviewers (M.A and N.S) extracted relevant information. The information extracted covered the country of the trial, year of publications, design of the intervention, type of the RCT and comparators, number of participants, duration of the trials,

baseline characteristics of the participants, and outcomes reported. The summary of these findings is presented in Table 2. Out of all reported outcomes, in this review, we only analysed fasting blood glucose (FBG), fasting insulin (FI), HOMA-IR, and HOMA-B.

Risk of bias assessment in the included studies

The Cochrane collaboration's tool for assessing the risk of bias (RoB) was used as recommended by Higgins et al[23]. 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[24] 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 in (Figure 2 supplementary materials).

GRADE scoring

The strength of the evidence for each desired outcome: fasting blood glucose (FBG), fasting insulin (FI), homeostatic model assessment of insulin resistance (HOMA-IR), homeostatic model assessment of beta-cell (HOMA-B) was assessed using recommendations from the Grading of Recommendations, Assessments, Development and Evaluation (GRADE) system[25]. GRADEpro GDT software was used to grade the quality of each outcome and to produce "Summary of findings table" Table 1 supplementary materials**.** For each outcome, four points were assigned to begin with, and then we assessed factors reducing the quality of the evidence. Points were reduced in the presence of the following: the overall RoB for each comparison, inconsistency (significant statistical heterogeneity across the trial), indirectness of evidence (significant differences across the population, intervention, and outcomes),

166 imprecision (sample size, the width, and the statistical significance of the confidence intervals). Based
167 on these factors, we reported the overall GRADE scores for the quality of the outcome of each
168 comparison; high (at least 4 points), moderate (3 points), low (2 points) and very low (1 point or less)
169 quality.

170

171 **Data analysis and evidence synthesis**

172 The pooled effect estimate (mean difference (MD) or standardised mean difference (SMD)) and its
173 95% confidence intervals (95% CIs) on the difference between the intervention and comparison group
174 was quantified using the random-effects model and inverse variance[24]. The meta-analysis was
175 performed if there were at least two effect estimates assuming that data for reported continuous
176 outcome variable are normally distributed. Extremely skewed data or data reported as range were
177 excluded from the meta-analysis. Mean, and standard deviation (SD) values for both post-intervention
178 results and changes from baseline scores were combined for the meta-analysis. For data presented as
179 standard error (SE), CIs, *p*-values and *t* values, the RevMan calculator was used when necessary to
180 convert them to means and standard deviations (SD). Mean difference (MD) was used when the same
181 continuous data presented using the same scales across the trials. Otherwise SMD was used to pool
182 estimates from trials used different scales to measure the outcomes. For trials with more than one
183 intervention arm on the same outcome, data from all arms were combined using the method
184 recommended in the *Cochrane Handbook's* [24]. Post-intervention scores and data from crossover trials
185 were used from the last point the trials were reported. For missing data, the authors were contacted,
186 asking them to provide the missing information.

187 Meta-analysis was performed using the Review Manager software (RevMan 5.4, The Cochrane
188 collaboration).

Assessment of heterogeneity

Heterogeneity for outcomes across the trials was assessed using the I-squared (I^2) test statistics. Heterogeneity was described as either not significant (I^2 0 - 40 %), moderate (I^2 30 - 60 %), substantial (I^2 50 -90 %) and considerable (I^2 75 -100 %) heterogeneity[24]. For substantial heterogeneity, the source was investigated by removing the study that represented the largest weight from the analysis, and the I^2 was re-evaluated. If heterogeneity was still not resolved, subgroup analyses were performed.

Subgroup analysis

Subgroup analysis was performed at different levels according to the nature, dosages, frequencies of administration (one/day (QD), twice/ day (BID) and trice/day (TDS)), and duration (weeks /months) of the pharmacological intervention.

Sensitivity analysis

The impact of each individual study on heterogeneity and the strength of the summary was assessed using sensitivity analysis. Small sample-sized trials and those with overall high RoB were removed from the analysis while observing their effects on the cumulative results. Thus, no significant effect was found, and hence no trial was removed from the meta-analysis.

Results

In total, 6,326 articles were identified from the database search, of which 3,186 were screened for eligibility based on titles and abstracts after removing duplicates. 814 full-text articles were retrieved for detailed assessment for eligibility, of which 58 RCTs were found eligible and included in the study (Figure1).

Scope of the included RCTs

The 58 RCTs were published until 2020, of which 35 RCTs (60.3%) [26-58] diagnosed PCOS based on the Rotterdam criteria 2003[59]; nine (15.5%) RCTs [60-68] used the National Institute of Health 1990 (NIH, NICHD) criteria[69] while no diagnostic criteria were given for the rest of the RCTs (Table 2).

Interventions and comparisons details

Sixteen (27.5%) RCTs assessed the effect of metformin compared with placebo [26,32,36,41,44,53,55,64,66,70-77]. Six (10%) RCTs evaluated metformin compared with pioglitazone[51,52,58,70,78,79]. Four (6.8%) RCTs assessed pioglitazone compared with placebo [27,60,80,81]. Eight (13.8%) RCTs examined rosiglitazone compared with metformin [28,40,43,46,56,62,68,82]. Three (5.2%) RCTs assessed liraglutide compared with liraglutide added to metformin[38,39,63].Two (3.4%) RCTs examined sitagliptin compared with placebo[30,35]. Two (3.4%) RCTs assessed exenatide compared with metformin [45,57]. Two (3.4%) RCTs compared orlistat with placebo[31,47]. Three (5.2%) RCTs examined acarbose with metformin [49,61,67]. Two (3.4%) RCTs compared saxagliptin with metformin [33,54]. Two (3.4%) RCTs compared simvastatin with metformin[65,83]. Two (3.4%) RCTs assessed metformin with N-Acetylcysteine (NAC)[37,48]. Two (3.4%) RCTs examined atorvastatin compared with placebo[50,84].Two (3.4%) RCTs assessed sitagliptin added to metformin compared with metformin alone[34,85]. Two (3.4%) RCTs examined acarbose compared with placebo[86,87].

Characteristics of the outcomes measured.

All RCTs were assessed outcomes at baseline and post-intervention**.** Forty-six (79.3%) RCTs reported changes in FBG[26,27,30-33,35-39,41,43-45,47-55,57,60,65,67,68,71-73,77-80,82-84]. Forty-eight (82.8%) RCTs reported FI [26-28,30-32,35-40,42-48,50-53,55-57,60-64,66-68,70,72-76,78-81,84].Thirty-seven (63.8%) RCTs reported the homeostatic model of insulin resistance (HOMA-IR)[27,29-36,38-40,44,45,47,52,54,55,57,58,62,63,68,70-72,74,79,80,82,85-89].Two(3.4%)RCTs reported the homeostatic model of β-cells (HOMA-B)[29,72].Table 2 presents more descriptive information on the included 58 RCTs.

Risk of bias assessment

The risk of bias (RoB) item for the included RCTs, and the overall RoB are presented in Figure 1,2 in the supplementary material**.** One RCT was judged to have a high risk of selection bias due to an inappropriate method used to generate sequences[60]. Twenty-one RCTs were judged to have a high risk of performance bias due to lack of blinding the participants[31,32,34-36,38,39,43,45,46,52,54,57,58,63,70,78,79,88]. Nineteen RCTs were judged to have a high risk of detection bias due to lack of blinding outcome assessors[26,34-36,38,39,43,45,46,52,54,57,63,70,78,79,88]. Two RCTs were judged to have a high risk of selective reporting [40,83]. Low RoB was judged for the majority of domains among the included RCTs. However, an unclear RoB was also judged due to a lack of sufficient reporting.

Assessment of publication bias

For the effect of metformin versus placebo on fasting blood glucose and fasting insulin, we have assessed for publication bias as there was more than 10 RCTs. The funnel plot of RevMan showed no significant asymmetry which reflect the low chance of publication bias (Figure 6-A,B).

Effects of interventions on the insulin resistance outcomes

The outcome of the meta-analyses on the effect of pharmaceutical medications compared with placebo presented in Figures 1-5 and compared with other medications was shown in Table 3.

Outcome: Fasting Blood Glucose

Metformin versus placebo

In one RCT, metformin 850 mg BID for six months was associated with insignificant reduction in the mean FBG (SMD: -0.66; 95% CI: -1.57, 0.24). In eight RCTs and compared with placebo, metformin 1500 mg QD for three months was associated with a significant reduction in the mean FBG (SMD: -0.20; 95% CI: -0.42, 0.01). In one RCT, metformin 1500 mg QD for six months was associated with an

insignificant reduction in the mean FBG (SMD: -0.41; 95% CI: -0.96, 0.15). In one RCT, metformin 2000 mg QD was associated with an insignificant reduction in the mean FBG (SMD: -0.16; 95% CI: -0.51, 0.18). Overall, regardless of the administered dosage and duration, metformin was associated with a significant reduction in the mean FBG (SMD: -0.23; 95% CI: -0.40, -0.06, I^2 = 0%) in women who received metformin compared with women received placebo (Figure 2-A) (low grade of evidence).

Metformin versus Acarbose

In one RCT, Acarbose 100 mg QD for three months has significantly reduced the mean FBG (MD: -10.30 mg/dL; 95% CI: -15.61, -4.99) compared with metformin. In one RCT Acarbose 300 mg QD for three months has insignificant effect on the mean FBG (MD: -20.80 mg/dL; 95% CI: -58.84, 17.24). However, in the two RCTs, regardless of the dosage, frequency, and duration, acarbose showed a significant reduction in the mean FBG (MD: -10.50 mg/dL; 95% CI: -15.76, -5.24, I^2 = 0%) (Table 3) (low grade evidence).

Metformin versus Simvastatin

A significant reduction in the FBG level was also evident when metformin at various dosage was compared with Simvastatin 20 mg QD. In one RCT, metformin 1500 mg QD for three months has significantly reduced the mean FBG (MD: -2.79; 95% CI: -6.20, 0.26). In one RCT, metformin 1000 mg QD for six months has significantly reduced the mean FBG by 7.27 mg/dL (95% CI: -13.05, -1.49). Overall, regardless of the dosage and duration, metformin has significantly reduced the mean FBG compared to simvastatin (MD: -4.43 mg/dL; 95% CI: -8.41, -0.44, I^2 = 38%) (Table 3) (very low-grade of evidence).

Metformin versus N-Acetylcysteine (NAC)

There was a significant increase in the mean FBG when Metformin was compared with NAC. In one RCT, when metformin 1500 mg QD was compared with NAC 1800 mg QD for 12 weeks has significantly increased the mean FBG level (MD: 5.10 mg/dL; 95% CI: -0.96, 11.16). One RCT, metformin 1500 mg QD, was compared with NAC 600 mg TDS for 24 weeks showed a significant increase in the mean FBG level (MD: 3.41 mg/dL; 95% CI: 0.54, 6.28). Overall, metformin has significantly increased the mean FBG level (MD: 3.72 mg/dL; 95% CI: 1.13, 6.31, I^2 = 0%) compared with NAC (Table 3) (very low-grade of evidence).

The meta-analysis had also shown that there were no significant differences in the mean FBG when pioglitazone, sitagliptin, orlistat and atorvastatin were compared with placebo (Figure 4-B, C, D, E). Similarly, no significant effect in the mean FBG when metformin alone or in combination with liraglutide was compared with other medications (rosiglitazone, pioglitazone, liraglutide, exenatide and saxagliptin) (Table 3).

Outcome: Fasting Insulin

Pioglitazone versus placebo

In three RCTs, pioglitazone 30 mg QD has significantly reduced the mean FI (SMD: -0.60; 95% CI: -1.26,0.06) compared with placebo. In one RCT, pioglitazone 45 mg QD insignificantly reduced the mean FI (SMD: -0.44; 95% CI: -1.28,0.39). Overall, pioglitazone on various dosages has significantly reduced the mean FI (SMD: -0.55; 95% CI: -1.03, -0.07, I^2= 37%) (Figure 3-A) (very low-grade of evidence).

Metformin versus NAC

In one RCT, NAC 1800 mg QD has shown no significant effect in the mean FI when compared with Metformin 1500 mg QD for 12 weeks (MD: -1.20 pmol/L; 95% CI: -10.72, 8.32). One RCT compared NAC 600 mg QD with Metformin 1500 mg QD for 24 weeks showed a significant increase in the mean FI (MD: 1.51 pmol/L; 95% CI: 0.53, 2.49). Overall, metformin compared with NAC has significantly increased the mean FI (MD: 1.48 pmol/L; 95% CI: 0.51, 2.46, I^2 = 0%) (Table 3) (low grade evidence).

The meta-analysis also showed no significant effect in the mean FI when metformin, sitagliptin, orlistat and atorvastatin were compared with placebo (Figure 3-B,C, D, E). Similarly, no significant effect was observed in the mean FI when metformin was used alone or in combination with liraglutide compared with other medications (pioglitazone, rosiglitazone, liraglutide, exenatide and acarbose) (Table 3).

Outcome: HOMA-IR

Exenatide versus Metformin

In one RCT, exenatide 10 µg BID compared with Metformin 1000 mg BID for 12 weeks showed insignificantly but the lower mean level of HOMA-IR (MD: -0.23; 95% CI: -0.83, 0.37). However, in one RCT comparing exenatide 10 µg BID with metformin 1000 mg BID for 24 weeks, a significant reduction in the mean HOMA-IR was observed (MD: -0.38; 95% CI: -0.74, -0.02). Overall, exenatide has significantly reduced the mean HOMA-IR (MD: -0.34; 95% CI: -0.65, -0.03, I^2= 0%) compared with metformin (Table 3) (low grade of evidence).

The meta-analysis showed no significant effect in the mean HOMA-IR when metformin, pioglitazone, sitagliptin, orlistat and acarbose were compared with placebo (Figure 4-A, B, C, D, E). Similarly, no significant effect in the mean HOMA-IR when metformin alone or in combination with liraglutide or

sitagliptin compared with other medications (pioglitazone, rosiglitazone, liraglutide, orlistat, sitagliptin and saxagliptin) (Table 3).

Outcome: HOMA-B

Metformin versus placebo

One RCT compared metformin 850 mg BID for six months with placebo showed an insignificant effect on the mean HOMA-B (MD: 30.70; 95% CI: -66.18, 127.58). In one RCT, metformin 1500 mg for three months also showed an insignificant effect on the mean HOMA-B (MD: 39.73; 95% CI: -79.61, 159.07) compared with placebo. Overall, metformin was associated with an increased but insignificant effect in the mean HOMA-B level (MD: 34.29; 95% CI: -40.93, 109.50, I^2= 0%) compared with placebo (Figure 5)(low-grade evidence).

Discussion

This systematic review summed up the current evidence supporting the effect of various pharmacological interventions on insulin resistance. To our knowledge, this is the first systematic review to report on the effect of various pharmacological interventions on insulin resistance in women with PCOS. When metformin was administered at various doses compared with placebo, there was a significant reduction in the mean FBG and FI. This was also evident when metformin was compared with simvastatin and acarbose. The result also showed a significant increase in the mean FBG and FI when metformin was compared with NAC. On the other hand, exenatide significantly reduced HOMA-IR compared with metformin. The strength of evidence for these data ranged from very low to moderate, and therefore, care should be applied when interpreting these findings.

Metformin is a widely used drug that exerts its action by targeting various organs via multiple molecular mechanisms. Metformin acts on the liver to reduce hepatic glucose production by opposing the glucagon action and activating the activated protein kinase (AMPK), which also enhances insulin sensitivity by modulating lipid metabolism[14,90]. In the current systematic review, there were significant reductions in FBG and FI with metformin at various doses and when administered for both long and short duration compared with placebo. These results are in accord with what has been reported in a non-randomised cohort study of 108 insulin resistant and obese women with PCOS who received Metformin 1500 mg QD for six months[91]. However, in a meta-analysis of RCTs evaluating the effects of metformin on the metabolic, hormonal, and clinical outcomes in women with PCOS, no effects on FBG, FI and HOMA-IR were found[92]. However, there was a significantly high level of heterogeneity amongst those studies. Furthermore, a recent systematic review and meta-analysis of RCTs evaluating the effect of metformin in overweight women with PCOS reported that although there was a significant effect on the anthropometric indices, no effect was seen on the parameters of insulin resistance[93]. Therefore, considering these previous findings, it appears that metformin alone has a variable effect on the parameters of insulin resistance in women with PCOS. In the present review, we reported a significant reduction in FI with pioglitazone compared with placebo and metformin. However, data from a meta-analysis assessed the effect of metformin versus thiazolidinediones in women with PCOS showed no changes in insulin sensitivity [94]. We also found a significant increase in FBG when metformin was compared with NAC. However, a recent meta-analysis of RCTs that compared the efficacy of metformin versus NAC showed no significant changes in the parameters of insulin resistance[95]. This review did not establish any significant effect on HOMA-B with various pharmacological interventions used in the management of PCOS.

To our knowledge, this is the most comprehensive and up-to-date systematic review and meta-analysis on the impact of pharmacological interventions on insulin resistance in women with PCOS.

The review followed a comprehensive and systematic search of the relevant databases and grey sources that only included RCTs and randomised crossover trials. Observational studies and non-randomised clinical trials were excluded to reduce the risk of bias.

We applied a language filter, and only trials reported in the English language were included, and therefore several clinical trials in foreign languages may not have been retrieved. Assessing such trials requires sophisticated translation, which is challenging that could also affect the methodology of this review. The majority of the trials were of smaller sample size, and the statistical power used to calculate sample size and to detect the meaningful differences between the groups were not fully reported. All the trials were of short duration and reported baseline and immediate post-intervention data. Therefore, the long-term effect of the different pharmacological interventions in women with PCOS is not clear.

This systematic review acknowledges the poor quality of the included clinical trials, which is also reflected in the summary of evidence of the GRADE score. Due to the nature of the clinical trials, there was a significantly high level of heterogeneity as well as performance bias among the included studies. Although a simple logistical approach could have been taken by blinding the outcome assessors, there was a significantly high level of detection bias. Reporting and selection bias were inadequately reported amongst the trials, so the judgment of unclear risk of bias was made in nearly 75% of the included trials. Disproportionately, only 20% of the trials reported information of the method used to blind the participants and the outcome assessor and 49% were judged to have an unclear risk of attrition bias. Around 25% of the included trials had a high risk of performance and detection bias. For the insulin resistance outcomes, the grade of evidence was rated from very low to moderate due to the unclear or high risk of performance bias. Even though in 16 RCTs (27.58%) no clear PCOS diagnostic criteria was laid out, this was due to incomplete reporting which was considered during assessing the overall risk of bias as one of the main limitations of the included RCTs.

Based on our findings, it is clear that there is a lack of robust clinical trials assessing the different pharmacological interventions in the management of PCOS. Furthermore, trials examining the clinical effectiveness of these interventions are of low or very low quality and therefore, the available data are not suitable to draw definite conclusions and recommendations for clinical practice. Furthermore, these trials are of small sample sizes that clearly undermined the statistical power used to calculate the meaningful effects of the outcomes. Therefore, further clinical trials with robust design are needed to enable better-informed decisions, recommendations and draw guidelines for the various pharmacological interventions used in women with PCOS.

In conclusion, data pooled in this meta-analysis showed that pharmacological interventions including metformin, pioglitazone, acarbose and exenatide reduce FBG, FI and HOMA-IR. However, some other therapeutic agents have no effect on the parameters of insulin resistance. Even though data presented in this systematic review and meta-analysis are drawn mainly from clinical trials, caution should be taken when interpreting these results. The majority of the interventions showed modest effects with wide confidence intervals that indicate significant uncertainties. Therefore, further clinical trials with rigorous methodology and sufficiently power are needed for each of these pharmacological interventions.

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410 **Ethical approval**

411 Not needed as no patients involved.

412 **Conflict of interest**

413 None to declare.

414 **Availability of data**

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

417 **Authors contributions**

418 M.A; designed the review, completed the databases searches, assessed the quality, extracted,
419 collected, and analysed the data, written, revised, and edited the final manuscript. N.S; assessed the
420 quality, extracted, and collected the data, and revised and edited the final manuscript. H.D; revised
421 and edited the final manuscript. A.S; revised and edited the final manuscript; L.Ö; developed and
422 performed the systematic search, assessed for predatory journals and revised and edited the final
423 manuscript. R.H.A; participated in the critical discussion and revised and edited the final manuscript.
424 S.A; participated in the critical discussion and revised the final draft of the manuscript. T.S; acted as a
425 mediator for the assessment of the quality of the evidence, supervised the study, participated in the
426 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).

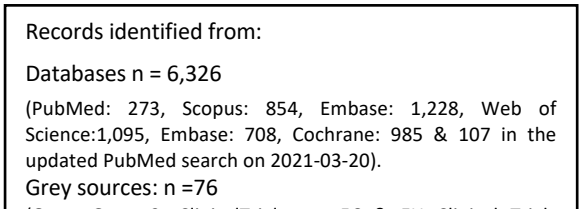
2. Patients population: adult females aged 18 and over with a diagnosis of PCOS based on a robust diagnostic criterion.
3. Comparators: reported pharmacological interventions compared to placebo or other pharmacological agents.
4. Outcomes: reported outcomes such as fasting blood glucose, fasting insulin, HOMA-IR, and HOMA-B.

Exclusion criteria

1) Study design: case studies and animal studies.
2) Patients population: adolescents females, postmenopausal women, and women without PCOS.
3) Comparators: non-pharmacological interventions, pharmacological interventions versus dietary interventions, pharmacological interventions versus physical activities or surgery.

PCOS: polycystic ovary syndrome, **HOMA-IR**: homeostatic model assessment in the insulin resistance, **HOMA-B**: homeostatic Model assessment of beta-cell.

Figure 1: PRISMA flow diagram



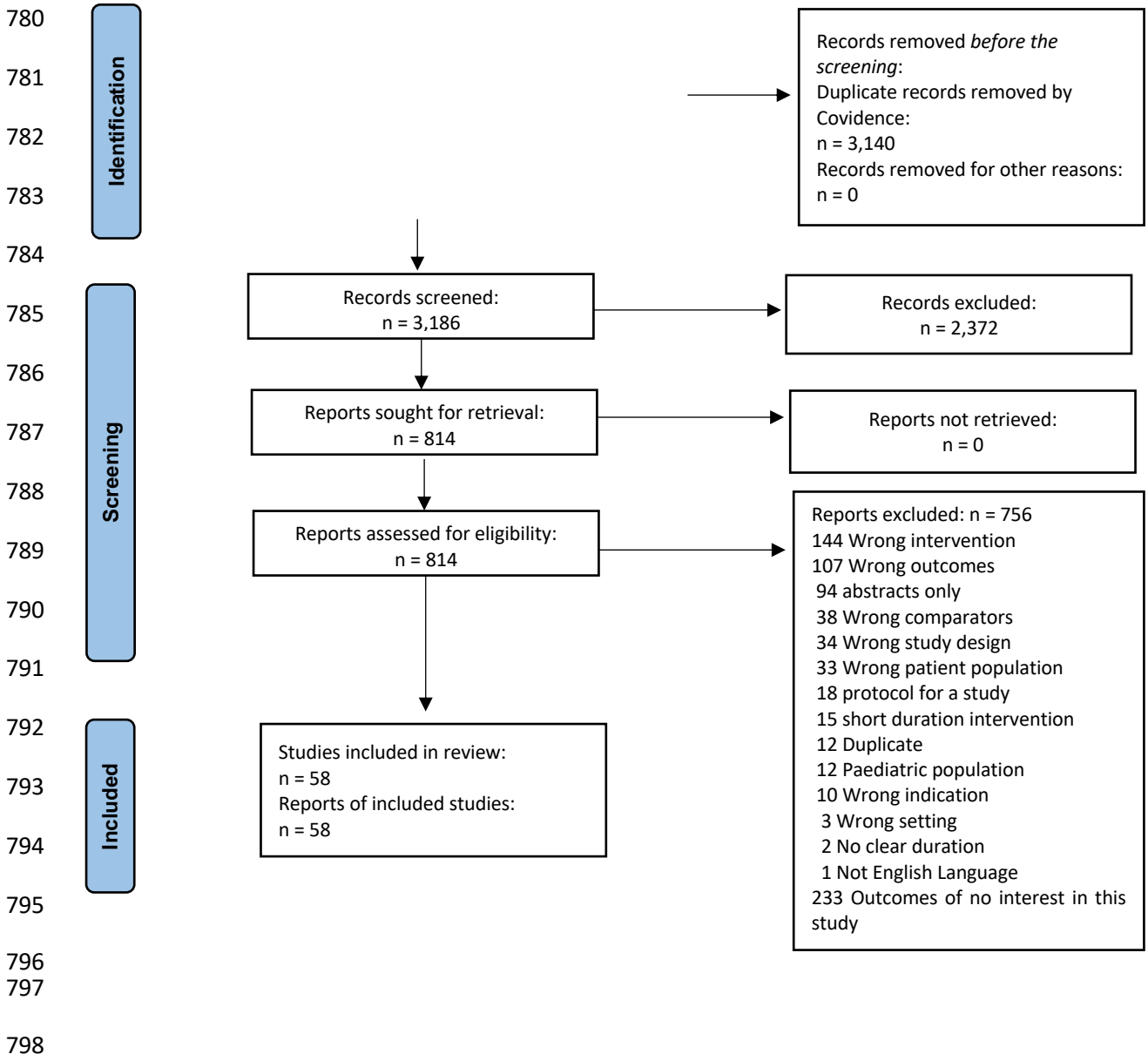


Table 2: Characteristics of the studies included in the systematic review and meta-analysis

Author	Study design	Country	POCS diagnostic Criteria	Participants characteristics (PCOS)	Interventions	Durations	Outcomes
Amiri et al[26]	RCT	Iran	Rotterdam	Age:25.6±4.02 BMI: 28.9±5	Metf, Flu, Metf+ Flu, Placebo	6 months	FBG
Aroda et al[60]	RCT	USA	NIH	Age: 27.87 ±0.87 BMI: 36.29 ±1.34	Piog, Placebo	6 months	FBG,FI
Brettenthaler et al[27]	RCT	Switzerland	Rotterdam	Age: 30.2± 1.4 BMI: 29.4± 1.7	Piog, placebo	3 months	FBG, FI, HOMA-IR
Cetinkalp et al[28]	RCT	Turkey	Rotterdam	Age: N/A BMA:25.82±6.12	Met, Rosigl , ECA	4 months	FBG,FI, HOMA-IR
Cheng et al[29]	RCT	Australia	Rotterdam	Age: 26 ± 4 BMI:24.2±5.3	Metf, placebo	6 months	HOMA-IR, HOMA-B
Cho et al[70]	RCT	UK	Rotterdam	Age: 26·4 ± 1·5 BMI: 36·0 ± 1·2	Metf, Orlistat, Piog	12 weeks	HOMA-IR
Ciotta et al[86]	RCT	Italy	N/A	Age:20.5±0.6 BMI:22.7±0.34	Acarbose, Placebo	3 months	HOMA-IR
Devin et al[30]	RCT-cross over	USA	Rotterdam	Age:N/A BMI:N/A	Sitag, placebo	4 weeks	FBG
Diamanti-Kandarakis et al[31]	RCT	Greece	Rotterdam	Age: 27·52 ± 5·77 BMI: 35·43 ± 5·3	Orli, placebo	6 months	HOMA-IR
Eisenhardt et al[32]	RCT	Germany	Rotterdam	Age: 27.0 BMI: 28.9	Metf,Placebo	12 weeks	FBG.FI,HOMA-IR
Elkind-Hirsch et al[33]	RCT	USA	Rotterdam	Age: 28.2 ± 1.1 BMI: 39.9 ±1.5	Exen, Metf,Exen+Metf	24 weeks	FBG
Ferjan et al[35]	RCT	Slovenia	Rotterdam	Age: 34.3 ± 6.8 BMI: 36.3 ±5.2	Metf, Metf+Sitag	12 weeks	HOMA-IR
Ferjan et al[34]	RCT	Slovenia	Rotterdam	Age: 35.0 ± 7.2 BMI: 36.9 ± 5.5	Sitag, Placebo	12 weeks	HOMA-IR, HOMA-B, FBG
Gambineri et al[71]	RCT	Italy	N/A	Age: 27·1 ± 3·6 BMI: 37·6 ± 4·1	Plac, metfo, flut, metf + flut	6 months	FBG,FI,HOMA-IR
Glintborg et al[80]	RCT	USA	N/A	Age: 32 BMI: N/A	Piog, Placebo	16 weeks	FI, HOMA-IR
Glintborg et al[81]	RCT	USA	N/A	Age: 32 BMI: 32.2	Piog,Plcebo	16 weeks	FI
Hanjalic-Beck et al[61]	RCT	Germany	NIH	Age:N/A BMI:N/A	Metf, Acarbose	12 weeks	FBG,FI
Heidari et al[36]	RCT	USA	Rotterdam	Age: 32.47.5 BMI: 37.19.1	Metf, placebo	3 months	FBG, FI
Javanmanesh et al[37]	RCT	Iran	Rotterdam	Age: 29.75 ± 4.90 BMI: 29.05 ± 2.80	Metf, NAC	24 weeks	FBG,FI, HOMA-IR

Jayagopal et al[88]	RCT	UK	N/A	Age: 27 ±0.9 BMI: 36.7 ±3.3	Orlistat, Metf	3 months	FBG, FI

Table 2 continued…….

Jensterle et al[62]	RCT	Slovenia	NIH	Age: 27.6±7.2 BMI: 39.5±6.2	Metf, Rosi	6 months	FBG, FI
Jensterle et al[40]	RCT	Slovenia	Rotterdam	Age: 30.7 ± 7.9 BMI: 38.6 ± 6.0	Metfo, Rosi	6 months	FI, FBG, HOMA-IR
Jensterle et al[38]	RCT	Slovenia	Rotterdam	Age: 33.1 ± 6.1 BMI: 37.2±4.5	Met+Lira, Lira	12 weeks	FBG,FI, HOMA-IR
Jensterle et al[39]	RCT	Slovenia	Rotterdam	Age: 34.4 ± 6.5 BMI: 39.0 ± 4.9	Met+Lira,Lira	12 weeks	FI,FBG
Jensterle Sever et al[63]	RCT	Slovenia	NIH	Age: 31.3±7.1 BMI: 37.1±4.6	Lira,Metf, Lira+Metf	12 weeks	FBG,FI
Kazerooni et al[41]	RCT	Iran	Rotterdam	Age: 25.6± 4.32 BMI: 28.52± 1.61	Metf, simva,placebo	12 weeks	FI,FBG
Kocak et al[42]	RCT	Turkey	Rotterdam	Age: 26.2 ±3.7 BMI: 31.91± 5.38	Metf, Placebo	2 months	FI,FBG
Ladson[64]	RCT	USA	NIH	Age: 29±4.5 BMI: 38±7.8	Metfo, placebo	6 months	FBG, FI
Li et al[43]	RCT	China	Rotterdam	Age: 25.95± 4.36 BMI: 27.54 ±2.21	Rosi, metformin	6 months	FI,FBG
Lingaiah et al[44]	RCT	Finland	Rotterdam	Age: 27.6 ±4.0 BMI: 26.5 ±6.0	Metf, placebo	3 months	FI,FBG
Liu et al[45]	RCT	China	Rotterdam	Age: 27.69 ± 3.80 BMI: 28.29 ± 1.86	Metf, Exena	24 weeks	FI,FBG, HOMA-IR
Lord et al[72]	RCT	UK	N/A	Age: 27.76 ±4.89 BMI: 33.74± 6.74	Metf, placebo	3 months	FI,FBG, HOMA-IR
Mehrabian et al[65]	RCT	Iran	NIH	Age: 29.18±8.28 BMI: 29.83±4.1	Metf, flut, simva	6 months	FBG
Moghetti et al[66]	RCT	Italy	NICHD	Age: 23.9 6 1.2 BMI: 27.1 6 1.5	Metformin, placebo	6 months	FBG, FI
Mohiyiddeen et al[46]	RCT	UK	Rotterdam	Age: 29.0 ±1.0 BMI: 29.7 ±1.0	Metf,Rosig	3 months	FI,FBG
Moini et al[47]	RCT	Iran	Rotterdam	Age: 27.42 ± 3.31 BMI: 29.01 ± 2.09	Orlistat, placebo	3 months	FI,FBG
Naka et al[78]	RCT	Greece	N/A	Age: 23.3± 4.9 BMI: 28.7± 5.5	Metf,Piogl	6 months	FI,FBG
Navali et al[83]	RCT	Iran	N/A	Age:26.43±4.67 BMI:27.71±0.73	Metf, Simva	3 months	FI,FBG
Nemati et al[48]	RCT	Iran	Rotterdam	Age:N/A BMI: 36.3± 8.4	Metf, NAC	12 weeks	FBG,FI
Ng et al[73]	RCT	China	N/A	Age:30.5	Metf, placebo	3 months	FBG,FI

Ortega-González et al[79]	RCT	Mexico	N/A	BMI:N/A Age: 28.8 ±0.9 BMI: 32.2 ±1.0	Metf, Piogl	6 months	FBG, FI

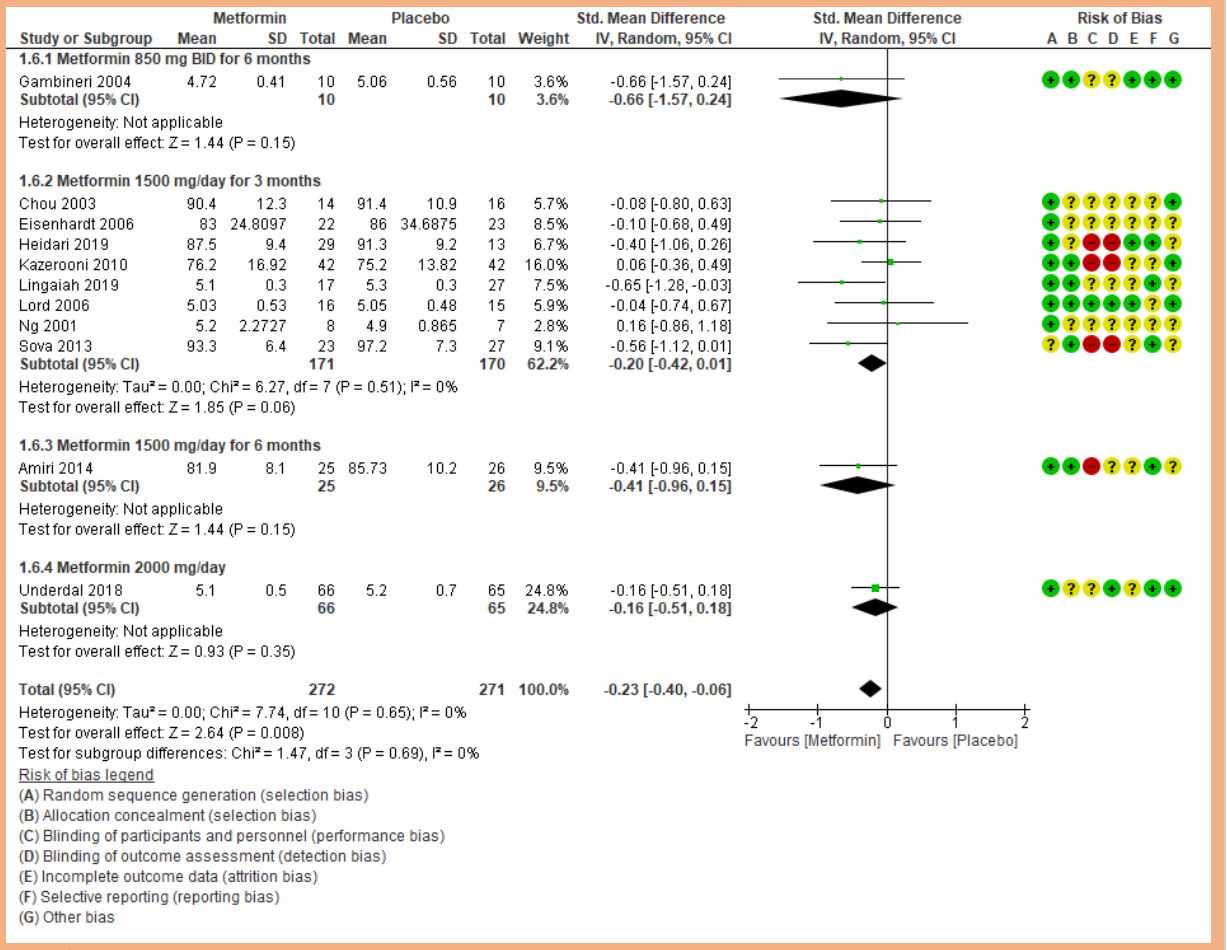
Table 2 continued…….

Paredes Palma et al[85]	RCT	Mixeco	N/A	Age:N/A BMI: N/A	Metf, Sitag	N/A	HOMA-IR
Penna et al[87]	RCT	Brazil	NA	Age: 26.69 ±1.46 BMI: 35.8± 2.60	Acarbose, Placebo	6 months	FI
Puurunen et al[84]	RCT	Finland	N/A	Age: 40.5 ±5.9 BMI: 30.4 ±8.6	Atorva, placebo	6 months	FI, HOMA-IR
Rezai et al[49]	RCT	Iran	Rotterdam	Age: 26.3±4 BMI: 26.9 ± 1.8	Metf, Acarbose	3 months	FBG
Sathyapalan et al[50]	RCT	UK	Rotterdam	Age: 27.7± 1.4 BMI: 33.20 ±1.4	Atorvas, placebo	12 weeks	HOMA-IR, FBG,FI
Shahebrahimi et al[51]	RCT	Iran	Rotterdam	Age: 27.5 ± 3.68 BMI: 27.71±4.36	Metf, piog	3 months	FBG
Sohrevardi et al[52]	RCT	Iran	Rotterdam	Age:N/A BMI: 27.5±3.6	Metf,piog, Metf+Piog	3 months	HOMA-IR, FBG, FI
Sönmez et al[67]	RCT	Turkey	NIH	Age: 26.13 ±5.08 BMI: 27 ±2.2	Metf, Acarbose	3 months	FBG,FI
Sova et al[53]	RCT	Finland	Rotterdam	Age: : 27.7 ±4.0 BMI: 27.5 ±6.2	Metf, placebo	3 months	FBG,FI
Steiner et al[68]	RCT	Germany	NIH	Age: 22.9±4.5 BMI: 27.4±6.0	Metf, Rosig	6 months	HOMA-IR, FBG,FI
Tao et al[54]	RCT	China	Rotterdam	Age: 30 ± 5 BMI: 27.2	Saxag, Metf	24 weeks	HOMA-IR
Trolle et al[74]	RCT	Denmark	N/A	Age: 31 BMI:32	Metf, placebo	6 months	FBG,FI,HOMA-IR
Underdal et al[55]	RCT	Denmark	Rotterdam	Age: 29.5 ±3.9 BMI: 28.7± 6.9	Metf, placebo	NA	FBG, FI
Vandermolen et al[76]	RCT	USA	N/A	Age: 29 6 ±1.2 BMI: 37.6 ± 4.3	Metf, Placebo	7 weeks	FBG,FI
Yarali et al[75]	RCT	Turkey	N/A	Age:29.7±5.6 BMI:28.6±4	Metf, placebo	6 weeks	FBG,FI
Yilmaz et al[56]	RCT	Turkey	Rotterdam	Age: 24.67+4.60 BMI: 27.12+6.18	Metf, Rosig	24 weeks	FBG,FI
Zheng et al[57]	RCT	China	Rotterdam	Age: 27.70 ± 3.41 BMI: 28.27 ± 4.85	Exena, Metf	12 weeks	FBG,FI
Ziaee et al[58]	RCT	Iran	Rotterdam	Age: 25.28±4.38 BMI: 26.13 ±3.03	Metf, piog	12 weeks	HOMA-IR

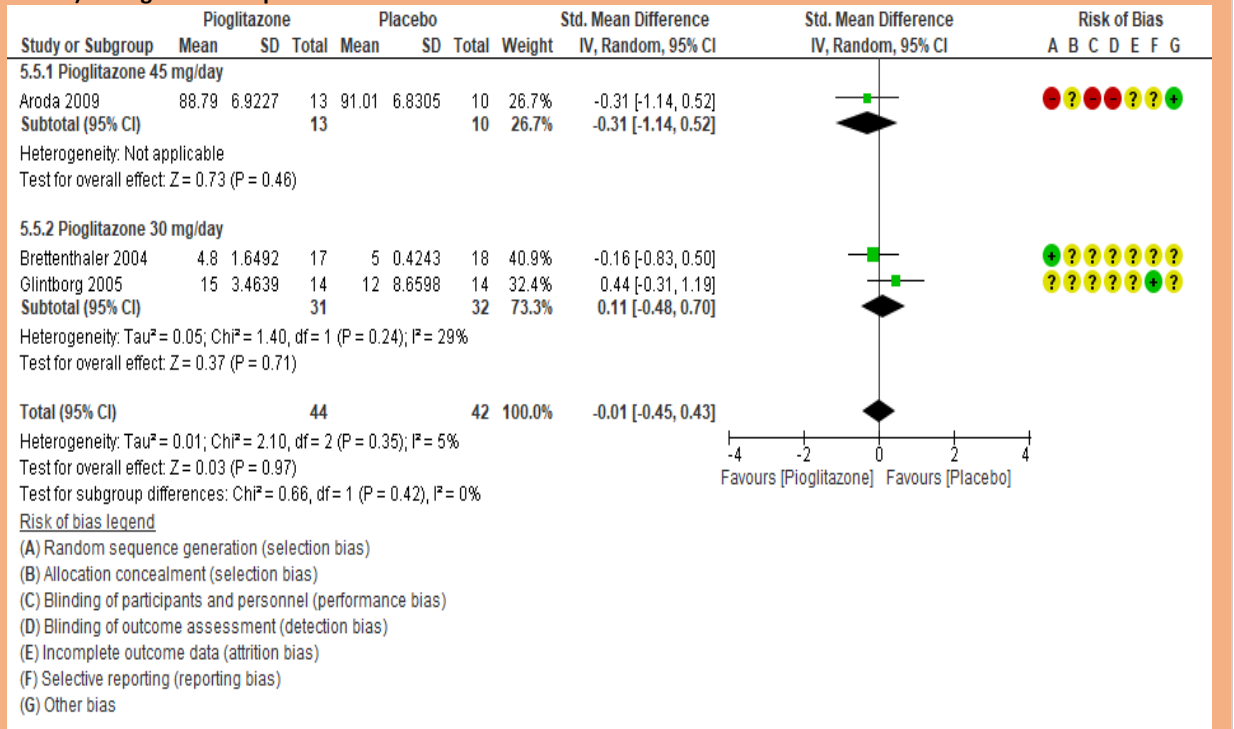
RCT: randomised clinical trial, **N/A**: not available, **FBG**: fasting blood glucose, **FI**: fasting insulin, **HOMA-IR:** homeostatic model of insulin resistance**,NIH**: national institute for health, **NICHD**:national inistitute of child health and development. **Metf:**metformin, **Saxa:** saxagliptin,**Piog**: pioglitazone, **Rosig**: rosiglitazone,**Atrova:** atorvastatin, **Simva**:simvastatin, **WHO:** world health organisation,**Lira**:liraglutide, **USA:** united state of America,**UK**: united kingdom, **HOMA-B:** homeostatic model of the beta cell.

Figure 2: Forest plot of comparisons on FBG

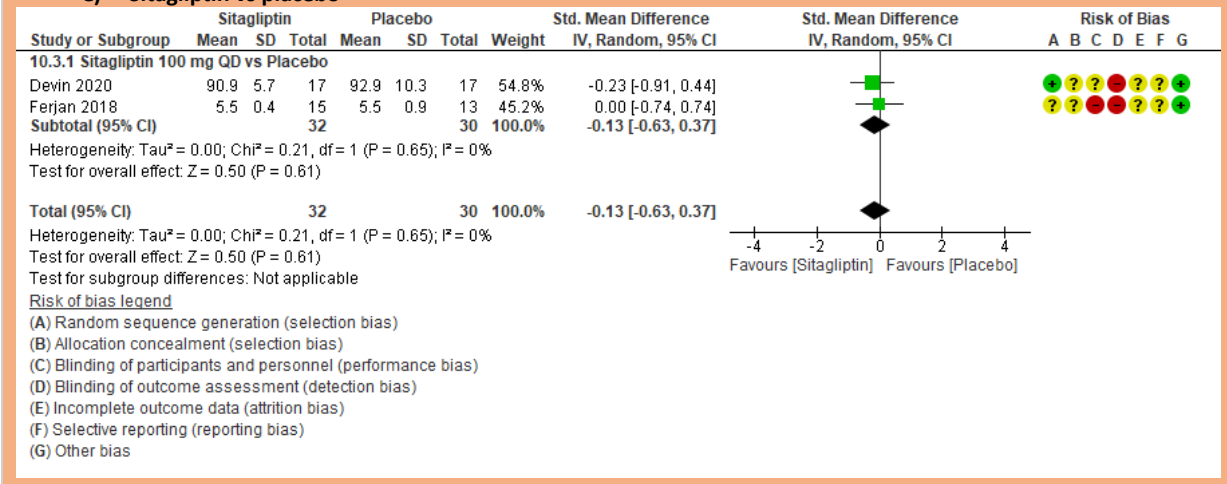
A) Metformin vs Placebo



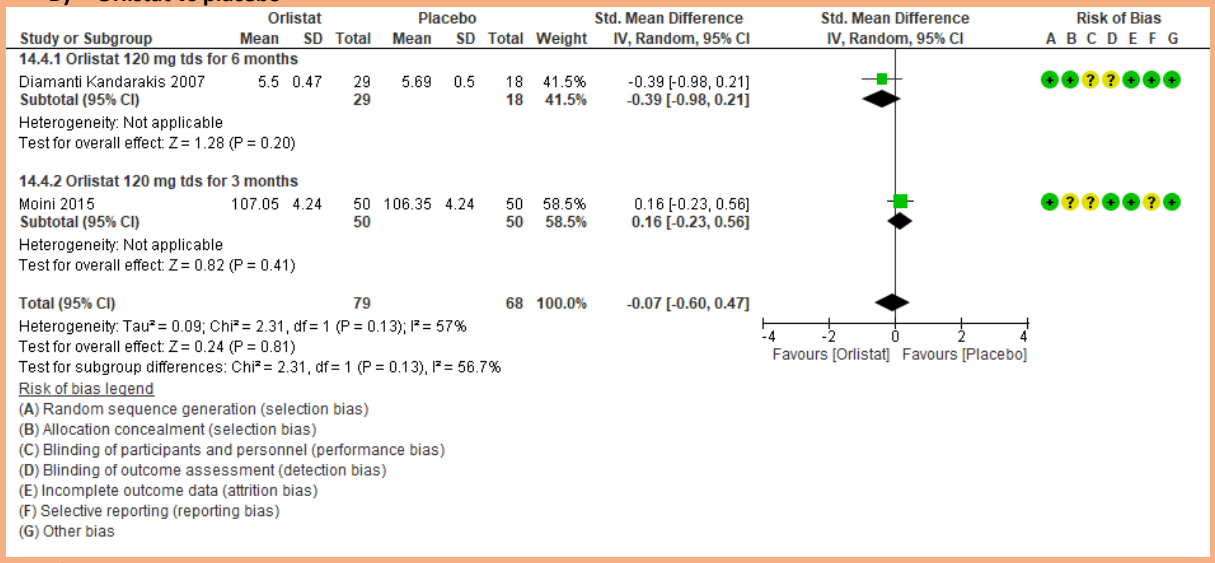
B) Pioglitazone vs placebo



C) Sitagliptin vs placebo



D) Orlistat vs placebo



E) Atorvastatin vs placebo

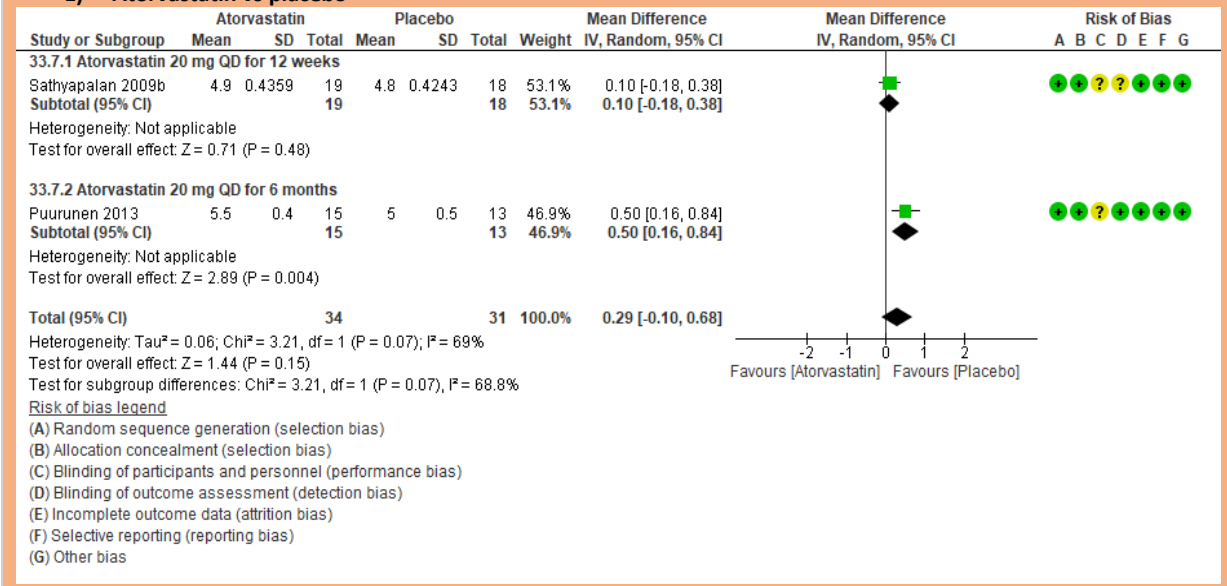
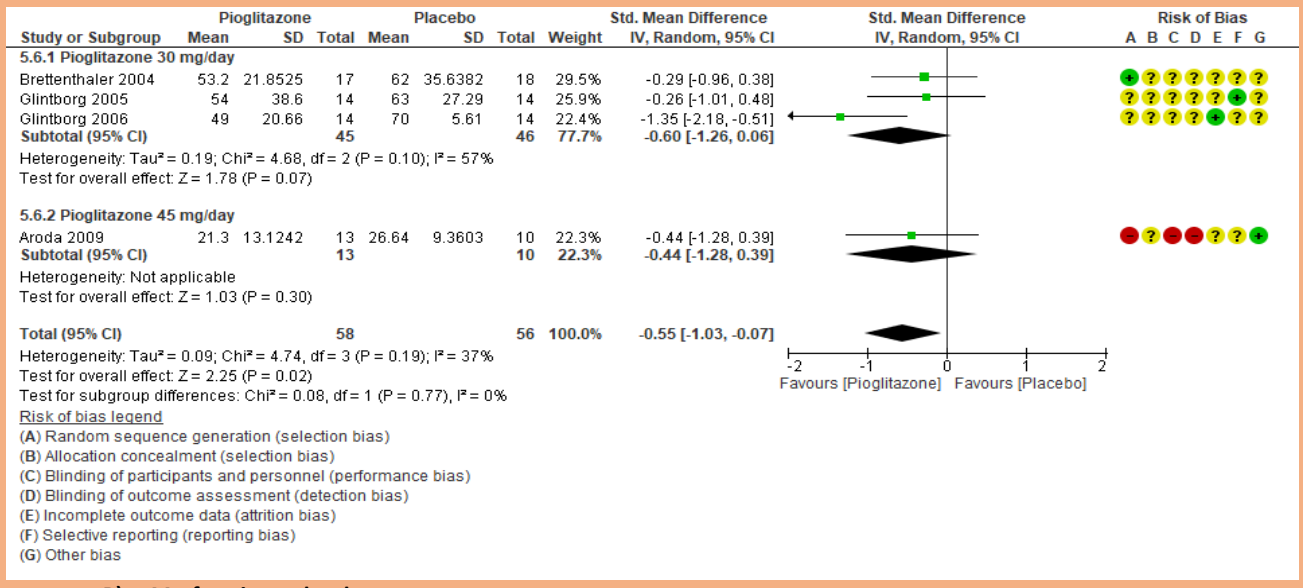
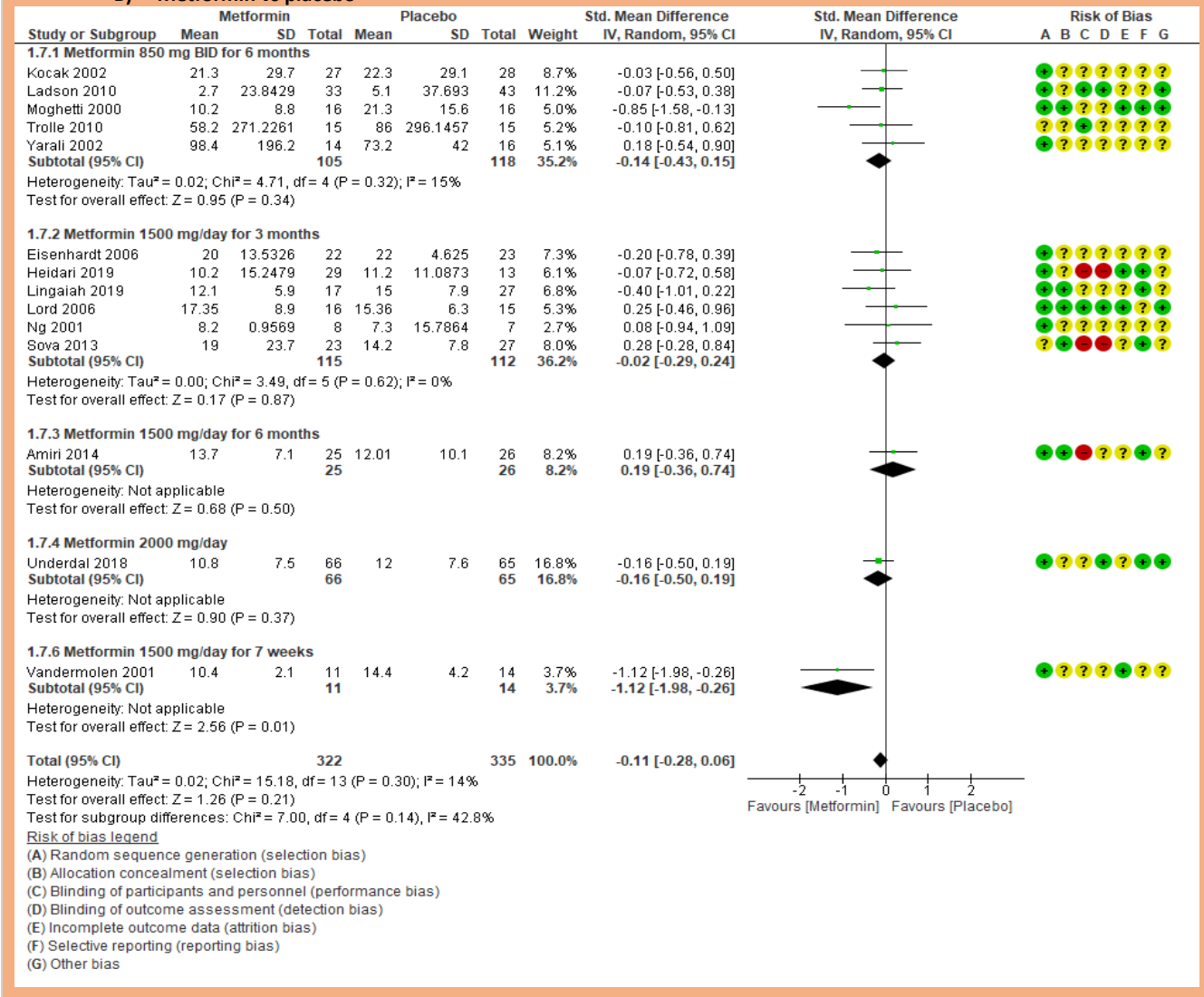


Figure 3: Forest plot of comparisons on FI

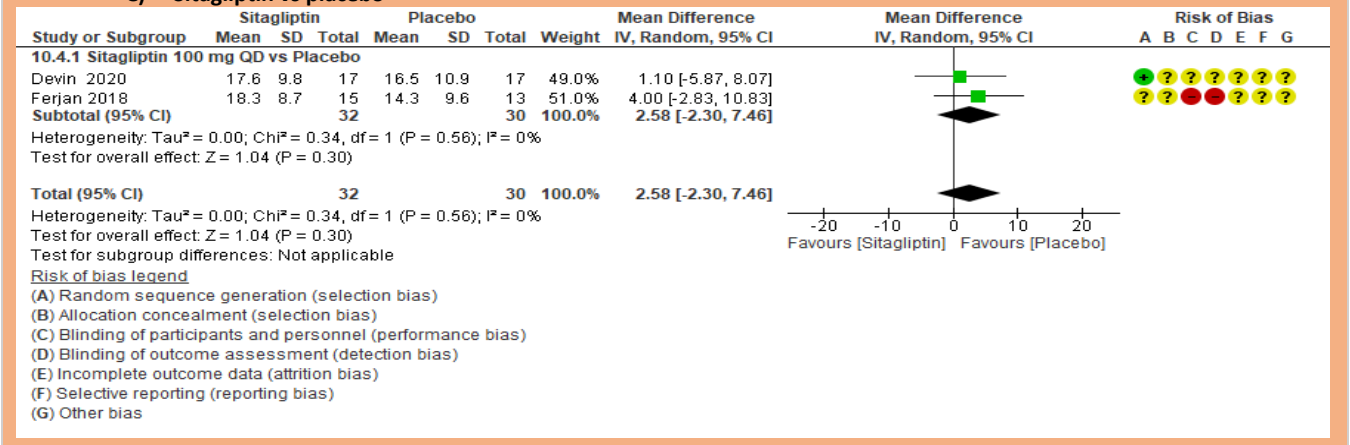
A) Pioglitazone vs placebo



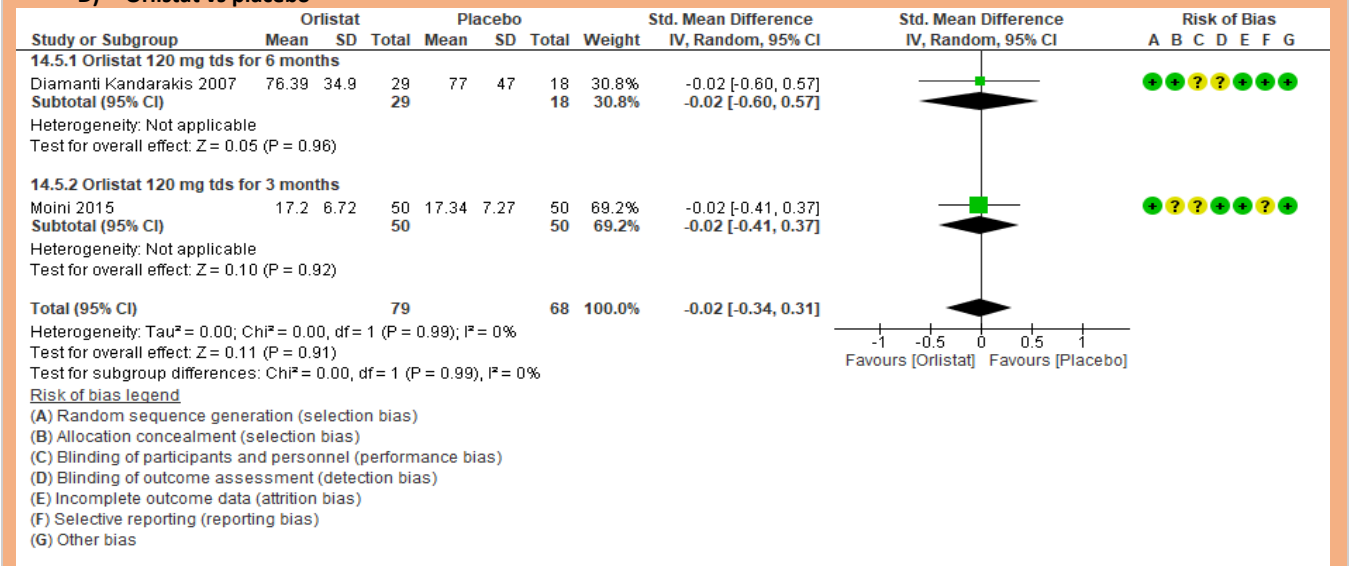
B) Metformin vs placebo



C) Sitagliptin vs placebo



D) Orlistat vs placebo



E) Atorvastatin vs placebo

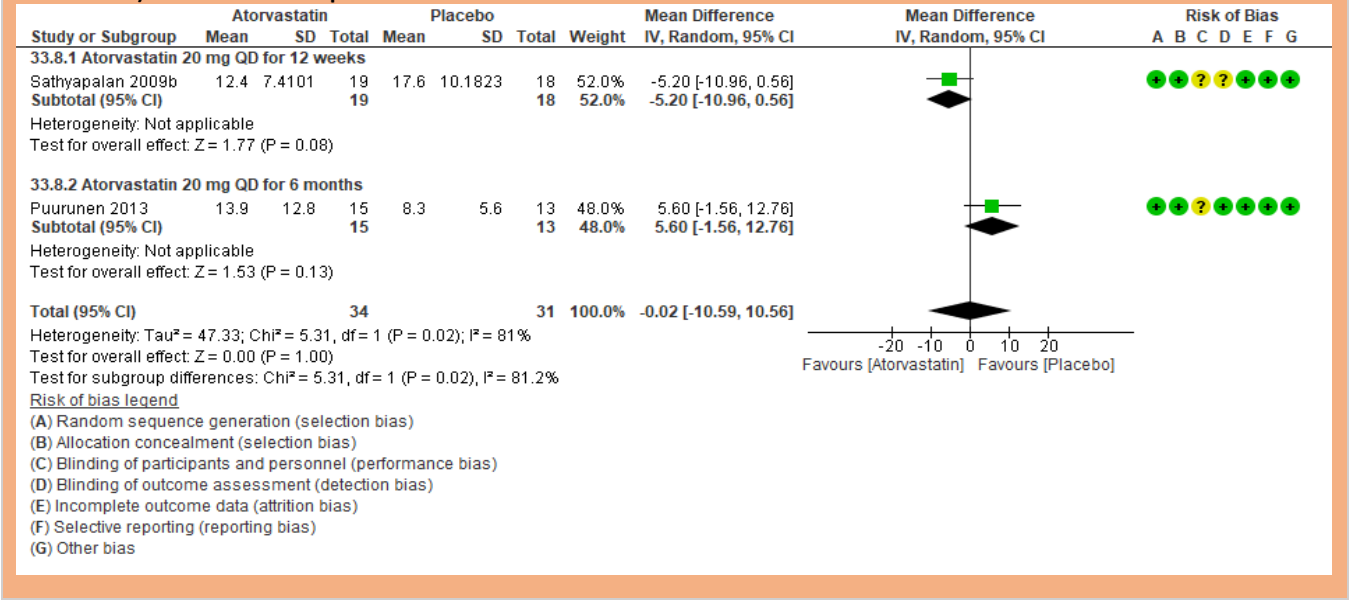
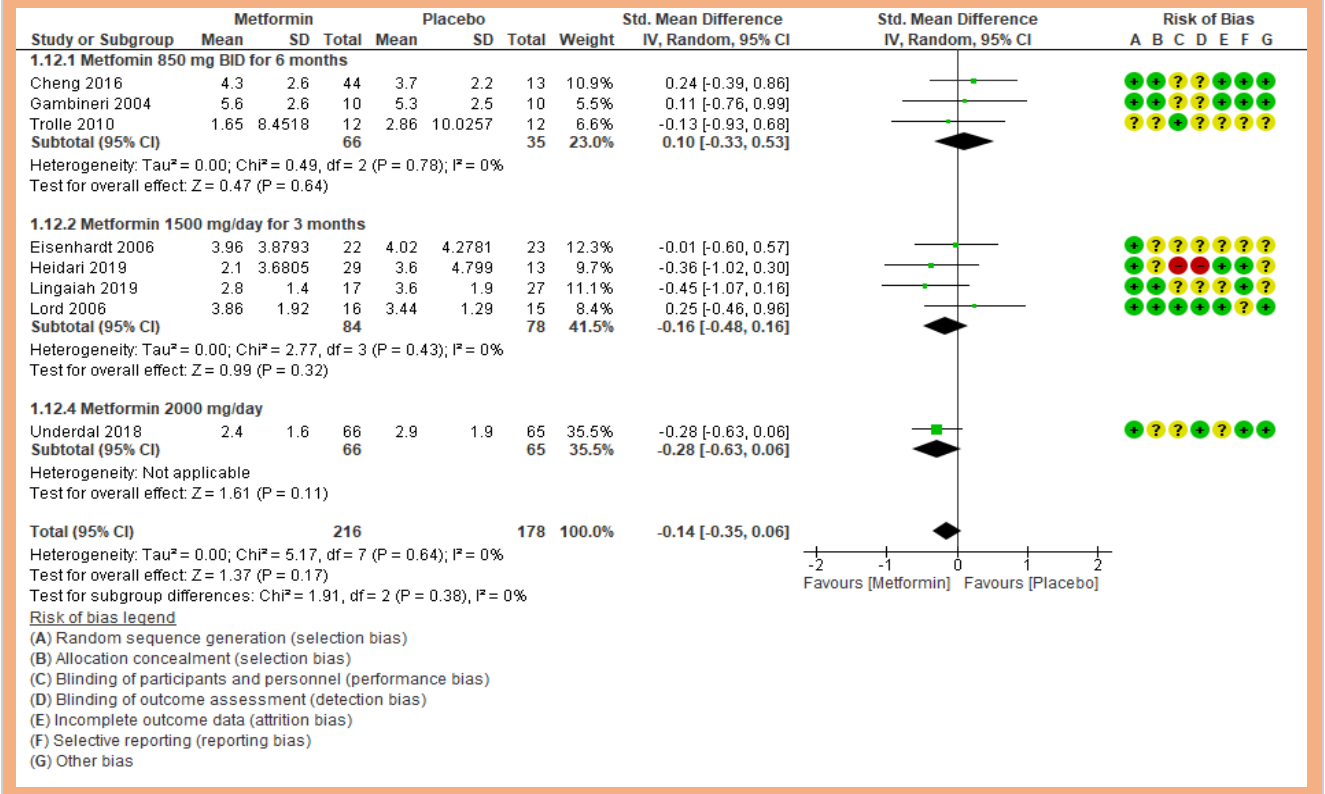
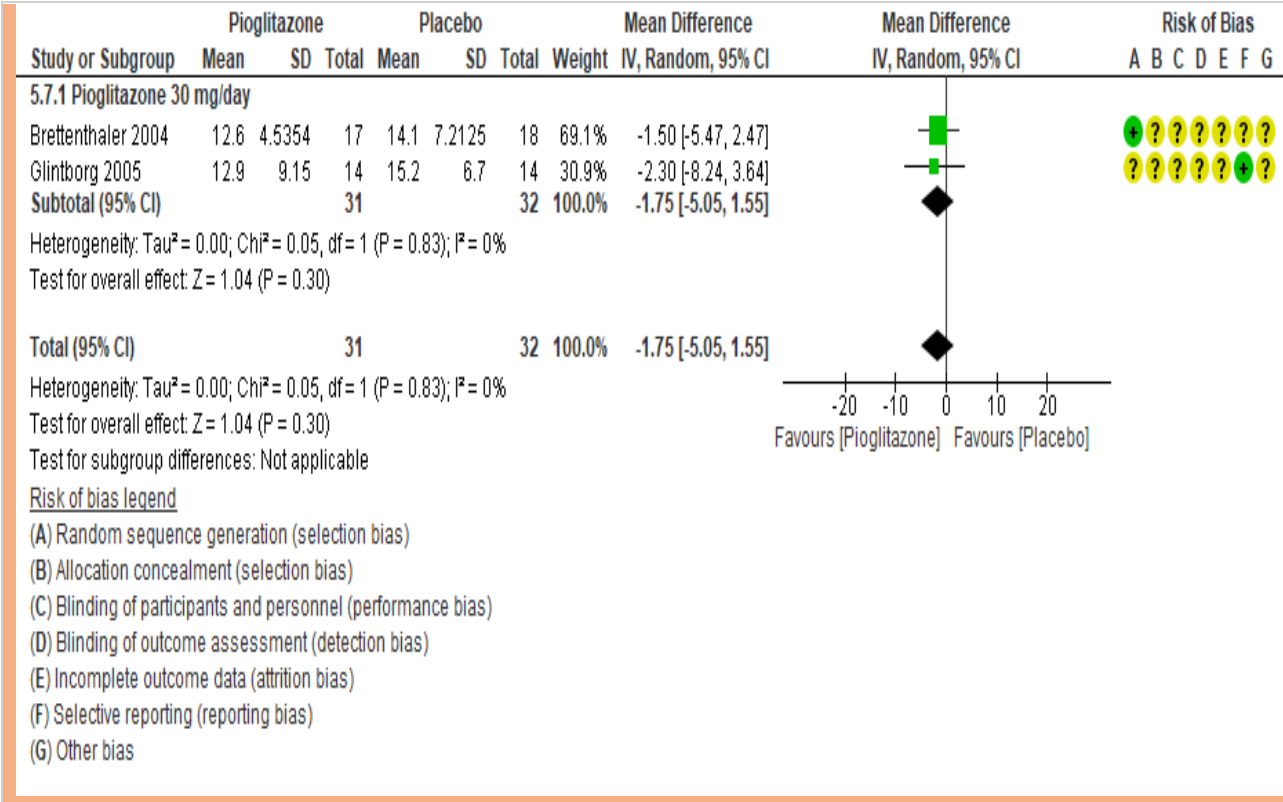


Figure 4: Forest plot of comparisons on HOMA-IR

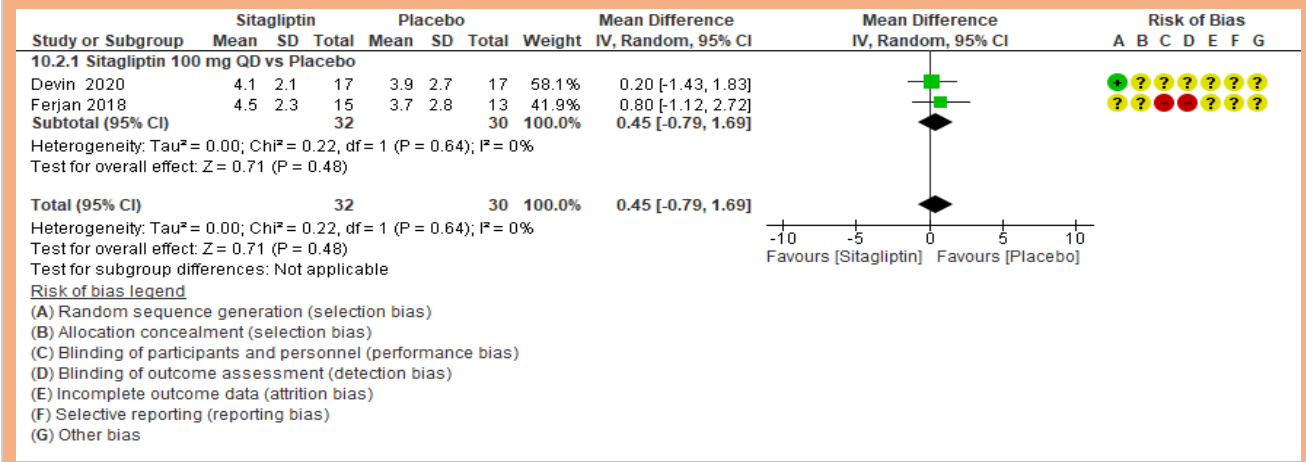
A) Metformin vs placebo



B) Pioglitazone vs placebo



C) Sitagliptin vs placebo



D) Orlistat vs placebo

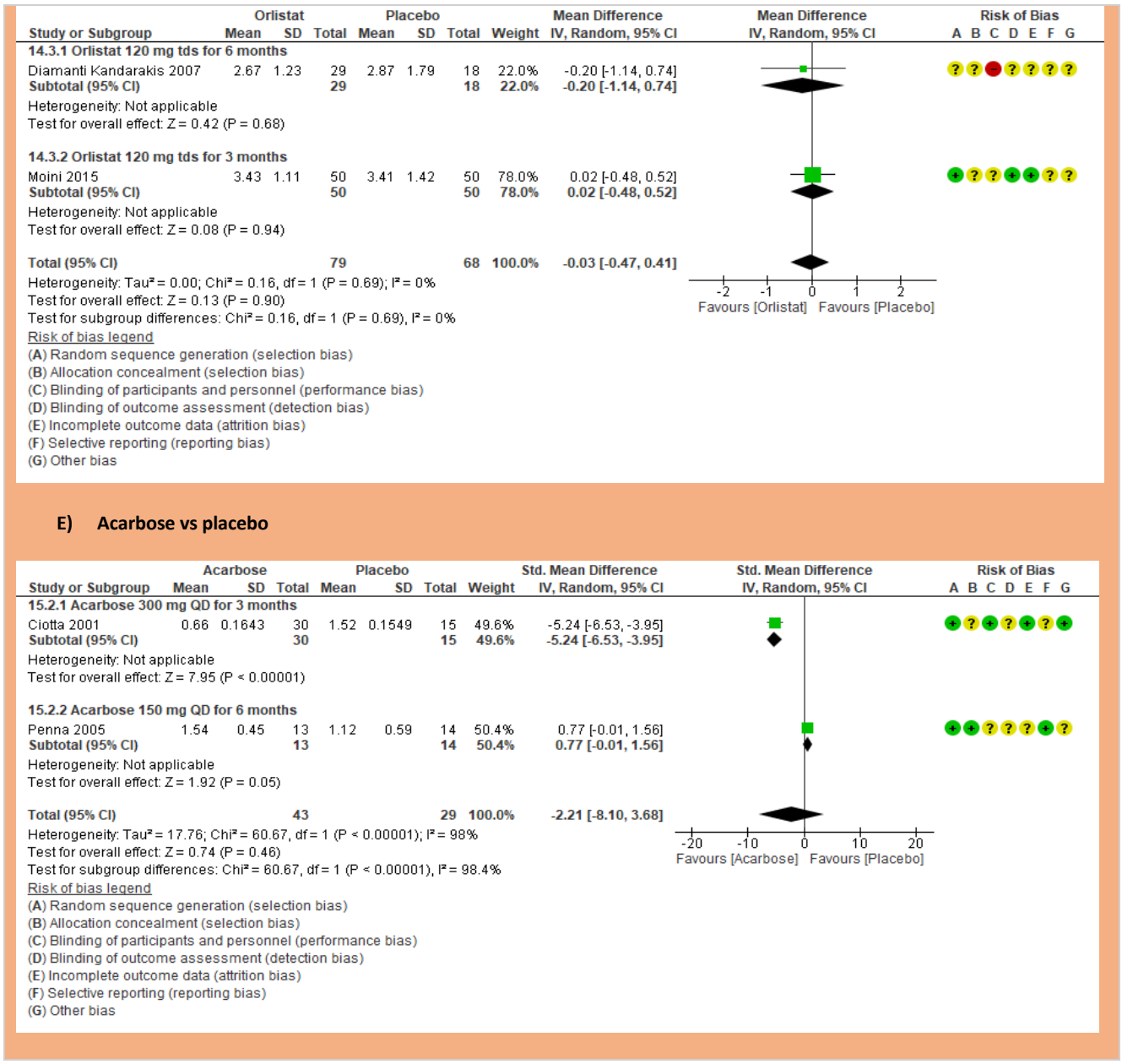


Figure 5: Forest plot of comparisons on HOMA-B

Metformin vs placebo

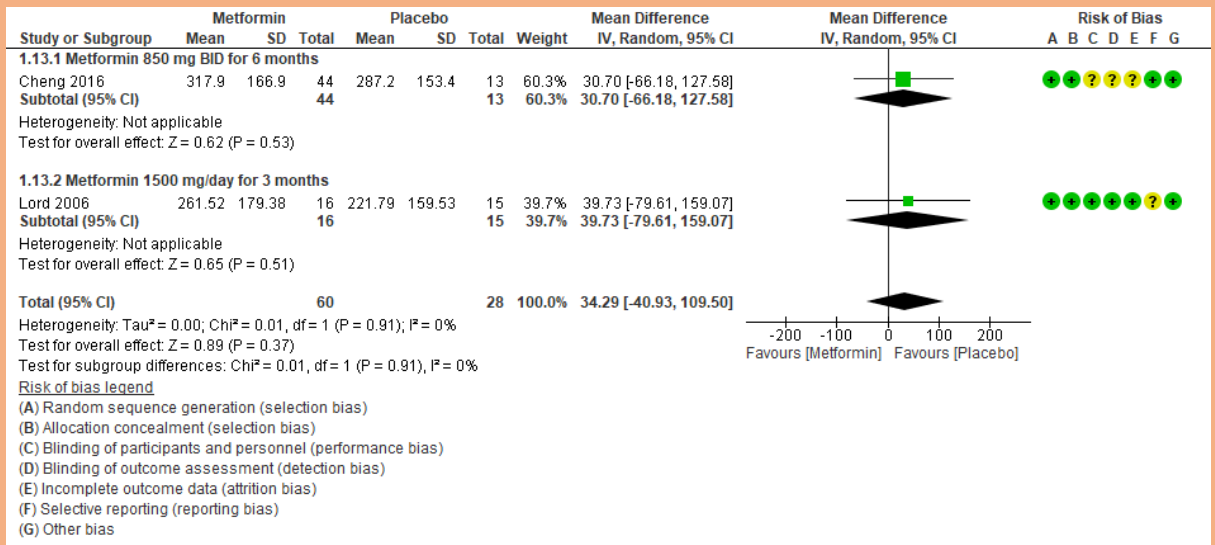


Table 3: summary pooled effect estimates of various medications on FBG, FI, HOMA-IR and HOMA-B in women with PCOS

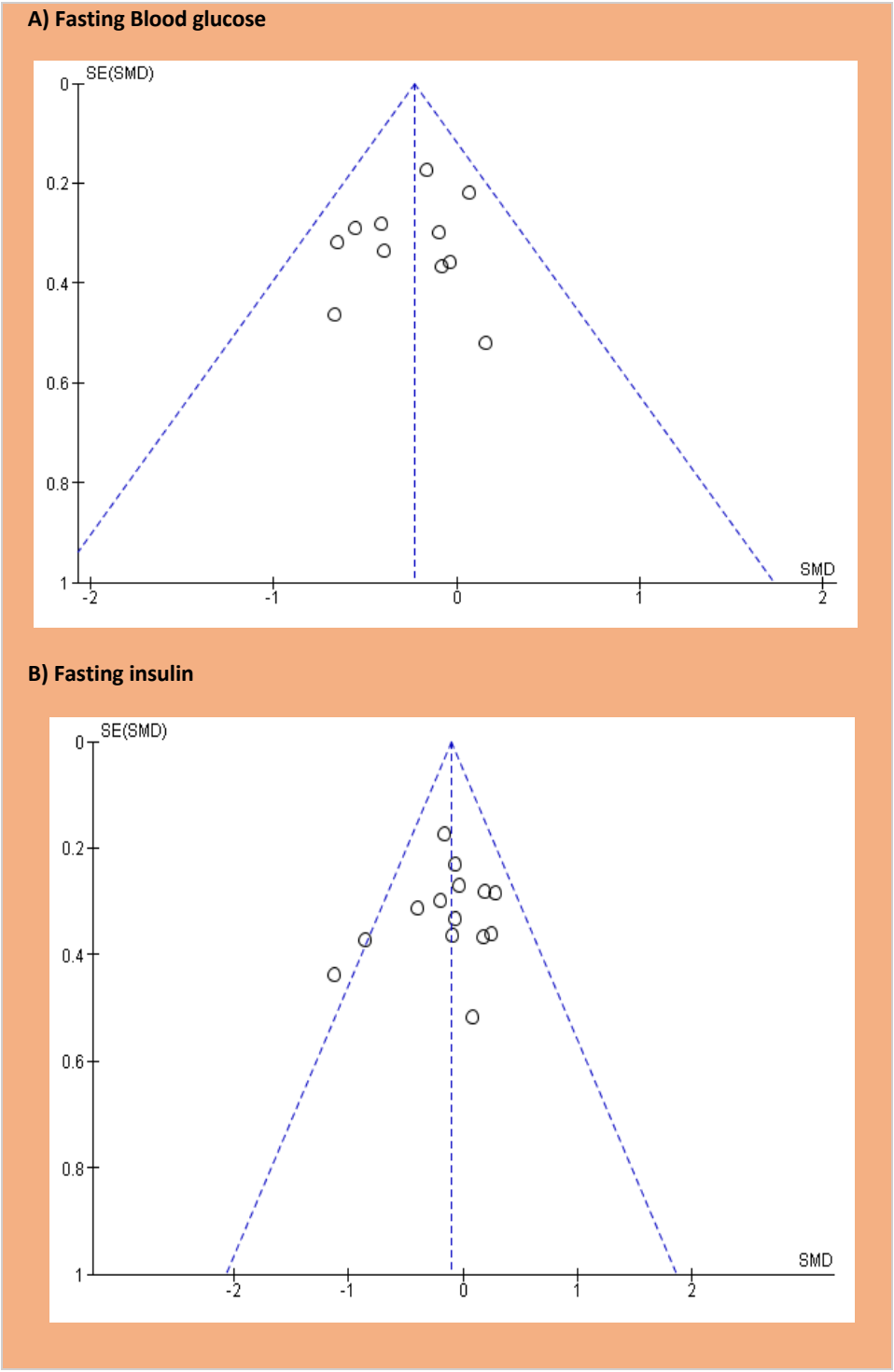
Intervention	Comparison	No of women in the intervention arm	No of women in the control arm	No of RCTs	Pooled effect estimates	95% CI	I^2 (%)	I^2 (*p*-value)	Overall effect (*p*- value*)
Outcome: mean fasting blood glucose.									
Acarbose 100 mg QD for Three months	Metformin	30	30	1	-10.30	-15.61-4.99	-	-	0.0001
Acarbose 300 mg QD for Three months	Metformin	15	15	1	-20.80	-58.84-17.24	-	-	0.28
Overall: Acarbose versus Metformin		45	45	2	-10.50	-15.67-5.24	0.0	0.59	<0.0001
Metformin 1500 mg QD for 3months	Simvastatin 20 mg for three months	100	100	1	-2.97	-6.20-0.26	-	-	0.07
Metformin 1000 mg QD	Simvastatin 20 mg for six months	34	34	1	-7.27	-13.05-1.49	-	-	0.01
Overall: Metformin versus Simvastatin		134	134	2	-4.43	-8.41-0.44	38	0.20	0.03
Metformin 1500 mg QD	NAC 1800 mg QD for 12 weeks	54	54	1	5.10	-0.96-11.16	-	-	0.10
Metformin 1500 mg QD	NAC 600 mg TDS for 24 weeks	48	46	1	3.41	0.54-6.28	-	-	0.02
Overall: Metformin versus NAC		102	100	2	3.72	1.13-6.31	0.0	0.62	0.005
Rosiglitazone 4 mg QD	Metformin 850 mg BID	61	65	4	-0.23	-0.75-0.30	17	0.31	0.40
Rosiglitazone 4 mg QD	Metformin 1500 mg QD	67	68	1	0.09	-0.36-0.54	-	-	0.69
Overall: Rosiglitazone versus Metformin		128	133	5	-0.09	-0.47-0.28	16	0.31	0.63
Metformin 850 mg BID for six months	Pioglitazone 45 mg QD	33	31	2	-0.57	-3.97-2.84	0.0	0.76	0.74
Metformin 1500 mg QD for three months	Pioglitazone 45 mg QD	76	75	3	0.10	-0.13-0.32	0.0	0.61	0.39
Overall: Metformin versus Pioglitazone		109	106	5	0.10	-0.13-0.32	0.0	0.87	0.40
Liraglutide 1.2 mg QD for 12 weeks	Liraglutide 1.2 mg QD with Metformin 1000 mg QD for 12 weeks	46	47	3	0.03	-0.19-0.25	0.0	0.52	0.79
Exenatide 10 µg BID	Metformin 1000 mg BID for 24 weeks	78	80	1	0.13	0.00-0.26	-	-	0.05
Exenatide 10 µg BID	Metformin 1000 mg BID for 12 weeks	31	32	1	-0.02	-0.13-0.09	-	-	0.71
Overall: Exenatide versus Metformin		109	112	2	0.05	-0.10-0.20	67	0.08	0.50
Saxagliptin 5 mg QD	Metformin 2000 mg QD for 24 weeks	42	21	1	0.38	0.33-0.43	-	-	<0.0001
Saxagliptin 5 mg QD	Metformin 2000 mg QD for 16 weeks	22	12	1	-0.10	-0.55-0.35	-	-	0.66

Overall: Saxagliptin versus Metformin		64	33	2	0.19	-0.26-0.65	77	0.04	0.41
Outcome: mean fasting insulin									
Metformin 1500 mg BID	NAC 1800 mg QD for 12 weeks	54	54	1	-1.20	-10.71-8.32	-	-	0.80
Metformin 1500 mg QD	NAC 600 mg TDS for 24 weeks	48	46	1	1.51	0.53-2.49	-	-	0.003
Overall: Metformin versus NAC		102	100	2	1.48	0.51-2.46	0.0	0.58	0.003
Metformin 850 mg BID for six months	Pioglitazone	33	31	2	1.37	-1.11-3.86	0.0	0.33	0.28
Metformin 1500 mg QD for three months	Pioglitazone	114	140	4	0.28	-2.76-3.32	24	0.27	0.86
Overall: Metformin versus Pioglitazone		147	171	6	0.80	-1.07-2.67	5.0	0.38	0.40
Rosiglitazone 4 mg QD	Metformin 850 mg BID	91	93	4	-1.42	-3.11-0.27	0.0	0.54	0.10
Rosiglitazone 4 mg QD	Metformin 1000 mg QD	18	17	1	1.81	-4.65-8.27	-	-	0.58
Rosiglitazone 4 mg QD	Metformin 1500 mg QD	67	68	1	-0.20	-1.92-1.52	-	-	0.82
Rosiglitazone 4 mg QD	Metformin 2000 mg QD	14	47	1	-1.00	-6.44-4.44	-	-	0.72
Rosiglitazone versus Metformin		190	225	7	-0.74	-1.90-0.41	0.0	0.71	0.21
Liraglutide 1.2 mg QD for 12 weeks	Liraglutide 1.2 mg QD with Metformin 1000 mg QD for 12 weeks	46	47	3	-1.84	-6.04-2.35	0.0	0.38	0.39
Exenatide 10 ug BID	Metformin 1000 mg BID for 12 weeks	31	32	1	0.47	-1.89-2.83	-	-	0.70
Exenatide 10 ug BID	Metformin 1000 mg BID for 24 weeks	78	80	1	-0.25	-0.59-0.09	-	-	0.15
Exenatide versus Metformin		109	112	2	-0.24	-0.57-0.10	0.0	0.55	0.17
Acarbose 300 mg QD for three months	Metformin	44	42	2	0.86	-1.92-3.63	0.0	0.82	0.55
Outcome: mean HOMA-IR									
Exenatide 10 ug BID	Metformin 1000 mg BID for 12 weeks	31	32	1	-0.23	-0.83-0.37	-	-	0.45
Exenatide 10 ug BID	Metformin 1000 mg BID for 24 weeks	92	94	2	-0.38	-0.74-0.02	0.0	0.96	0.04

Overall: Exenatide versus Metformin		123	126	3	-0.34	-0.65-0.03	0.0	0.91	0.03
Metformin 850 mg BID for six months	Pioglitazone	18	17	1	0.01	-0.19-0.21	-	-	0.92
Metformin 1500 mg QD for three months	Pioglitazone	63	67	3	1.06	0.11-2.00	0.0	0.62	0.03
Overall: Metformin versus Pioglitazone		81	84	4	0.47	-0.33-1.28	45	0.14	0.25
Rosiglitazone 4 mg QD	Metformin 850 mg BID	61	65	4	-0.23	-0.75-0.30	17	0.31	0.40
Rosiglitazone 4 mg QD	Metformin 1500 mg QD	67	68	1	0.09	-0.36-0.54	-	-	0.96
Overall: Rosiglitazone versus Metformin		128	133	5	-0.09	-0.47-0.28	16	0.31	0.63
Liraglutide 1.2 mg QD	Liraglutide 1.2 mg with Metformin 1000 mg QD for 12 weeks	46	47	3	-0.37	-1.53-0.78	20	0.20	0.53
Orlistat 120 mg TDS	Metformin 1500 mg QD for three months	25	26	2	-0.19	-1.18-0.80	43	0.19	0.71
Sitagliptin 100 mg QD plus Metformin 850 mg BID	Metformin 850 mg BID	5	5	1	0.00	-3.61-3.61	-	-	1.00
Sitagliptin 100 mg QD plus Metformin 1000 mg BID	Metformin 1000 mg BID	12	12	1	-0.80	-2.13-0.53	-	-	0.24
Overall: Sitagliptin plus Metformin versus Metformin		17	17	2	-0.71	-1.95-0.54	0.0	0.68	0.27
Saxagliptin 5 mg QD	Metformin 2000 mg QD for 24 weeks	21	21	1	0.53	-0.08-1.14	-	-	0.09
Saxagliptin 5 mg QD	Metformin 2000 mg QD for 12 weeks	11	11	1	-1.50	-4.28-1.28	-	-	0.29
Overall: Saxagliptin versus Metformin		32	32	2	-0.01	-1.78-1.75	49	0.16	0.99

***RCT**: randomised control trials, **I²:** heterogeneity, *The overall effect was significant at < 0.05, **CI:** confidence interval, **QD**: once a day, **BID:** Twice a day, **HOMA-IR:** the homeostatic model of insulin resistance.*

Figure 6 : Funnel plot of comparison metformin vs placebo



SE: standard error, **SMD:** standardised mean difference