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## Efficacy and safety of GLP-1 receptor agonists on weight management and metabolic parameters in PCOS women: a meta-analysis of randomized controlled trials

Shike Lin<sup>1,5,6</sup>, Yan Deng<sup>7</sup>, Jing Huang<sup>2</sup>, Meiyang Li<sup>5,6</sup>, Suren Rao Sooranna<sup>8</sup>, Minzhen Qin<sup>3,4</sup>✉ & Bing Tan<sup>2,5</sup>✉

This meta-analysis aimed to evaluate the efficacy and safety of glucagon-like peptide-1 receptor agonists (GLP-1RAs) when compared to metformin and placebo in the management of body weight, glucose homeostasis and hormone levels in women polycystic ovary syndrome (PCOS). A systematic search of “PubMed”, “EMBASE”, “Cochrane Library”, “Web of Science” and “Google Scholar” was conducted up to October 2024 for randomized controlled trials involving adult women with PCOS treated with GLP-1RAs compared to metformin or placebo. The primary outcomes were changes in body mass index (BMI), body weight, waist circumference (WC), waist-to-hip ratio (WHR) and abdominal girth (AG). Secondary outcomes included glucose homeostasis (fasting glucose, fasting insulin, OGTT results and HOMA-IR), hormone levels (DHEAS, SHBG, total and free testosterone and FAI), lipid profiles (total cholesterol, HDL, LDL and triglycerides) and safety. GLP-1RAs significantly reduced BMI, body weight, WC, WHR and AG ( $P < 0.0001$  in all cases). For glucose homeostasis, GLP-1RAs significantly reduced fasting insulin, glucose level at 2 h after OGTT, and HOMA-IR. There was also a reduction in HDL. All the other parameters measured were unchanged. In addition, GLP-1RAs increased nausea ( $P = 0.02$ ), vomiting (0.04) and dizziness (0.03). GLP-1RAs effectively reduced body weight, BMI and insulin resistance in patients with PCOS, although they were accompanied by nausea, vomiting and dizziness. Further studies are needed to explore their long-term effects on glucose homeostasis and lipid profiles.

**Keywords** Polycystic ovary syndrome, GLP-1 receptor agonists, Anthropometric measurement, Glucose homeostasis, Metabolic outcomes, Meta-analysis of RCTs

Polycystic ovary syndrome (PCOS) is the most common reproductive endocrine disorder among women of reproductive age. Its clinical manifestations are highly heterogeneous, primarily characterized by infrequent or absent ovulation, elevated androgen levels and polycystic ovarian changes<sup>1,2</sup>. It is often associated with insulin

<sup>1</sup>Office of Science and Technology, Youjiang Medical University for Nationalities, Baise 533000, Guangxi, China.

<sup>2</sup>Department of Pharmacy, Affiliated Hospital of Youjiang Medical University for Nationalities, No.18#, Zhongshan 2nd Road, Baise 533000, Guangxi, China. <sup>3</sup>Department of Gastroenterology, Baise People's Hospital, Baise 533000, Guangxi, China. <sup>4</sup>Department of Gastroenterology, Affiliated Southwest Hospital of Youjiang Medical University for Nationalities, No.8#, Chengxiang Road, Baise 533000, Guangxi, China. <sup>5</sup>National Immunological Laboratory of Traditional Chinese Medicine, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise 533000, Guangxi, China. <sup>6</sup>Department of Obstetrics and Gynaecology, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise 533000, Guangxi, China. <sup>7</sup>Department of Obstetrics and Gynaecology, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong, China. <sup>8</sup>Department of Metabolism, Digestion and Reproduction, Imperial College London, 369 Fulham Road, London SW10 9NH, UK. ✉email: qinminzhen@ymun.edu.cn; tanbing@ymun.edu.cn

resistance (IR), obesity, dyslipidemia and other metabolic disturbances<sup>3</sup>. In long-term sufferers of this condition, it can lead to type 2 diabetes mellitus (T2DM), cardiovascular disease, non-alcoholic fatty liver disease and endometrial cancer<sup>4</sup>. These issues affect women throughout their lives, impacting approximately 5–10% of women of reproductive age<sup>5</sup>.

The exact cause of PCOS remains unclear, but it is generally reported that IR plays a crucial role in its onset and progression<sup>6</sup>. Studies have shown that patients with PCOS exhibit selective IR, primarily characterized by abnormalities in the insulin signaling pathways, often associated with altered metabolic parameters<sup>7</sup>. Further research has revealed varying degrees of IR in different tissues of PCOS patients, including adipose tissues, fibroblasts and skeletal muscle cells<sup>8,9</sup>. This suggests that, in addition to systemic IR, PCOS may involve localized IR in the ovaries. There is often a reduction in insulin receptor phosphorylation in PCOS ovarian tissues, which can lead to impaired insulin signaling and decreased glucose uptake in the granulosa cells.

The phosphoinositide 3-kinase (PI3K)/Akt pathway is central to the action of insulin and Akt is a downstream molecule that regulates cellular processes such as proliferation, differentiation and metabolism. Reduced phosphorylation of the PI3K/Akt pathway is a hallmark of IR in PCOS patients<sup>10–12</sup>. The transcription factor, FOXO1, is one of the regulators of this pathway, and it is involved in processes such as the cell cycle and apoptosis. In PCOS, FOXO1 promotes follicle atresia and granulosa cell apoptosis by activation of pro-apoptotic proteins such as p27<sup>Kip1</sup> and Bim, thereby contributing to the cystic changes in the ovaries<sup>13,14</sup>. Additionally, compensatory hyperinsulinemia caused by IR may lead to excessive activation of IGF-1 and it can directly stimulate theca cells to produce androgens, exacerbating hyperandrogenism and inhibiting follicular development and ovulation, thus worsening the symptoms associated with PCOS<sup>15,16</sup>. Overall, localized IR and hyperinsulinemia in the ovaries are the central mechanisms in the pathogenesis of PCOS, leading to ovarian dysfunction, impaired folliculogenesis and hyperandrogenism, which manifest as clinical symptoms of the syndrome.

Currently, the treatment for PCOS primarily focuses on addressing issues related to hyperandrogenism and anovulation, with medications aimed at improving IR. Since the long-term use of estrogen-progestin-based ovulation-inducing drugs and androgen-lowering treatments carry a risk of endometrial cancer, and since weight loss and the effects on IR are often minimal, clinical approaches are now seeking therapies that can simultaneously address both reproductive hormone imbalances and disturbances in glucose metabolism<sup>17</sup>. Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs), such as exenatide, and GLP-1 analogs, such as liraglutide, which are primarily used for the treatment of T2DM, have been studied in PCOS. Reduced levels of GLP-1 in PCOS patients suggest that it may be involved in the pathogenesis and progression of the condition, and that it is potentially linked to obesity and IR. For PCOS patients with obesity and infertility, a combined treatment with metformin and liraglutide has been shown to effectively reduce body weight, improved glucose metabolism and relieved IR<sup>18</sup>. However, while individual studies have shown promising results, the overall efficacy and safety of GLP-1RA therapy in women with PCOS require further comprehensive evaluation.

This meta-analysis systematically assessed the impact of GLP-1RA therapy on anthropometric outcomes and key metabolic parameters in women with PCOS. Specifically, the analysis will evaluate changes in fasting glucose levels, body mass index (BMI), body weight, waist circumference (WC), insulin sensitivity as measured by the homeostatic model assessment of IR (HOMA-IR) and other relevant hormonal and metabolic markers. In addition, we also evaluated the safety of the combined treatment of metformin and GLP-1RAs. By using the data from multiple studies, in this analysis we attempted to clarify the role of IR in the pathogenesis of PCOS and assess the efficacy of GLP-1RAs in improving both the reproductive and metabolic outcomes for patients with PCOS.

## Methods

### Study design and data sources

This meta-analysis adhered to the PRISMA guidelines. A comprehensive literature search was conducted across multiple databases, including “PubMed”, “EMBASE”, “Cochrane Library”, “Google scholar” and “Web of Science” from their inception until October 2024. The search strategy focused on randomized controlled trials (RCTs) comparing treatment with a combination of GLP-1RAs and metformin or placebo. Keywords and medical subject headings (MeSH) terms used in the search included: “Polycystic ovary syndrome”, “PCOS”, “GLP-1 receptor agonist”, “GLP-1RA”, “Semaglutide”, “Liraglutide”, “Exenatide” and “Metformin”. The search strategy was customized for each database. Additionally, reference lists of identified studies were manually checked for additional relevant articles. The studies were selected based on inclusion and exclusion criteria, and those reporting relevant anthropometric and metabolic outcomes were included in the final analysis<sup>19</sup>.

### Inclusion and exclusion criteria

Studies were eligible if they met the following criteria: (1) The participants were adult women aged 18–45 years diagnosed with PCOS. (2) The intervention group received GLP-1RAs, while the control group received either metformin or placebo. (3) The study reported outcomes related to anthropometric measures (BMI, body weight, WC, waist-to-hip ratio (WHR), abdominal girth (AG)) and metabolic markers (fasting glucose, fasting insulin, HOMA-IR, dehydroepiandrosterone sulfate (DHEAS), SHBG, total testosterone, free testosterone and cholesterol levels). The exclusion criteria were: (1) Studies with incomplete data for key outcomes. (2) Non-RCT studies. (3) Trials with a follow-up period of less than 12 weeks. Adherence to inclusion and exclusion criteria was assessed by two independent reviewers through detailed screening of the study characteristics, participant descriptions, and reported outcomes in the full texts.

## Data extraction

Two independent reviewers extracted the data from eligible studies using a standardized extraction protocol. The data extracted included study characteristics (first author, publication year, sample size and duration of follow-up), participant demographics (age and gender), intervention type (GLP-1RAs, metformin and placebo) and outcomes related to anthropometric and metabolic parameters. Discrepancies between reviewers were resolved by consensus.

## Outcomes assessment

The primary outcomes included reductions in BMI, body weight, WC, WHR and AG. Secondary outcomes included fasting glucose, fasting insulin, glucose level at 2 h after an oral glucose tolerance test (OGTT), insulin at 2 h after OGTT, HOMA-IR, DHEAS, SHBG, total testosterone, free testosterone, and lipid levels (total cholesterol, HDL, LDL, and triglycerides (TG)).

## Statistical analysis

All analyses were performed using the review manager (RevMan) software package version 5.0. The mean differences (MDs) with 95% confidence intervals (CIs) were calculated for continuous outcomes. A random effects model was used for analyses with high heterogeneity ( $I^2 > 50\%$ ), while a fixed effects model was applied when the heterogeneity of the data was low ( $I^2 < 50\%$ ). Heterogeneity was assessed using the  $I^2$  statistic and Chi-square test, and a P-value of less than 0.10 was considered significant for heterogeneity. Subgroup analyses were conducted to examine the effects of GLP-1RAs compared to metformin or placebo. Subgroup comparisons were made based on the control group intervention for each of the anthropometric and metabolic parameter measured. Funnel plots were generated to assess publication bias for key outcomes.

## Quality assessment

The quality of included studies was assessed using the Cochrane risk-of-bias tool. This evaluation considered random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data and selective reporting. Studies with a high risk of bias were noted, and their impact on overall findings was considered during the sensitivity analysis employed.

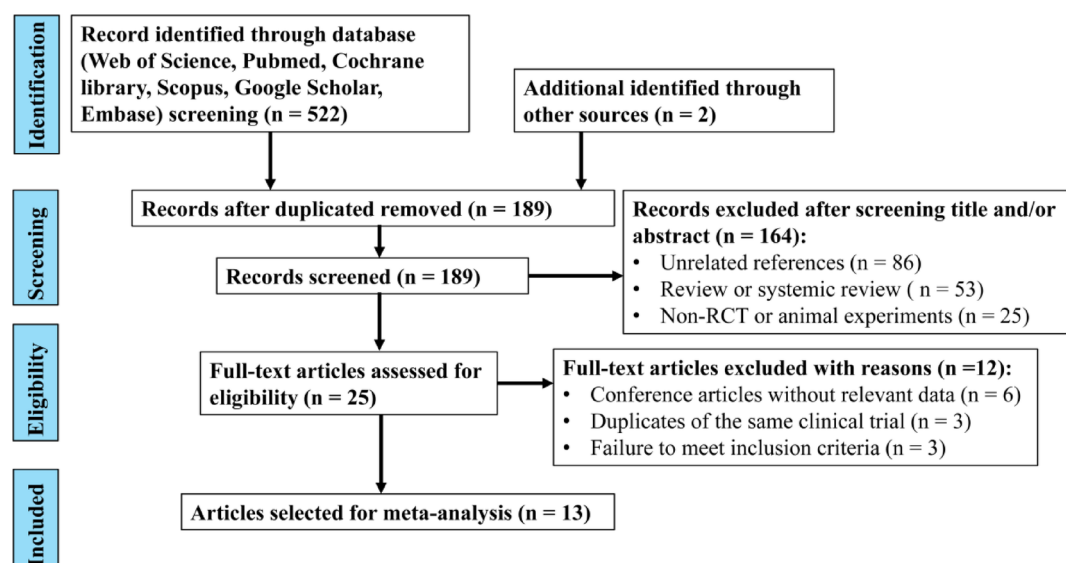
## Results

### Study screening

A flow diagram of the meta-analysis conducted in this study is shown in Fig. 1. 524 studies were included for initial analysis and after removing duplicated reports, 189 remained. After screening the titles and abstracts, the full text of 25 articles were collected and 13 RCTs that met the exclusion and inclusion criteria were used for subsequent meta-analysis.

### Study characteristics

The characteristics of the individual studies are presented in Table 1. The meta-analysis included a total of 397 and 330 individuals who received the invention of GLP-1RAs and metformin, respectively, as well as 68 individuals who received a placebo. With respect to GLP-1RAs, 23, 87 and 308 patients respectively received semaglutide, liraglutide and exenatide.



**Fig. 1.** A PRISMA flow diagram for the literature selection.

Study	Study design	Diagnostic criteria	Study site	Number of subjects	Age (years old)		Body weight (kg)		BMI (kg/m <sup>2</sup> )		Type of GLP-1RA used	Intervention	Duration of treatment
					GLP-1RA	Control	GLP-1RA	Control	GLP-1RA	Control			
Elkind-Hirsch 2008 <sup>34</sup>	Open-label prospective RCT	Rotterdam criteria	United States	GLP-1RA group = 20, control group = 20	28.2 ± 1.1	27.7 ± 1.3	111.1 ± 5.5	109.1 ± 5	39.9 ± 1.5	41.3 ± 1.8	Exenatide	Exenatide (10 µg, BID), Metformin (1000 mg, BID)	24 weeks
Elkind-Hirsch 2022 <sup>35</sup>	Double-blind placebo-controlled RCT	Modified National Institutes of Health (NIH) 1990 criteria	United States	GLP-1RA group = 44, control group = 23	31 ± 0.8	32 ± 1.1	111 ± 2.8	119 ± 4.7	41.6 ± 1.1	43.9 ± 1.7	Liraglutide	Liraglutide (3 mg, QD), Placebo	32 weeks
Frossing 2018 <sup>36</sup>	Double-blind placebo-controlled RCT	Rotterdam criteria	Denmark	GLP-1RA group = 48, control group = 24	N/A	N/A	94.2 ± 15.4	91.3 ± 13.6	33.3 ± 5.1	33.3 ± 4.6	Liraglutide	Liraglutide (1.8 mg, QD), Placebo	26 weeks
Jensterle 2014 <sup>37</sup>	Open-label prospective RCT	National Institute of Child Health and Human Development (NICHD) criteria	Slovenia	GLP-1RA group = 11, control group = 14	31.5 ± 6.4	31.3 ± 9.4	108.9 ± 15.1	103.2 ± 6.3	39.3 ± 4.2	36.6 ± 3.5	Liraglutide	Liraglutide (1.2 mg, QD), Metformin (1000 mg, BID)	12 weeks
Jensterle 2015 <sup>38</sup>	Open-label prospective RCT	Rotterdam criteria	Slovenia	GLP-1RA group = 14, control group = 13	N/A	N/A	102.8 ± 16.3	108.3 ± 17.0	36.7 ± 5.6	39.4 ± 6.9	Liraglutide	Liraglutide (1.2 mg, QD), Metformin (1000 mg, BID)	12 weeks
Jensterle 2015a <sup>39</sup>	Open-label prospective RCT	National Institute of Child Health and Human Development (NICHD) criteria	Slovenia	GLP-1RA group = 14, control group = 14	29.5 ± 7.7	25.3 ± 5.2	112.3 ± 20.6	105.3 ± 20.1	40.8 ± 6.1	38.2 ± 7	Liraglutide	Liraglutide (1.2 mg, QD), Metformin (1000 mg, BID)	12 weeks
Jensterle 2021 <sup>40</sup>	Single-blind placebo-controlled RCT	Rotterdam criteria	Slovenia	GLP-1RA group = 13, control group = 12	N/A	N/A	100.8 ± 11.8	98.8 ± 13.1	36.8 ± 3.9	35.4 ± 3.8	Semaglutide	Semaglutide (0.5 mg/week), Placebo	16 weeks
Jensterle 2022 <sup>41</sup>	Single-blind placebo-controlled RCT	Rotterdam criteria	Slovenia	GLP-1RA group = 10, control group = 9	N/A	N/A	104.5 (89.8–111.8)*	99.5 (82.8–106)*	37.9 (33.2–41.4)*	31.0 (29.3–39.5)*	Semaglutide	Semaglutide (1 mg/week), Placebo	12 weeks
Li 2022 <sup>42</sup>	Open-label prospective RCT	Rotterdam criteria	China	GLP-1RA group = 72, control group = 75	28.19 ± 3.96	27.83 ± 3.52	73.72 ± 11.43	72.37 ± 10.98	29.07 ± 3.92	29.15 ± 4.11	Exenatide	Exenatide (10 µg, BID), Metformin (1000 mg, BID)	12 weeks
Liu 2017 <sup>43</sup>	Open-label prospective RCT	Rotterdam criteria	China	GLP-1RA group = 78, control group = 80	27.93 ± 2.70	27.69 ± 3.80	72.96 ± 9.79	70.39 ± 4.57	29.16 ± 3.11	28.29 ± 1.86	Exenatide	Exenatide (10 µg, BID), Metformin (1000 mg, BID)	24 weeks
Nylander 2017 <sup>44</sup>	Double-blind placebo-controlled RCT	Rotterdam criteria	Denmark	GLP-1RA group = 47, control group = 23	31.4 (24.6–35.6)*	31.4 (24.6–35.6)*	94.2 ± 15.4	91.3 ± 13.6	33.3 ± 5.1	33.3 ± 4.6	Exenatide	Exenatide (10 µg, BID), Metformin (1000 mg, BID)	12 weeks
Tao 2021 <sup>45</sup>	Open-label prospective RCT	Rotterdam criteria	China	GLP-1RA group = 50, control group = 50	N/A	N/A	80.00 (72.88, 92.75)*	80.00 (74.70, 86.00)*	30.99 (27.84, 33.34)*	29.64 (28.23, 33.14)*	Exenatide	Exenatide (10 µg, BID), Metformin (1000 mg, BID)	12 weeks
Zheng 2017 <sup>46</sup>	Open-label prospective RCT	Rotterdam criteria	China	GLP-1RA group = 41, control group = 41	27.70 ± 3.41	28.16 ± 3.92	72.58 ± 11.29	74.24 ± 11.27	29.18 ± 4.15	29.00 ± 4.10	Exenatide	Exenatide (10 µg, BID), Metformin (1000 mg, BID)	12 weeks

**Table 1.** Study characteristics of the included studies. \*Median (25th percentile–75th percentile).

## Quality assessment

Six studies were classified as having a “high risk” of performance bias and one was categorized as having a “unclear risk” of performance bias. Four, 1 and 6 studies were categorized as having “high risk”, “medium risk” and “unclear risk” of detection bias, respectively. Four studies were categorized as having an “unclear risk” of selection bias. One study was categorized as having an “unclear risk” of attrition bias. Three studies were classified as having an “unclear risk” of other forms of biases. A visual representation of the eligibility of the quality of the clinical studies included is shown in Fig. 2.

## Changes in anthropometrics

For anthropometric measurements, we compared the results of reduction in BMI, body weight, BMI, WC, WHR and AG. In terms of reduction in BMI, 11 studies (with 349 and 310 subjects from the experimental and control groups, respectively) were included in the analysis. Due to the heterogeneity observed in the included studies ( $I^2 = 74\%$ ,  $P < 0.0001$ ), we used a random-effects model (Fig. 3A). GLP-1RA intervention was associated with a reduction in BMI when compared to either metformin or placebo (MD =  $-1.59$ ; 95% CI  $-2.07$  to  $-1.10$ ;  $P < 0.0001$ ; Fig. 3A).

For the subgroup analysis, the studies were classified based on whether the patients from the control group received either metformin or placebo. As shown in Fig. S1A, GLP-1RA intervention was associated with a reduction in BMI when compared to metformin (MD =  $-1.11$ ; 95% CI  $-1.84$  to  $-0.38$ ;  $P = 0.003$ ) or placebo (MD =  $-1.59$ ; 95% CI  $-2.07$  to  $-1.10$ ;  $P < 0.0001$ ).

In terms of reduction in body weight, 10 studies (with 339 and 301 participants from the experimental and control groups, respectively) were included for analysis. Due to the presence of heterogeneity among the included studies ( $I^2 = 87\%$ ,  $P < 0.0001$ ), a random-effects model was used (Fig. 3B). GLP-1RA intervention was associated with a reduction in body weight when compared to those given metformin or placebo (MD =  $-3.57$ ; 95% CI  $-5.15$  to  $-1.99$ ;  $P < 0.0001$ ; Fig. 3A). For the subgroup analysis, the studies were classified based on if the patients from the control group received metformin or placebo. As shown in Fig. S1B, GLP-1RA intervention was associated with a reduction in body weight when compared to metformin (MD =  $-1.81$ ; 95% CI  $-2.60$  to  $-1.01$ ;  $P < 0.0001$ ) or placebo (MD =  $-5.44$ ; 95% CI  $-5.90$  to  $-4.99$ ;  $P < 0.0001$ ).

In terms of reduction in WC, 8 studies (with 232 and 189 participants from the experimental and control groups, respectively) were included for analysis. No heterogeneity was presented in the included studies, ( $I^2 = 0\%$ ,  $P = 0.47$ ), and therefore the fixed effects model was used (Fig. 3C). GLP-1RA intervention was associated with a reduction in WC when compared to those given metformin or placebo (MD =  $-4.97$ ; 95% CI  $-5.56$  to  $-4.37$ ;  $P < 0.0001$ ; Fig. 3C). For the subgroup analysis, the studies were classified based on whether the patients from the control group received metformin or placebo. As shown in Fig. S1C, GLP-1RAs intervention was associated with a reduction in body weight when compared to metformin (MD =  $-3.82$ ; 95% CI  $-5.33$  to  $-2.31$ ;  $P < 0.0001$ ) or placebo (MD =  $-5.17$ ; 95% CI  $-5.82$  to  $-4.53$ ;  $P < 0.0001$ ).

With respect to the reduction in WHR, 4 studies (with 225 and 210 participants from the experimental and control groups, respectively) were included for analysis. No heterogeneity was presented in the included studies, ( $I^2 = 19\%$ ,  $P = 0.30$ ), and so the fixed effects model was used (Fig. 3D). GLP-1RA intervention was associated with a reduction in WHR when compared to those given metformin or placebo (MD =  $-0.03$ ; 95% CI  $-0.03$  to  $-0.03$ ;  $P < 0.0001$ ; Fig. 3D). For the subgroup analysis, the studies were classified based on whether the patients from the control group received metformin or placebo. As shown in Fig. S1D, GLP-1RA intervention was associated with a reduction in WHR when compared to metformin (MD =  $-0.03$ ; 95% CI  $-0.04$  to  $-0.02$ ;  $P < 0.0001$ ) or placebo (MD =  $-0.03$ ; 95% CI  $-0.03$  to  $-0.03$ ;  $P < 0.0001$ ).

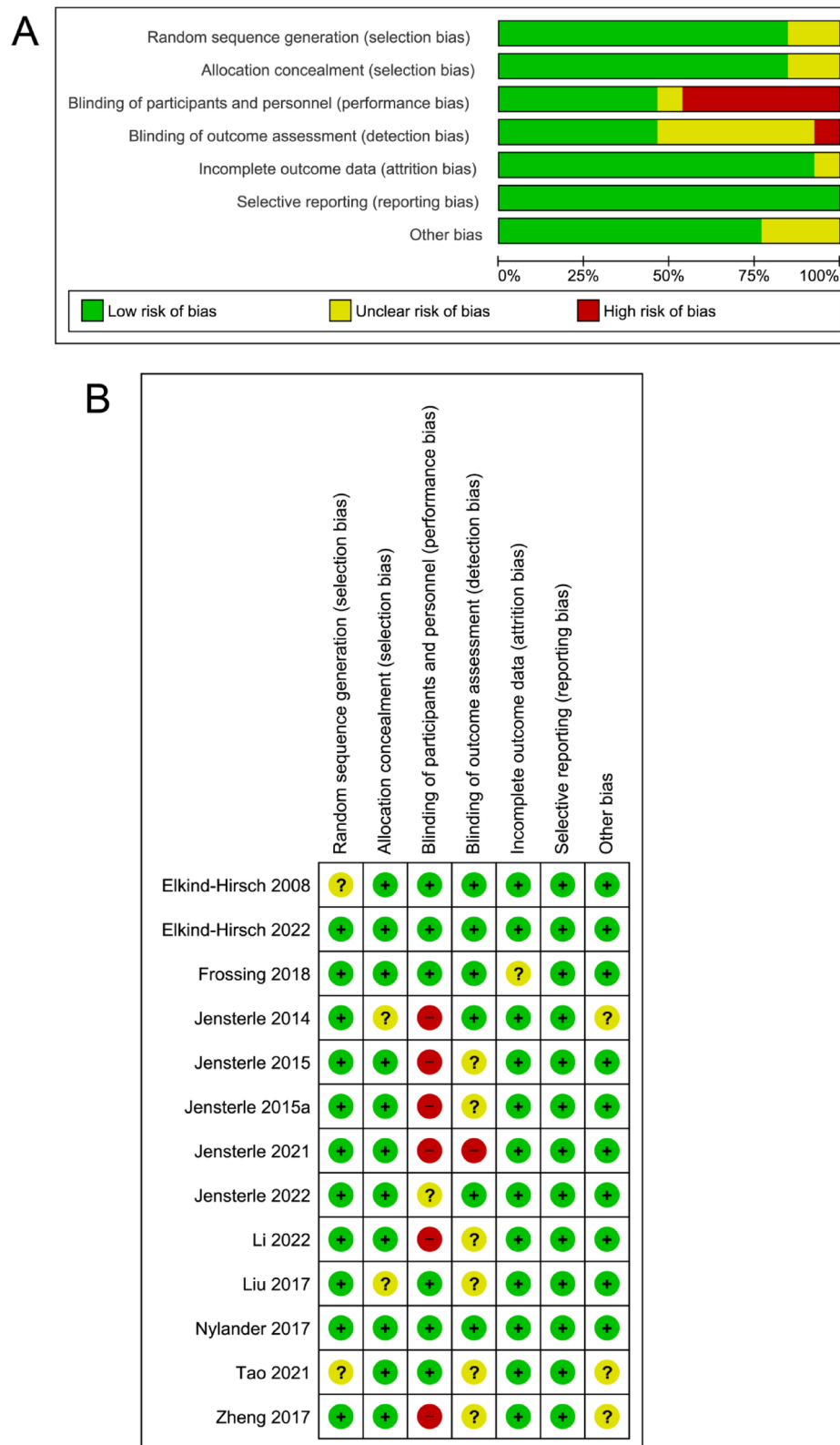
In terms of reduction in AG, 3 studies (with 117 and 121 subjects from the experimental and control groups, respectively) were included for analysis. No heterogeneity was presented in the included studies, ( $I^2 = 0\%$ ,  $P = 0.65$ ), and so the fixed effects model was used (Fig. 3E). GLP-1RA intervention was associated with a reduction in AG when compared to those given metformin or placebo (MD =  $-2.05$ ; 95% CI  $-2.93$  to  $-1.16$ ;  $P < 0.0001$ ; Fig. 3E). Funnel plots of the reductions in BMI, body weight, WC, WHR and AG of the patients indicated no publication bias (Fig. S2).

## Changes in glucose homeostasis

For glucose homeostasis, we compared the results for the reduction in fasting glucose and insulin levels, their levels at 2 h after OGTT and HOMA-IR. In terms of reduction in fasting glucose levels, 6 studies (with 252 and 235 subjects from the experimental and control groups, respectively) were included for analysis. Due to the heterogeneity presented in the included studies, ( $I^2 = 95\%$ ,  $P < 0.0001$ ), we used the random effects model (Fig. 4A). GLP-1RA intervention was not associated with a reduction in fasting glucose level when compared to those given metformin or placebo (MD =  $-0.12$ ; 95% CI  $-0.28$  to  $0.04$ ;  $P = 0.14$ ; Fig. 4A). For the subgroup analysis, the studies were classified based on whether the patients from the control group received metformin or placebo. As shown in Fig. S3A, GLP-1RA intervention was associated with a reduction in fasting glucose level when compared to placebo (MD =  $-0.29$ ; 95% CI  $-0.33$  to  $-0.25$ ;  $P < 0.0001$ ), but not metformin (MD =  $-0.02$ ; 95% CI  $-0.07$  to  $0.04$ ;  $P = 0.57$ ).

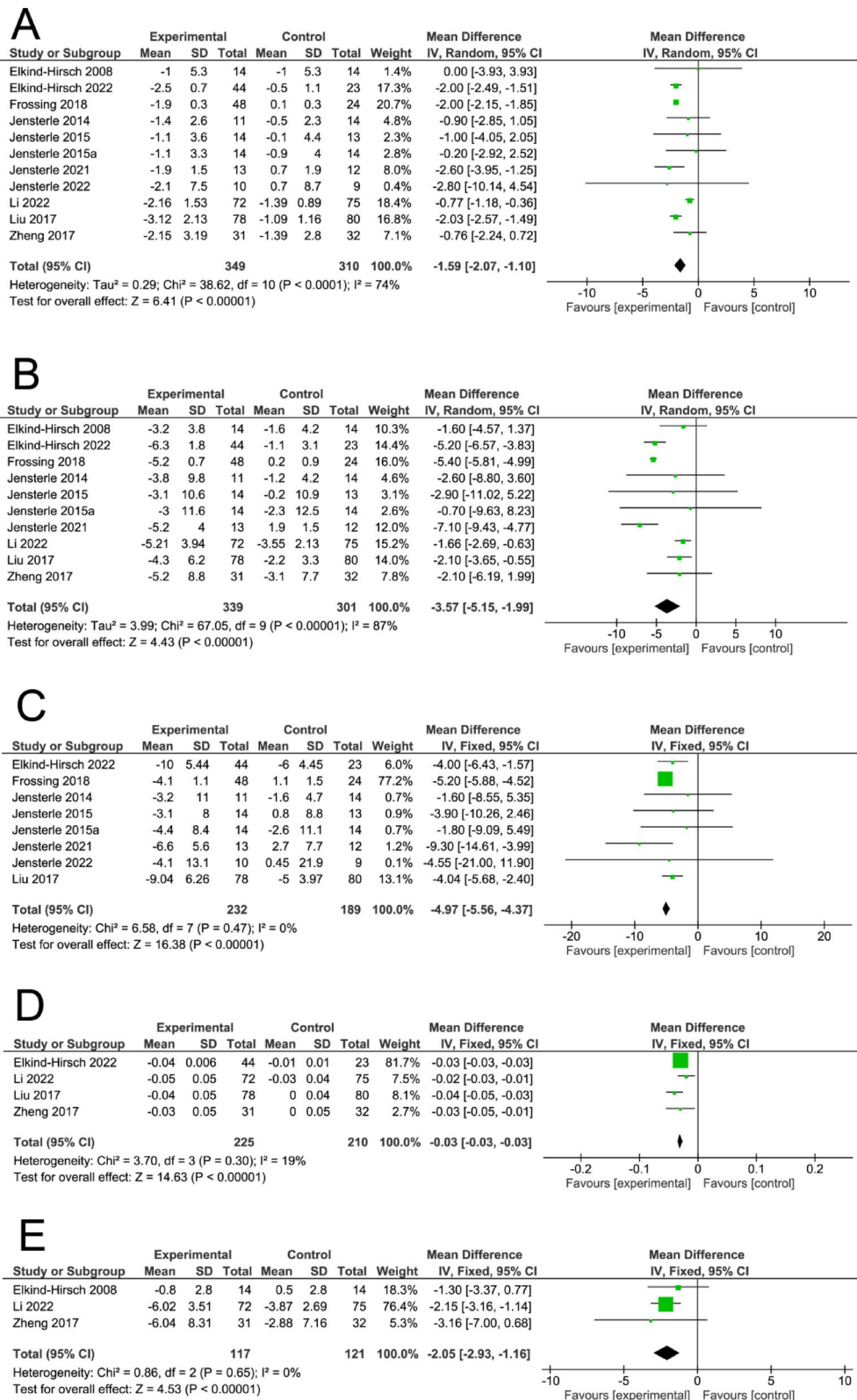
In terms of reduction in glucose levels at 2 h after OGTT, 5 studies (with 205 and 213 subjects the experimental and control groups, respectively) were included for analysis. Due to the heterogeneity presented in the included studies, ( $I^2 = 86\%$ ,  $P < 0.0001$ ), we used the random effects model (Fig. 4B). GLP-1RA intervention was associated with a reduction in glucose levels at 2 h after OGTT when compared to those given metformin or placebo (MD =  $-0.54$ ; 95% CI  $-1.01$  to  $0.07$ ;  $P = 0.02$ ; Fig. 4B). For the subgroup analysis, the studies were classified based on whether the patients from the control group received metformin or placebo. As shown in Fig. S3B, GLP-1RA intervention was associated with a reduction in glucose levels at 2 h after OGTT when compared to placebo (MD =  $-2.14$ ; 95% CI  $-3.33$  to  $-0.95$ ;  $P = 0.0004$ ), but not metformin (MD =  $-0.34$ ; 95% CI  $-0.76$  to  $0.09$ ;  $P = 0.12$ ).



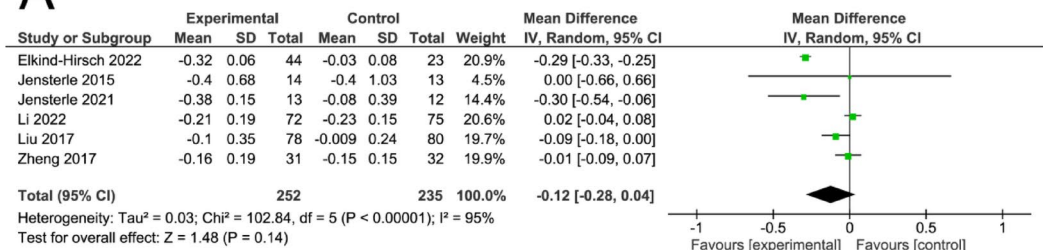
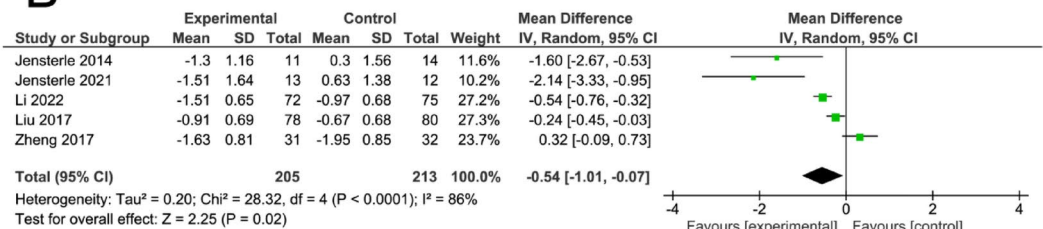
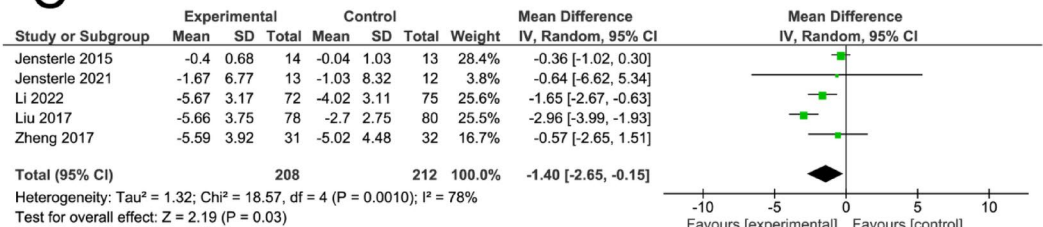
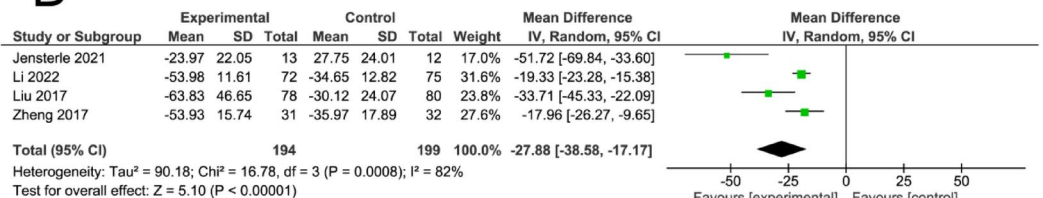
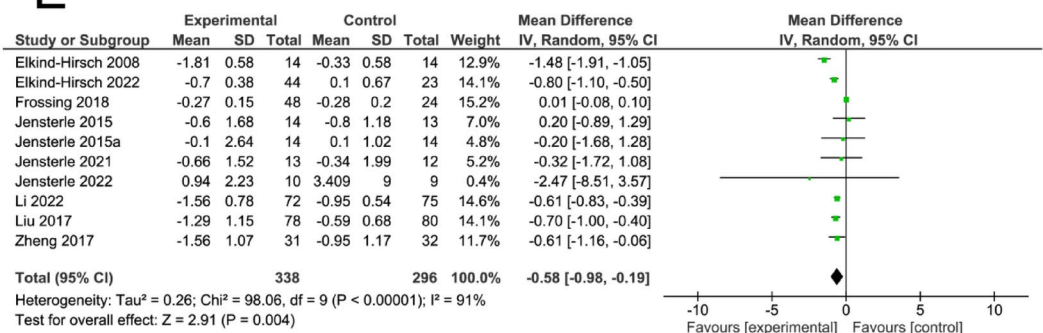


**Fig. 2.** A bias assessment of this study. (A) Risk of bias bar. (B) Risk of bias summary.

In terms of reduction in fasting insulin levels, 5 studies (with 208 and 212 subjects from the experimental and controls groups, respectively) were included for analysis. Due to the heterogeneity presented in the included studies, ( $I^2 = 78\%$ ,  $P = 0.001$ ), we used the random effects model (Fig. 4C). GLP-1RA intervention was associated with a reduction in fasting insulin levels when compared to those given metformin or placebo ( $MD = -1.40$ ; 95%



**Fig. 3.** A meta-analysis of BMI changes found in this study (A), body weight changes (B), WC (C), WHR (D) and AG (E).

**A****B****C****D****E**

**Fig. 4.** Meta-analysis of the fasting glucose (A), glucose at 2 h (B), fasting insulin (C), insulin at 2 h (D) and HOMA-IR (E) levels found in this study.



CI  $-2.65$  to  $-0.15$ ;  $P=0.03$ ; Fig. 4C). For the subgroup analysis, the studies were classified based on whether the patients from the control group had received metformin or placebo. As shown in Fig. S3C, GLP-1RA intervention was associated with a reduction in fasting insulin when compared to those given metformin (MD =  $-1.43$ ; 95% CI  $-2.75$  to  $-0.11$ ;  $P=0.03$ ), but not placebo (MD =  $-0.64$ ; 95% CI  $-6.62$  to  $5.34$ ;  $P=0.83$ ).

In terms of reduction in insulin levels at 2 h after OGTT, 5 studies (with 194 and 199 subjects from the experimental and control groups, respectively) were included for analysis. Due to the heterogeneity presented in the included studies, ( $I^2=82\%$ ,  $P=0.0008$ ), we used the random effects model (Fig. 4D). GLP-1RA intervention was associated with a reduction in insulin levels at h after OGTT when compared to those given metformin or placebo (MD =  $-27.88$ ; 95% CI  $-38.58$  to  $-17.17$ ;  $P<0.0001$ ; Fig. 4D). For the subgroup analysis, the studies were classified based on whether the patients from the control group had received metformin or placebo. As shown in Fig. S3D, GLP-1RA intervention was associated with a reduction in insulin levels at 2 h after OGTT when compared to metformin (MD =  $-22.18$ ; 95% CI  $-29.57$  to  $-14.79$ ;  $P<0.00001$ ) or placebo (MD =  $-51.72$ ; 95% CI  $-69.84$  to  $-33.60$ ;  $P<0.00001$ ).

In terms of reduction in HOMA-IR, 10 studies (with 338 and 296 subjects from the experimental and control groups, respectively) were included for analysis. Due to the heterogeneity presented in the included studies, ( $I^2=91\%$ ,  $P<0.00001$ ), we used the random effects model (Fig. 4E). GLP-1RA intervention was associated with a reduction in HOMA-IR when compared to those given metformin or placebo (MD =  $-0.58$ ; 95% CI  $-0.98$  to  $-0.19$ ;  $P=0.004$ ; Fig. 4E). For the subgroup analysis, the studies were classified based on whether the patients from the control group received metformin or placebo. As shown in Fig. S3E, GLP-1RA intervention was associated with a reduction in HOMA-IR when compared to metformin (MD =  $-0.73$ ; 95% CI  $-1.07$  to  $-0.38$ ;  $P<0.0001$ ) but not placebo (MD =  $-0.40$ ; 95% CI  $-0.98$  to  $-0.19$ ;  $P=0.26$ ). Funnel plots of reduction in the fasting glucose and insulin levels as well as the patients' levels at 2 h after OGTT, and their HOMA-IR indicated no publication bias (Fig. S4).

### Changes in hormones

In terms of the reduction in DHEAS, 6 studies (with 128 and 110 subjects from the experimental and control groups, respectively) were included in the analysis. Due to the presence of heterogeneity in the included studies ( $I^2=96\%$ ,  $P<0.00001$ ), the random effects model was used (Fig. 5A). GLP-1 RA intervention was not associated with changes in DHEAS levels when compared to those given metformin or placebo (MD =  $-12.84$ ; 95% CI  $-31.99$  to  $7.03$ ;  $P=0.21$ ; Fig. 5A). For subgroup analysis, the studies were classified based on whether the control group received metformin or placebo. As shown in Fig. S5A, GLP-1 RA intervention was associated with a reduction in DHEAS levels when compared to placebo (MD =  $-18.20$ ; 95% CI  $-23.13$  to  $-13.23$ ;  $P<0.0001$ ), but not when compared to those given metformin (MD =  $-10.83$ ; 95% CI  $-38.87$  to  $17.22$ ;  $P=0.45$ ).

In terms of the reduction in SHBG, 5 studies (with 151 and 153 subjects from the experimental and control groups, respectively) were included in the analysis. No heterogeneity was present in the included studies ( $I^2=0\%$ ,  $P=0.87$ ), and so a fixed effects model was used (Fig. 5B). GLP-1 RA intervention was not associated with changes in SHBG levels when compared to those given metformin or placebo (MD =  $0.96$ ; 95% CI  $-1.05$  to  $2.97$ ;  $P=0.35$ ; Fig. 5B).

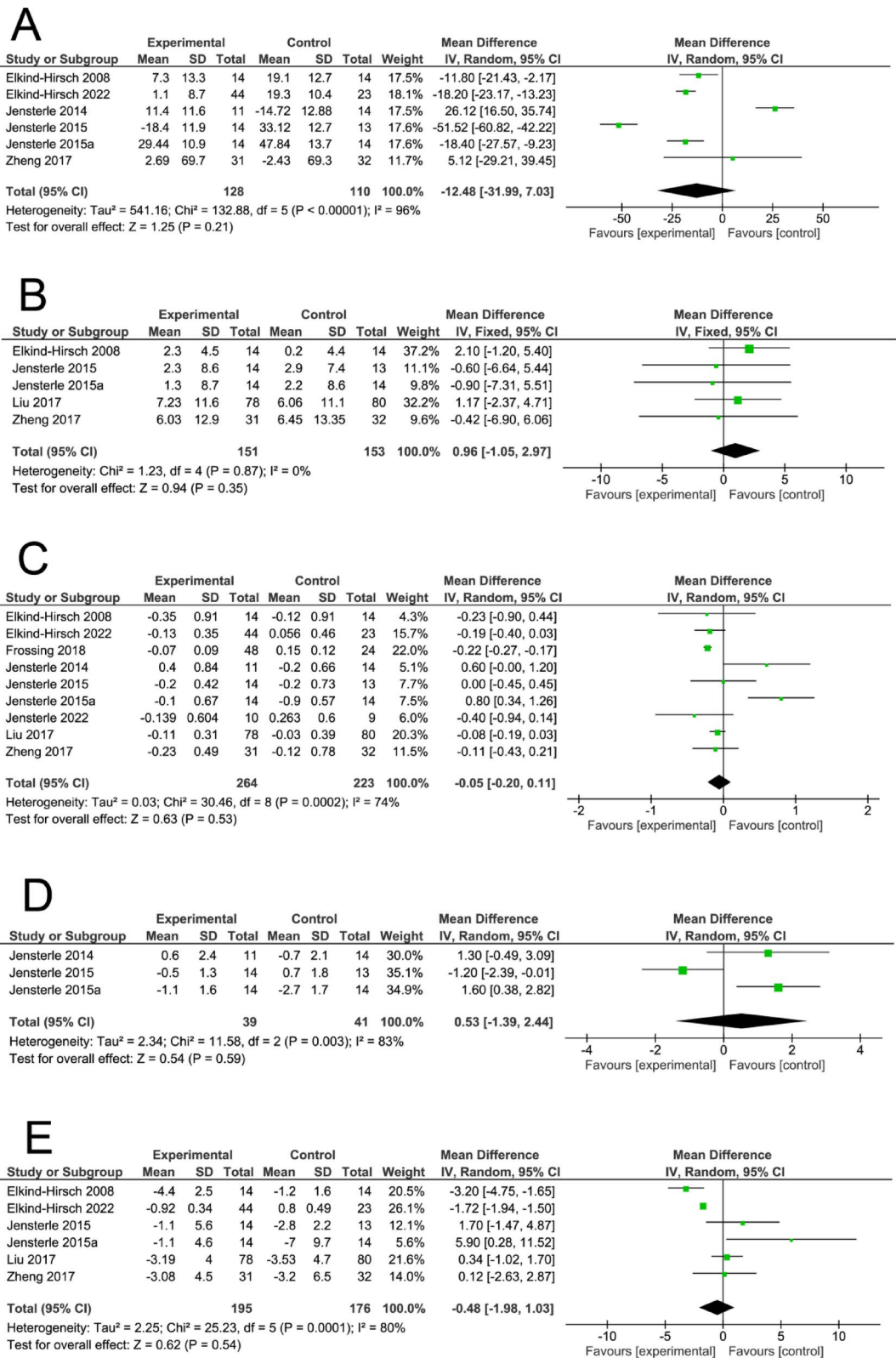
In terms of the reduction in total testosterone, 9 studies (with 264 and 223 subjects from the experimental and control groups, respectively) were included in the analysis. Due to the presence of heterogeneity in the included studies ( $I^2=74\%$ ,  $P=0.0002$ ), the random effects model was used (Fig. 5C). GLP-1 RA intervention was not associated with changes in total testosterone when compared to those given metformin or placebo (MD =  $-0.05$ ; 95% CI  $-0.20$  to  $0.11$ ;  $P=0.53$ ; Fig. 5C). For subgroup analysis, the studies were classified based on whether the control group received metformin or placebo. As shown in Fig. S5B, GLP-1 RA intervention was associated with a reduction in total testosterone levels when compared to those given placebo (MD =  $-0.22$ ; 95% CI  $-0.27$  to  $-0.17$ ;  $P<0.0001$ ), but not to those given metformin (MD =  $0.13$ ; 95% CI  $-0.16$  to  $0.42$ ;  $P=0.37$ ).

In terms of the reduction in levels of free testosterone, 3 studies (with 39 and 41 subjects from the experimental and control groups, respectively) were included in the analysis. Due to the heterogeneity in the included studies ( $I^2=83\%$ ,  $P=0.003$ ), the random effects model was used (Fig. 5D). GLP-1 RA intervention was not associated with changes in free testosterone when compared to those given metformin or placebo (MD =  $0.53$ ; 95% CI  $-1.39$  to  $2.44$ ;  $P=0.59$ ; Fig. 5D).

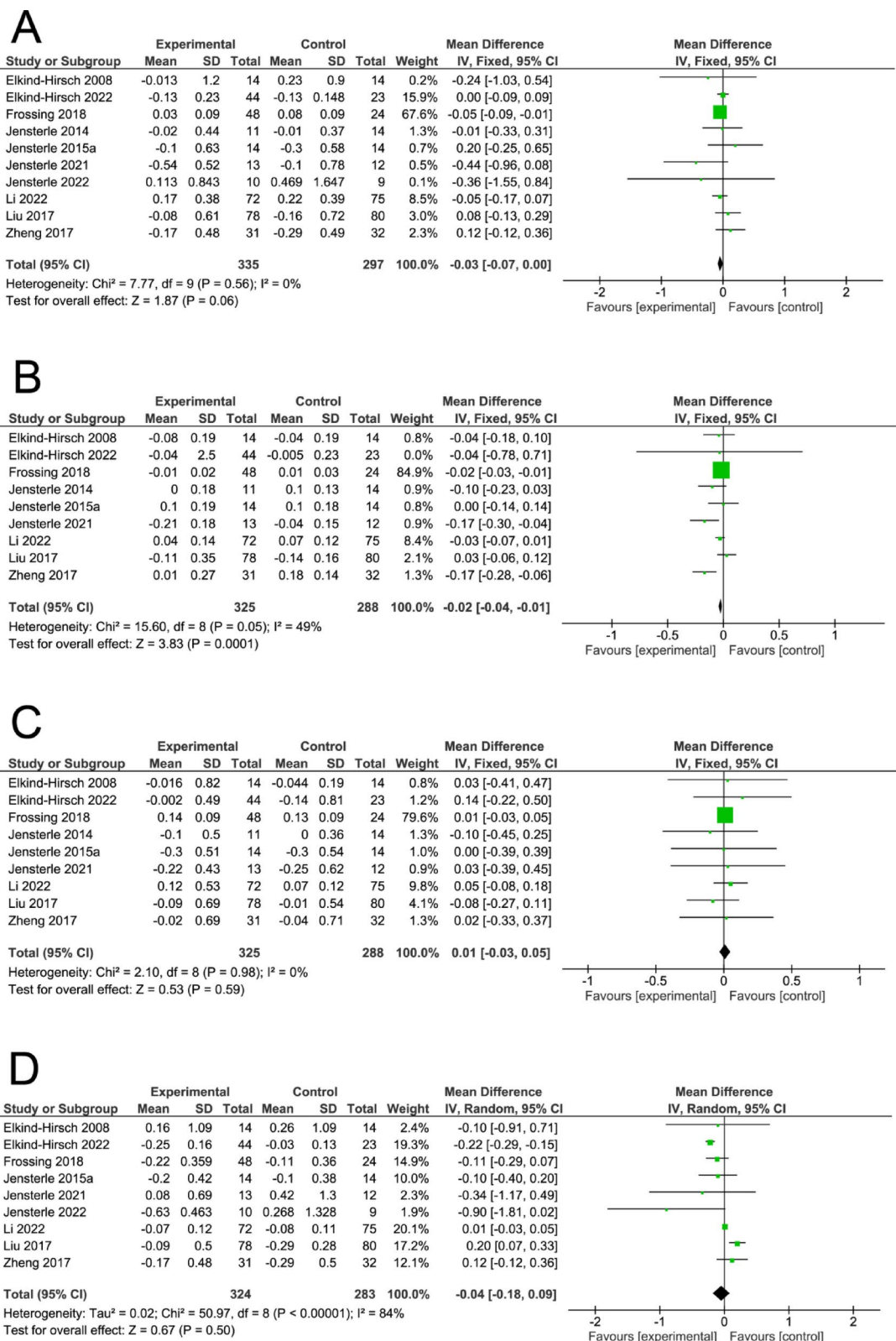
In terms of the reduction in FAI, 6 studies (with 195 and 176 subjects from the experimental and control groups, respectively) were included in the analysis. Due to the presence of heterogeneity in the included studies ( $I^2=80\%$ ,  $P=0.0001$ ), the random effects model was used (Fig. 5E). GLP-1 RA intervention was not associated with changes in FAI when compared to those given metformin or placebo (MD =  $-1.72$ ; 95% CI  $-1.94$  to  $-1.50$ ;  $P=0.54$ ; Fig. 5E). For subgroup analysis, the studies were classified based on whether the control group received metformin or placebo. As shown in Fig. S5E, GLP-1 RA intervention was associated with a reduction in FAI when compared to those given placebo (MD =  $-0.48$ ; 95% CI  $-1.98$  to  $-1.50$ ;  $P<0.0001$ ), but not to those given metformin (MD =  $0.26$ ; 95% CI  $-2.08$  to  $2.61$ ;  $P=0.83$ ). Funnel plots of the reduction in DHEAS, SHBG, total testosterone, free testosterone and FAI levels indicated no publication bias (Fig. S6).

### Changes in total cholesterol, HDL, LDL and TG

In terms of reduction in total cholesterol, 10 studies (with 335 and 237 subjects from the experimental and control groups, respectively) were included for analysis. No heterogeneity was presented in the included studies ( $I^2=0\%$ ,  $P=0.56$ ), and we used the fixed effects model (Fig. 6A). GLP-1RA intervention was not associated with the changes in total cholesterol levels when compared to those given metformin or placebo (MD =  $-0.03$ ; 95% CI  $-0.07$  to  $0.00$ ;  $P=0.06$ ; Fig. 6A). For the subgroup analysis, the studies were classified based on whether the patients from the control group received metformin or placebo. As shown in Fig. S7A, GLP-1RA intervention



**Fig. 5.** Meta-analysis of the DHEAS (A), SHBG (B), total testosterone (C), free testosterone (D) and FAI (E) levels found in this study.



**Fig. 6.** Meta-analysis of the total cholesterol (A), HDL (B), LDL (C) and TG (D) levels found in this study.

was associated with a reduction in total cholesterol when compared to placebo ( $MD = -0.04$ ; 95% CI  $-0.08$  to  $0.00$ ;  $P = 0.03$ ) but not metformin ( $MD = 0.01$ ; 95% CI  $-0.08$  to  $0.10$ ;  $P = 0.83$ ).

In terms of reduction in total HDL levels, 9 studies (with 325 and 288 subjects from the experimental and control groups, respectively) were included for analysis. No heterogeneity was presented in the included studies

( $I^2 = 49\%$ ,  $P = 0.05$ ), and we used the fixed effects model (Fig. 6B). GLP-1RA intervention was associated with a reduction in HDL when compared to those given metformin or placebo (MD =  $-0.02$ ; 95% CI  $-0.04$  to  $-0.01$ ;  $P = 0.0001$ ; Fig. 6B). For the subgroup analysis, the studies were classified based on whether the patients from the control group received metformin or placebo. As shown in Fig. S7B, GLP-1RA intervention was associated with a reduction in HDL when compared to placebo (MD =  $-0.02$ ; 95% CI  $-0.03$  to  $-0.01$ ;  $P = 0.001$ ) but not metformin (MD =  $-0.04$ ; 95% CI  $-0.07$  to  $-0.01$ ;  $P = 0.83$ ).

In terms of reduction in total LDL levels, 9 studies (with 325 and 288 subjects from the experimental and control groups, respectively) were included for analysis. No heterogeneity was presented in the included studies ( $I^2 = 0\%$ ,  $P = 0.98$ ), and we used the fixed effects model (Fig. 6C). GLP-1RA intervention was associated with a reduction in LDL when compared to those given metformin or placebo (MD =  $0.01$ ; 95% CI  $-0.03$  to  $0.05$ ;  $P = 0.59$ ; Fig. 6C). For the subgroup analysis, the studies were classified based on whether the patients from the control group received metformin or placebo. As shown in Fig. S7C, GLP-1RA intervention was not associated with a reduction in LDL when compared to placebo (MD =  $0.01$ ; 95% CI  $-0.03$  to  $-0.06$ ;  $P = 0.001$ ) or metformin (MD =  $0.00$ ; 95% CI  $-0.09$  to  $0.10$ ;  $P = 0.92$ ).

In terms of reduction in TG levels, 9 studies (with 324 and 283 subjects from the experimental and control groups, respectively) were included for analysis. Due to the heterogeneity presented in the included studies ( $I^2 = 84\%$ ,  $P < 0.0001$ ), we used the random effects model (Fig. 6D). GLP-1RA intervention was not associated with reduction in TG levels when compared to those given metformin or placebo (MD =  $-0.04$ ; 95% CI  $-0.18$  to  $0.09$ ;  $P = 0.50$ ; Fig. 6D). For the subgroup analysis, the studies were classified based on whether the patients from the control group received metformin or placebo. As shown in Fig. S7D, GLP-1RA intervention was associated with a reduction in TG when compared to placebo (MD =  $-0.20$ ; 95% CI  $-0.18$  to  $0.09$ ;  $P = 0.001$ ) but not metformin (MD =  $0.07$ ; 95% CI  $-0.05$  to  $0.18$ ;  $P = 0.26$ ). Funnel plots of reduction in total cholesterol, HDL, LDL and TG indicated no publication bias (Fig. S8).

### Safety assessment of GLP-1RAs

In terms of nausea, 11 studies (with 429 and 378 subjects from the experimental and control groups, respectively) were included for analysis. Due to the heterogeneity presented in the included studies ( $I^2 = 52\%$ ,  $P = 0.02$ ), we used the random effects model (Fig. 7A). GLP-1RA intervention was associated with higher nausea events when compared to the patients given metformin or placebo (OR =  $3.07$ ; 95% CI  $1.56$  to  $6.03$ ;  $P = 0.02$ ; Fig. 7A). For the subgroup analysis, the studies were classified based on whether the patients from the control group received metformin or placebo. As shown in Fig. S9A, GLP-1RA intervention was associated with increased nausea events when compared to placebo (OR =  $5.33$ ; 95% CI  $1.53$  to  $18.63$ ;  $P = 0.009$ ) or metformin (OR =  $2.58$ ; 95% CI  $1.15$  to  $5.76$ ;  $P = 0.02$ ).

In terms of vomiting, 7 studies (with 381 and 329 subjects from the experimental and control groups, respectively) were included for analysis. No heterogeneity was presented in the included studies ( $I^2 = 0\%$ ,  $P = 0.92$ ), and we used the fixed effects model (Fig. 7B). GLP-1RA intervention was associated with higher vomiting events when compared to the patients given metformin or placebo (OR =  $2.05$ ; 95% CI  $1.04$  to  $4.06$ ;  $P = 0.04$ ; Fig. 7B). For the subgroup analysis, the studies were classified based on whether the patients from the control group received metformin or placebo. As shown in Fig. S9B, GLP-1RA intervention was not associated with increased vomiting events when compared to placebo (OR =  $5.99$ ; 95% CI  $0.32$  to  $112.41$ ;  $P = 0.23$ ) or metformin (OR =  $1.85$ ; 95% CI  $0.91$  to  $3.76$ ;  $P = 0.09$ ).

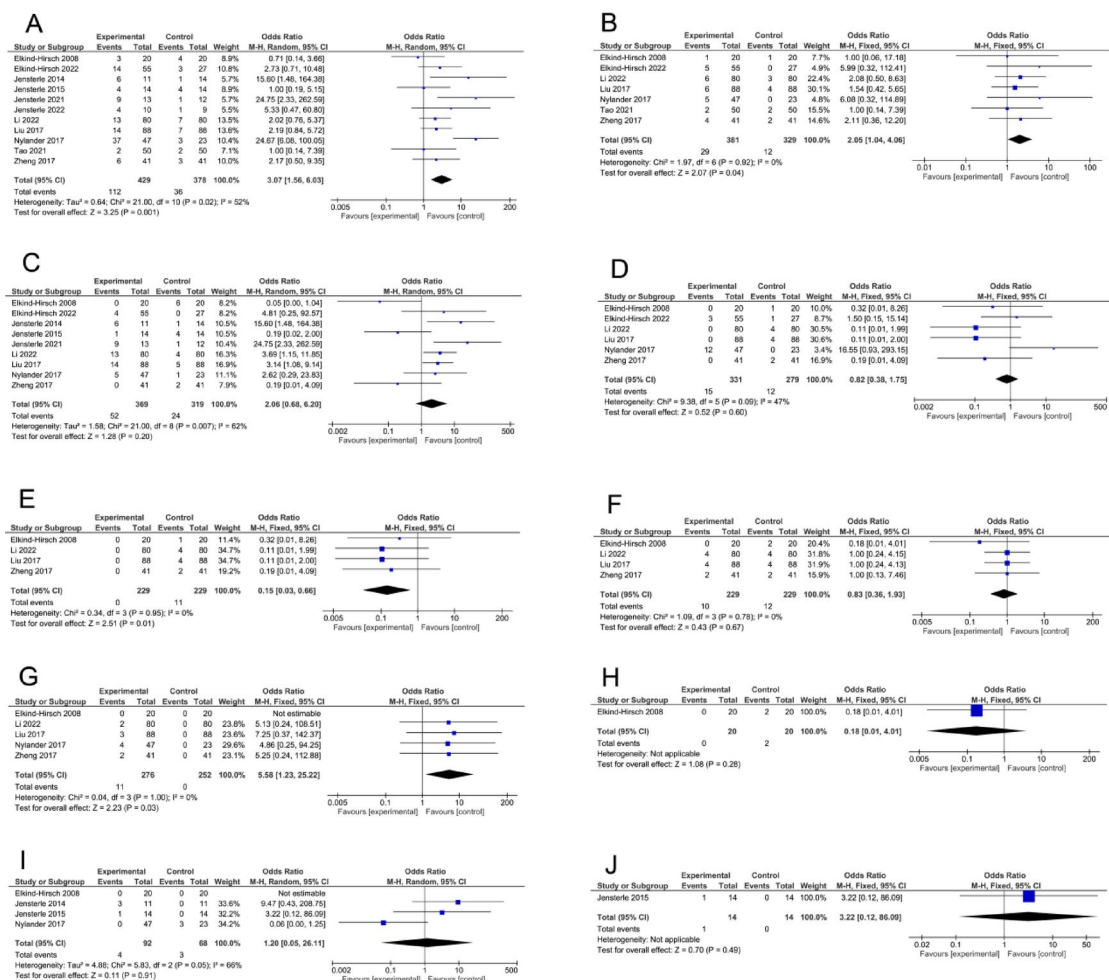
In terms of diarrhea, 9 studies (with 369 and 319 subjects from the experimental and control groups, respectively) were included for analysis. No heterogeneity was presented in the included studies ( $I^2 = 0\%$ ,  $P = 0.39$ ), and we used the fixed effects model (Fig. 7C). GLP-1RA intervention was not associated with higher diarrhea events when compared to the patients given metformin or placebo (OR =  $2.06$ ; 95% CI  $0.58$  to  $6.20$ ;  $P = 0.20$ ; Fig. 7C). For the subgroup analysis, the studies were classified based on whether the patients from the control group received metformin or placebo. As shown in Fig. S9C, GLP-1RA intervention was not associated with increased diarrhea events when compared to placebo (OR =  $13.08$ ; 95% CI  $2.06$  to  $82.80$ ;  $P = 0.006$ ) or metformin (OR =  $1.37$ ; 95% CI  $0.40$  to  $4.67$ ;  $P = 0.6$ ).

In terms of constipation, 7 studies (with 331 and 279 subjects from the experimental and control groups, respectively) were included for analysis. No heterogeneity was presented in the included studies ( $I^2 = 47\%$ ,  $P = 0.09$ ), and we used the fixed effects model (Fig. 7D). GLP-1RA intervention was not associated with higher constipation events when compared to the patients given metformin or placebo (OR =  $0.82$ ; 95% CI  $0.38$  to  $1.75$ ;  $P = 0.60$ ; Fig. 7D). For the subgroup analysis, the studies were classified based on whether the patients from the control group received metformin or placebo. As shown in Fig. S9D, GLP-1RA intervention was not associated with increased constipation events when compared to placebo (OR =  $1.50$ ; 95% CI  $0.15$  to  $15.14$ ;  $P = 0.73$ ) or metformin (OR =  $0.75$ ; 95% CI  $0.33$  to  $1.70$ ;  $P = 0.49$ ).

In terms of stomachache, 4 studies (with 229 subjects from each of the groups) were included for analysis. No heterogeneity was presented in the included studies ( $I^2 = 0\%$ ,  $P = 0.96$ ), and we used the fixed effects model (Fig. 7D). GLP-1RA intervention was associated with lower stomachache events when compared to the patients given metformin or placebo (OR =  $0.15$ ; 95% CI  $0.03$  to  $0.66$ ;  $P = 0.01$ ; Fig. 7E). In terms of bloating, 4 studies (with 229 subjects from each of the groups) were included for analysis. No heterogeneity was presented in the included studies ( $I^2 = 0\%$ ,  $P = 0.78$ ), and we used the fixed effects model (Fig. 7F). GLP-1RA intervention was not associated with increased bloating events when compared to those given metformin or placebo (OR =  $0.83$ ; 95% CI  $0.38$ – $1.93$ ;  $P = 0.67$ ; Fig. 7F).

In terms of dizziness, 5 studies (with 276 and 252 subjects from the experimental and control groups, respectively) were included for analysis. No heterogeneity was presented in the included studies ( $I^2 = 0\%$ ,  $P = 1.00$ ), and we used the fixed effects model (Fig. 7G). GLP-1RA intervention was associated with increased dizziness when compared to those given metformin or placebo (OR =  $5.58$ ; 95% CI  $1.23$ – $25.22$ ;  $P = 0.03$ ; Fig. 7G).





**Fig. 7.** Meta-analysis of nausea (A), vomiting (B), diarrhea (C), constipation (D), stomachache (E), bloating (F), dizziness (G), fatigue (H), headache (I) and insomnia (J) found in this study.

In terms of fatigue, 1 study (with 20 subjects from each of the groups) were included for analysis. GLP-1RA intervention was not associated with fatigue when compared to those given metformin or placebo ( $OR = 0.18$ ; 95% CI 0.01–4.01;  $P = 0.28$ ; Fig. 7H). In terms of headache, 4 studies (with 92 and 68 subjects from the experimental and control groups, respectively) were included for analysis. Due to the heterogeneity presented in the included studies ( $I^2 = 66\%$ ,  $P = 0.05$ ), we used the random effects model (Fig. 7I). GLP-1RA intervention was not associated with increased dizziness events when compared to those given metformin or placebo ( $OR = 1.20$ ; 95% CI 0.05–26.11;  $P = 0.91$ ; Fig. 7J).

In terms of insomnia, 1 study (with 14 subjects from each of the groups) were included for analysis. GLP-1RA intervention was not associated with insomnia events when compared to the patients given metformin or placebo ( $OR = 3.22$ ; 95% CI 0.12–86.09;  $P = 0.49$ ; Fig. 7J). Funnel plots of nausea, vomiting, diarrhea, constipation, stomachache, bloating, dizziness, fatigue, headache and insomnia indicated no publication bias (Fig. S10).

## Discussion

The findings from our meta-analysis suggested that GLP-1RAs were effective in improving the anthropometric parameters such as BMI, body weight, WC, WHR and AG, particularly when compared to the patients given either metformin or placebo. The consistent reductions in BMI and body weight across various studies highlight the potential of GLP-1RAs in managing PCOS-related conditions, even in populations where metformin has traditionally been the first-line therapy. These results are clinically significant, as GLP-1RAs may offer an alternative approach for patients with PCOS. Additionally, the significant reductions in WC and WHR align with the body of evidence suggesting that the visceral fat is a major contributor to the metabolic complications associated with PCOS, and GLP-1RAs can help target this specifically.

However, it is important to note the heterogeneity observed in some of the outcomes, particularly for BMI and body weight reductions. The random-effects model used in the analysis addresses this variation to some extent, but the underlying causes of the heterogeneity warrant further investigation. Differences in the study populations, treatment duration and adherence to the different GLP-1RA regimens might have contributed to the variations observed. For example, the studies included in this meta-analysis involved varying the patient



profiles, some of which included patients with more advanced metabolic disease conditions, potentially influencing the degree of weight reduction observed. Future studies could help clarify which specific subgroups of patients benefited the most from GLP-1RAs, whether this would be based on the baseline BMI, metabolic health or duration of therapy.

When examining the effects on glucose homeostasis, the results were mixed. While GLP-1RAs were associated with a reduction in glucose levels at 2 h post-OGTT and a modest decrease in fasting insulin and HOMA-IR, they were not significantly more effective than metformin in lowering fasting glucose levels. This could be attributed to the different mechanisms of action of these two drugs. Metformin primarily reduces hepatic glucose production, while GLP-1RAs enhance insulin secretion in response to meals<sup>20–22</sup>. Therefore, in patients where the fasting glucose is a more dominant feature of their hyperglycemia, metformin may be more appropriate, while GLP-1RAs could be better suited for those with postprandial hyperglycemia. The hormonal changes observed in our analysis further contribute to the therapeutic potential of GLP-1RAs, though the impact was less consistent compared to their effects on anthropometric measurements and glucose regulation. Specifically, no significant reductions in DHEAS, SHBG and testosterone levels were observed in the overall comparison with metformin or placebo. However, GLP-1RAs did show a favorable impact on these hormones when compared to placebo alone. This suggests that while GLP-1RAs may not outperform metformin in managing hormone levels, they are still beneficial in populations not already treated with metformin<sup>23–26</sup>. The heterogeneity observed in the hormonal analysis may stem from differences in baseline hormonal levels and other concurrent therapies used by the subjects in the included studies.

In terms of lipid profile management, GLP-1RAs showed modest effects. While total cholesterol and LDL levels were reduced, there was no significant differences in HDL and triglycerides. This highlights the limited role that GLP-1RAs play in lipid management, suggesting that additional lipid-lowering therapies may be necessary for comprehensive metabolic control<sup>27–29</sup>. Given that dyslipidemia is a key component of metabolic syndrome, and cardiovascular outcomes are of the utmost importance in managing such patients, a combination approach may yield better results than GLP-1RA monotherapy in this aspect<sup>30</sup>. Future studies evaluating the combination of GLP-1RAs with statins or other lipid-lowering agents could provide further insights into the optimal treatment strategies for such patients.

The safety outcomes of this meta-analysis highlighted significant gastrointestinal and neurological side effects associated with GLP-1RA interventions<sup>31,32</sup>. Notably, we found a significant increase in nausea events among participants receiving GLP-1RAs compared to those treated with metformin or placebo. This effect was particularly pronounced when the control group received a placebo. Additionally, vomiting occurrences were also elevated, although no significant differences were observed in subgroup analyses when comparing to those given either placebo or metformin. In contrast, GLP-1RAs did not significantly increase the rates of diarrhea, constipation and bloating, suggesting a relatively favorable gastrointestinal safety profile for these interventions. Interestingly, there was a notable decrease in stomachache events among those receiving GLP-1RAs. Conversely, dizziness was more frequently reported in the GLP-1RA group, indicating a potential safety concern in this domain. Other side effects, including fatigue, headache and insomnia, did not show significant differences when compared to the control group. Importantly, the funnel plot analysis demonstrated no evidence of publication bias, enhancing the credibility of our findings. Overall, while GLP-1RAs may offer metabolic benefits in PCOS management, the increased risk of nausea and dizziness should be carefully considered in clinical practice<sup>33</sup>.

Overall, our meta-analysis underscores the value of GLP-1RAs as a multifaceted therapeutic option, particularly in PCOS patients with obesity and IR. However, the variability in efficacy across different metabolic and hormonal outcomes suggested that individualized treatment strategies should be considered. More robust, long-term studies are needed to elucidate the long-term safety profiles of GLP-1RAs and their role in combination therapy for metabolic syndrome. In the meantime, the evidence supports GLP-1RAs as a strong alternative to metformin, especially in cases where weight loss is a primary treatment goal.

This meta-analysis study had some limitations regarding the efficacy of GLP-1RAs on the anthropometric measurements, glucose homeostasis and hormonal changes. Notably, the high levels of heterogeneity in the studies analyzed as well as other measures such as variability in study populations, interventions and methodologies, could have affected the reliability of the results obtained. While our methods focused on comparing GLP-1RAs to metformin or placebo, we acknowledge the possibility that additional background interventions may have been employed across some studies. However, the included studies generally lacked sufficient detail regarding these concurrent interventions, making it difficult to fully assess their potential impact on the outcomes. This absence of comprehensive reporting limits our ability to perform stratified or sensitivity analyses to determine how such interventions may have influenced the observed heterogeneity, particularly in metabolic and hormonal outcomes. While GLP-1RAs showed significant reductions in BMI, body weight and WC compared to either metformin or placebo, the lack of consistency in fasting glucose and hormone levels suggested that the impact of the interventions might have varied significantly across the different patient groups. Additionally, certain outcomes, such as reductions in DHEAS and total testosterone levels, were not consistently significant when compared to metformin, highlighting potential variations in responses based on the comparator group. Although the funnel plots indicated no publication bias, the variability in the findings calls for caution in interpreting the overall effectiveness of GLP-1RAs under these parameters.

## Conclusions

GLP-1RAs are effective in reducing body weight, BMI, and insulin resistance in patients with PCOS, particularly those with obesity or metabolic complications. These benefits support their role as an alternative or adjunct to metformin, especially when weight loss is a primary treatment goal. While side effects such as nausea and dizziness are more common, they are generally manageable and should be weighed against the potential metabolic improvements. The observed heterogeneity across studies highlights the importance of individualized treatment

strategies based on patient profiles and therapeutic goals. Clinically, these findings suggest that GLP-1RAs could be incorporated into PCOS management guidelines, particularly for patients who do not respond adequately to first-line therapies or present with postprandial hyperglycemia and central obesity. Their integration into care pathways offers a more tailored approach, potentially improving long-term outcomes. Future research should focus on identifying the most responsive patient subgroups, evaluating long-term safety, and exploring combination therapies to enhance metabolic and reproductive outcomes.

## Data availability

The data that support the findings of this study are available on request from the corresponding author (Bing Tan).

Received: 5 November 2024; Accepted: 22 April 2025

Published online: 13 May 2025

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## Acknowledgements

None.

## Author contributions

SL, MQ and BT designed the whole study; SL, YD and JH collected the data and performed the analysis; SL and ML prepared the figures and tables; SL, MQ, SRS and BT wrote the manuscript; all the authors approved the manuscript for submission.

## Funding

The Project for Enhancing Young and Middle-aged Teacher's Research Basis Ability in Colleges of Guangxi (Grant No.2023KY0576).

## Declarations

## Competing interests

The authors declare no competing interests.

## Ethical statement

Not applicable.

## Additional information

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1038/s41598-025-99622-4>.

**Correspondence** and requests for materials should be addressed to M.Q. or B.T.

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