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The safety and efficacy of liraglutide combined with metformin in clinical treatment of polycystic ovary syndrome patients: a meta-analysis

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Abstract

Objective This study aims to investigate the effectiveness and safety of the combination of liraglutide and metformin for clinical treatment of patients with polycystic ovary syndrome.

Methods Computerized searches were performed on PubMed, Embase, Web of Science, The Cochrane Library, CNKI, CBM, Wanfang, and VIP databases to collect randomized controlled trials(RCT) on the efficacy of metformin and liraglutide in the treatment of polycystic ovary syndrome. The search period spanned from the inception of the databases to August 2024. Following literature screening, data extraction, and risk of bias assessment in the included studies, two reviewers independently conducted meta-analysis using RevMan 5.4 software.

Results A total of 12 RCT involving 1096 patients were analyzed. The meta-analysis revealed that the group receiving metformin combined with liraglutide demonstrated superiority over the group receiving metformin alone in terms of body mass index (BMI), glucose levels, lipid levels, hormone levels, establishment of menstrual cycles, normal ovulation rate, and rate of spontaneous conception. However, the former group also exhibited a higher incidence of gastrointestinal reactions compared to the latter group.

Conclusion Current data indicates that the combination of liraglutide and metformin can effectively enhance glucose and lipid metabolism in Polycystic Ovary Syndrome infertility patients. Additionally, it can reduce serum sex hormone levels, leading to significant clinical therapeutic effects. This treatment also improves pancreatic islet and ovarian function, ultimately increasing the rate of ovulation and pregnancy. It is important to note that correct administration methods must be followed to minimize adverse reactions.

Keywords Polycystic ovary syndrome, Liraglutide, Metformin, Meta-analysis

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder that affects women of reproductive age. It is characterized by ovulatory dysfunction, ovarian changes, and increased androgen levels due to ovarian dysgenesia [1, 2]. PCOS is often associated with obesity, abnormal blood pressure, lipid abnormalities, glucose abnormalities, and pancreatic dysfunction, all of which pose a serious threat to women's health and safety [3]. The exact

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pathogenesis of PCOS is not fully understood, but it may be related to hyperandrogenemia, hyperinsulinemia, an imbalance of luteinizing hormone/follicle-stimulating hormone ratio, metabolic abnormalities, inflammation, advanced glycation end products, and endoplasmic reticulum stress [4, 5].Currently, the clinical treatment of polycystic ovary syndrome (PCOS) primarily involves adjusting menstrual cycles, antagonizing hyperandrogenism, controlling body weight, and reducing insulin resistance. Metformin is predominantly utilized to treat patients'insulin resistance by improving insulin sensitivity and reducing hepatic gluconeogenesis [6–8]. Glucagon-like peptide-1 (GLP-1) functions by improving patients'overweight and metabolism. Liraglutide, a GLP-1 receptor agonist, is more effective in treating PCOS patients with stage 1 and 2 insulin dysfunction [9–11]. Relevant studies have demonstrated that the combined use of metformin and liraglutide can better improve patients'blood glucose and lipid levels, effectively control their weight, and reduce the incidence of gestational diabetes mellitus. However, some studies have concluded that the clinical efficacy and safety of the combination of the two drugs are still debatable [12, 13]. Therefore, our objective is to conduct a comprehensive and systematic search of the relevant literature to provide a more reliable evidence-based approach to exploring the safety and efficacy of liraglutide combined with metformin in the clinical application of patients with PCOS. This will serve as a reference for clinicians.

Materials and methods

This meta-analysis was conducted in accordance with the recommendations of the Cochrane Handbook for the Systematic Evaluation of Interventions http://www.cochranehandbook.org and in accordance with the Prisma (preferred reporting entries for systematic evaluation and meta-analysis) checklist [14].

Search strategy

Computerized searches were conducted on PubMed, Embase, Web of Science, The Cochrane Library, CNKI, CBM, Wanfang, and VIP databases to identify comparative studies on the efficacy of metformin alone versus liraglutide combined with metformin in treating polycystic ovary syndrome. The search period covered all records up to August 2024. Please refer to Appendix Table 1 for the search terms and results used in the PubMed database search. Only English language literature was included, and randomized controlled trials (RCTs). Meta-analyses were performed to extract data from published papers. Literature selection, assessment of eligibility criteria, data extraction, and analysis of protocols registered in Prospero (CRD42024585579) were performed for our study protocols.

Eligibility and exclusion criteria

The selection criteria are as follows

Type of study: RCT;

Research objective: Patients diagnosed with polycystic ovary syndrome, regardless of their nationality, race, or age;

Intervention: Metformin was administered to the test group; while the control group received a combination of metformin and liraglutide;

Outcome indicator: The outcome indicators should include weight, waist circumference, body mass index(BMI), low-density lipoprotein(LDL), high-density lipoprotein(HDL), fasting blood glucose(FBG), two-hour postprandial glucose(2 hPG), glycosylated hemoglobin A_{1c}(HbA_{1c}), fasting insulin(FINS), homeostasis model assessment of insulin resistance(HOMA-IR), total cholesterol(TC), triglyceride(TG), luteinizing hormone(LH), follicle stimulating hormone(FSH), total testosterone(TT), anti-mullerian tubular hormone(AMH), rate of established menstrual cycles, rate of normal ovulation, rate of spontaneous conception, incidence of hypoglycemia, as well as the incidence and rate of gastrointestinal reactions;

The exclusion criteria are as follows

Literature with incomplete or no available data;

The inclusion of alternative treatment modalities in both the experimental and control groups should be considered;

Tests on cadavers or artificial models. Letters, reviews, editorials, systematic evaluations, and practice guidelines are also excluded;

Data extraction and quality assessment

Data extraction

Two evaluators extracted and recorded data in a spreadsheet. The data included patient demographics, author names, publication date, study design, sample size, follow-up duration, and measurements such as weight, waist circumference, BMI, LDL, HDL,FBG, 2 hPG, HbA_{1c}, FINS, HOMA-IR, TC, TG, LH, FSH, TT, AMH, rate of established menstrual cycles, rate of normal ovulation, rate of spontaneous conception, and incidence of hypoglycemic and gastrointestinal reactions. All data were recorded in a pre-generated Microsoft® Excel spreadsheet (Microsoft Corporation, Redmond Washington, USA). Any incomplete information was resolved by contacting the author. If this was not possible, the literature was excluded.

Quality assessment of the included studies

Risk of bias was assessed according to the Cochrane Collaboration and the following criteria: random

sequence generation, allocation concealment, participant blinding, outcome assessment blinding, incomplete outcome data, selective reporting, and other biases. Each item assessed as"yes","no"or"unclear"indic ates a low risk of bias, a high risk of bias and a lack of information or unknown risk of bias, respectively. For RCTs, we used modified Jadad and other scoring criteria to evaluate the quality of the included randomized controlled studies (RCTs), mainly from four aspects: (1) the generation of random sequences: yes (2 points), unclear (1 point), no (0 points). (2) Whether randomization is hidden: yes (2 points), unclear (1 point), no (0 points). (3) Whether to use blind method: yes (2 points), unclear (1 point), no (0 points). (4) Withdrawal and withdrawal with or without cases: the specific number and reasons are described (1 point), but the specific number or reasons are not described (0 point). The highest score is 7, of which 1–3 is regarded as low quality and 4–7 as high quality.

Statistical analysis

The outcome indicators investigated in this study included weight, waist circumference, BMI, LDL, HDL, FBG, 2 hPG, HbA_{1c}, FINS, HOMA-IR, TC, TG, LH, FSH, TT, AMH, rate of establishment of the menstrual cycle, rate of normal ovulation, rate of spontaneous conception, incidence of hypoglycemic reactions, and gastrointestinal reaction rate. The results are presented as mean differences (MDs) and 95% confidence intervals (CIs) for continuous outcomes such as weight, waist circumference, and BMI. For dichotomous outcomes such as the rate of established menstrual cycles, rate of normal ovulation, rate of spontaneous conception, incidence of hypoglycemic reactions, and incidence of gastrointestinal reactions, risk difference (OR) values with 95% CI were used. Statistical significance was set at $P < 0.05$. To summarize the trial results, a meta-analysis was performed using the software RevMan 5.3 (Cochrane Collaboration, Oxford, UK). The chi-square test and I^2 statistics were used, where a chi-square test result of $P > 0.05$ was considered to suggest statistical heterogeneity.The choice between fixed- and random-effects models was guided by the I^2 statistic: $I^2 < 50\%$ indicated low heterogeneity (fixed-effects), while $I^2 \geq 50\%$ warranted random-effects. Sensitivity analyses excluded outliers, and meta-regression adjusted for baseline BMI, age, and dosage.

Results

Literature search results

After eliminating duplicates, the initial screening process yielded 342 papers from various databases, including Pubmed ($n = 32$), Embase ($n = 49$), WebofScience ($n = 80$), CochraneLibrary ($n = 38$), CNKI ($n = 41$), CBM ($n = 30$), Wanfang ($n = 47$), and VIP ($n = 25$). A total of 192 papers were screened, and 142 studies were excluded at the title and abstract level. After reading the full text and applying criteria for data extraction and meta-analysis, 12 randomized controlled trials [12, 13, 15–24], comprising a total of 1096 patients, were ultimately included. These studies were rated as high quality. The study's inclusion and exclusion flow chart is presented in Fig. 1, and the basic characteristics of the included studies are provided in Table 1.

Evaluation of the methodological quality of the included studies

Quality evaluation results of 12 RCTs (Figs. 2 and 3).

Meta-analysis results

Weight

Five studies [12, 13, 16, 22, 24] comprising of 462 patients provided data on body weight and were included in the meta-analysis. Significant heterogeneity was observed among the studies ($P = 0.002$; $I^2 = 76\%$), therefore, a random-effects model was utilized for analysis. The pooled results revealed no significant difference in body weight between the combined treatment group and the treatment alone group (MD = −2.06, 95% CI: [−6.98,2.86], $P = 0.41$, Fig. 4).

Waist circumference

Five studies [13, 16, 17, 22, 24] comprising of 474 patients, provided data on waist circumference, which we included for meta-analysis. However, significant heterogeneity among the studies was observed ($P < 0.00001$; $I^2 = 89\%$), and therefore, a random-effects model was utilized for analysis. The pooled results indicated no significant difference in waist circumference between the combined treatment group and the treatment alone group (MD = −2.47, 95% CI: [−6.68, 1.75], $P = 0.25$, Fig. 5).

Body mass index

Nine studies [12, 13, 15–18, 22–24] (840 patients) were included in the meta-analysis, as they reported data on BMI. Significant heterogeneity was observed between the studies ($P < 0.00001$; $I^2 = 90\%$), thus a random-effects model was used for analysis. The results of the meta-analysis showed that the combination treatment group had a significantly smaller BMI than the treatment alone group (MD = −1.18, 95% CI: [−1.82,−0.54], $P = 0.0003$, Fig. 6).

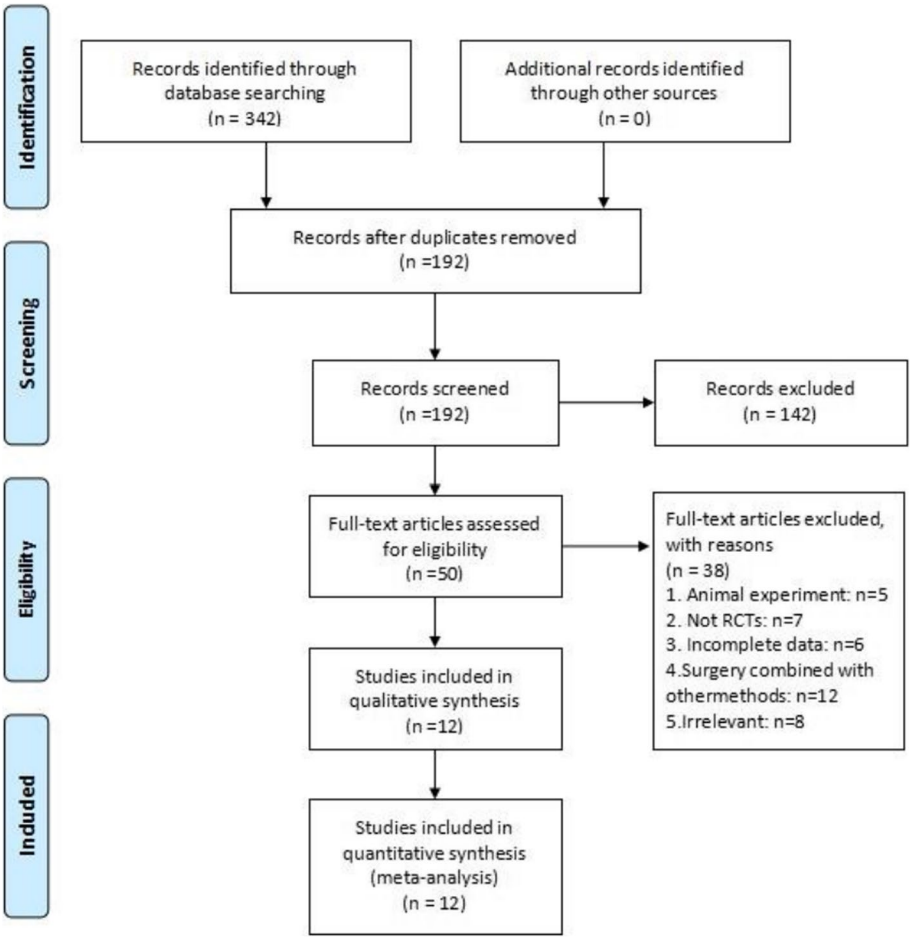

Fig. 1 Flow chart of inclusion and exclusion of studies

FBG

Ten studies [13, 15, 17–24], comprising a total of 872 patients, have reported data on FBG and were included in the meta-analysis. However, significant heterogeneity was observed between the studies ($P < 0.00001$; $I^2 = 96\%$), which required the use of a random-effects model for analysis. The pooled results indicate that FBG levels were lower in the combination treatment group than in the treatment alone group (MD = −0.95, 95% CI: [−1.32,−0.57], $P < 0.00001$, Fig. 7).

2 hPG

Nine studies [13, 17–24] (with a total of 852 patients) reported data on 2 hPG levels, and were included in our meta-analysis. Inter-study heterogeneity was found to be low ($P = 0.47$; $I^2 = 0\%$), allowing for the use of a fixed-effects model for data analysis. The pooled results revealed that the combination treatment group had significantly lower 2 hPG levels compared to the treatment alone group (MD = −0.98, 95% CI: [−1.01,−0.94], $P < 0.00001$, Fig. 8).

Glycosylated hemoglobin A1c

Four studies [16, 19, 21, 22] comprising of 428 patients reported data on HbA1c. Therefore, we have included them in the meta-analysis. However, there was significant heterogeneity observed between the studies ($P = 0.002$; $I^2 = 80\%$). Hence, a random-effects model was used for analysis. The pooled results indicated that the combination treatment group had significantly lower HbA1c levels than the treatment alone group (MD = −0.44, 95% CI: [−0.58,−0.30], $P < 0.00001$, Fig. 9).

Fasting insulin

Eight studies [12, 13, 15, 16, 19, 22–24], comprising a total of 754 patients, were included in our meta-analysis to provide data on FINS. However, significant heterogeneity was observed between the studies ($P < 0.00001$; $I^2 = 86\%$), and therefore, a random-effects model was used for analysis. Our pooled results indicate that the combination treatment group had significantly lower FINS levels than the treatment alone group (MD = −2.21, 95% CI: [−3.45,−0.97], $P = 0.0005$, Fig. 10).

Table 1 Characteristics of the included studies

Inclusion in the study	Country	Study design	Number of cases (T/C)	Age (mean ± SD,T/C)	BMI (kg/m^2,T/C)	Intervention	Results	Follow-up time（week）
Huang 2015 [16]	China	RCT	(87/85)	28.0±7.0/27.0±7.0	29.5±1.2/29.0±1.8	MET: 500 mg TID; MET + LIRA: MET, 500 mg TID + LIRA, 1.2 mg QD SC	①②③⑤⑥⑦⑧⑨⑩⑪⑫⑬⑭⑰⑱⑲⑳㉑	12、24
Sun 2021 [15]	China	RCT	(56/56)	28.9±10/28.3±10.0	24.5±1.6/24.7±1.4	MET: 500 mg TID; MET + LIRA: MET, 500 mg TID + LIRA, 1.2 mg QD SC	③④⑦⑧⑬⑭⑯⑳	12
Liang 2021 [17]	China	RCT	(33/33)	28.41±3.20/28.36±3.18	27.99±0.54/28.12±0.55	MET: 1000 mg BID; MET + LIRA: MET, 1000 mg BID + LIRA, 0.6 mg TID SC	①②③④⑤⑧⑬⑭⑯⑳	12、16
Yang 2022 [18]	China	RCT	(50/50)	31.5±3.7/32.2±3.3	27.98±0.56/28.11±0.54	MET: 1000 mg BID; MET + LIRA: MET, 1000 mg BID + LIRA, 0.6 mg TID SC	③④⑤⑧⑬⑭⑯	12
Huang 2023	China	RCT	(40/40)	30.41±1.37/30.38±3.31	NR/NR	MET: 500 mg BID; MET + LIRA: MET, 500 mg BID + LIRA, 1.2 mg QD SC	④⑥⑦⑧⑨⑩⑪⑫⑭⑮⑱⑲	12
Tan 2022 [20]	China	RCT	(46/46)	28.98±3.52/29.34±3.48	28.98±1.48/29.54±1.39	MET: 1000 mg BID; MET + LIRA: MET, 1000 mg BID + LIRA, 1.2 mg QD SC	④⑤⑥⑧⑨⑩⑪⑫⑬⑭⑮⑰⑱⑲⑳㉑	12、16
Zhang 2019 [21]	China	RCT	(42/42)	26.32±2.42/26.34±2.39	27.84±3.45/27.29±3.42	MET: 500 mg TID; MET + LIRA: MET, 500 mg TID + LIRA, 1.2 mg QD SC	④⑤⑥⑨⑩⑪⑫⑳㉑	12、16
Hao 2020 [22]	China	RCT	(93/93)	30.23±3.75/31.29±4.85	100.35±11.82/99.74±7.99	MET: 1000 mg BID; MET + LIRA: MET, 1000 mg BID + LIRA, 1.2 mg QD SC	①②③④⑤⑦⑧⑮⑳	12

Table 1 (continued)

Inclusion in the study	Country	Study design	Number of cases (T/C)	Age (mean ± SD,T/C)	BMI (kg/m^2,T/C)	Intervention	Results	Follow-up time（week)
Yang 2021 [23]	China	RCT	(50/50)	27.12±5.29/26.82±5.48	27.85±1.34/28.03±1.22	MET: 250 mg TID; MET + LIRA: MET, 250 mg TID + LIRA, 1.2 mg QD SC	③④⑤⑦⑧⑭⑮⑰⑱⑲⑳	12
Xing 2022 [12]	China	RCT	(27/25)	25.85±4.45/23.52±4.65	29.69±3.44/28.80±4.25	MET: 1000 mg BID; MET + LIRA: MET, 1000 mg BID + LIRA, 1.2 mg QD SC	①③⑦⑧⑬⑭⑮	12
Salamun 2018 [13]	Ljubljana	RCT	(13/14)	30.1±3.6/31.1±4.7	37.8±3.0/35.5±4.9	MET: 1000 mg BID; MET + LIRA: MET, 1000 mg BID + LIRA, 1.2 mg QD SC	①②③④⑤⑦⑧⑮⑳	12
Jensterle Sever2014 [24]	Ljubljana	RCT	(11/14)	31.1±5.1/31.3±9.4	37.6±5.1/36.6±3.5	MET: 1000 mg BID; MET + LIRA: MET, 1000 mg BID + LIRA, 1.2 mg QD SC	①②③④⑤⑦⑧⑩⑪⑫⑮⑳㉑	12

T/C = Test group/Control group;NR=not-reported;①=Weight;②=waist circumference;③=BMI;④=FBG;⑤=2 hPG;⑥=HbA1c

⑦=FINS;⑧=HOMA-IR;⑨=TC;⑩=TG;⑪=LDL;⑫=HDL;⑬=LH;⑭=FSH;⑮=TT;⑯=AMH;⑰=Establishing the Rate of Menstrual Cycle;⑱=Normal ovulation rate;⑲=natural conception rate;⑳=Incidence of gastrointestinal reactions;㉑=Incidence of hypoglycemic react

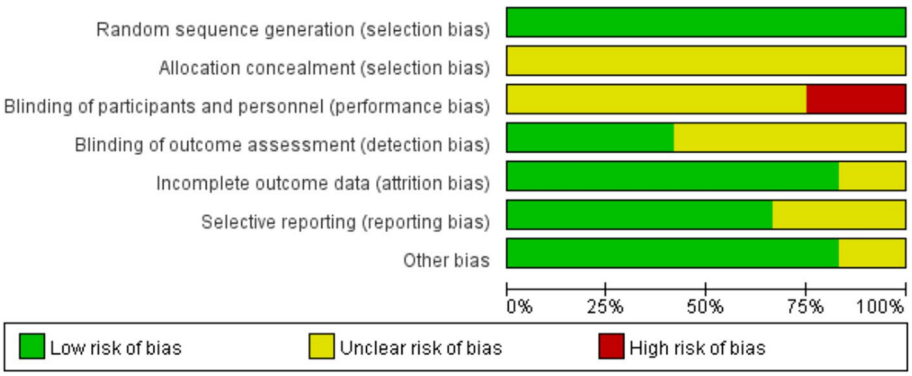

Fig. 2 Risk of bias assessment: domain-specific ratings

Homeostasis model assessment of insulin resistance

Eleven studies [12, 13, 15–20, 22–24] comprising 1012 patients were included in our meta-analysis as they reported data on HOMA-IR. There was significant heterogeneity among these studies ($P < 0.00001$; $I^2 = 90\%$), and thus, we used a random-effects model for analysis. The pooled results revealed that the HOMA-IR was significantly lower in the combination treatment group as compared to the treatment alone group (MD = −0.82, 95% CI: [−1.05,−0.59], $P < 0.00001$, Fig. 11).

Total cholesterol

Four separate studies [16, 19–21], consisting of 428 patients, provided data on TC which we included in our meta-analysis. However, we observed significant heterogeneity between the studies ($P < 0.00001$; $I^2 = 91\%$), thus necessitating the use of a random-effects model for analysis. Our pooled results showed that TC levels were lower in the combination therapy group as compared to the treatment alone group (MD = −0.90, 95% CI: [−1.38,−0.43], $P < 0.00001$; Fig. 12).

Triglyceride

Five studies [16, 19–21, 24] comprising of 453 patients reported data on TG. Hence, we included them in the Meta-analysis. However, there was significant heterogeneity between the studies ($P < 0.00001$; $I^2 = 92\%$); therefore, we used a random-effects model for analysis. The

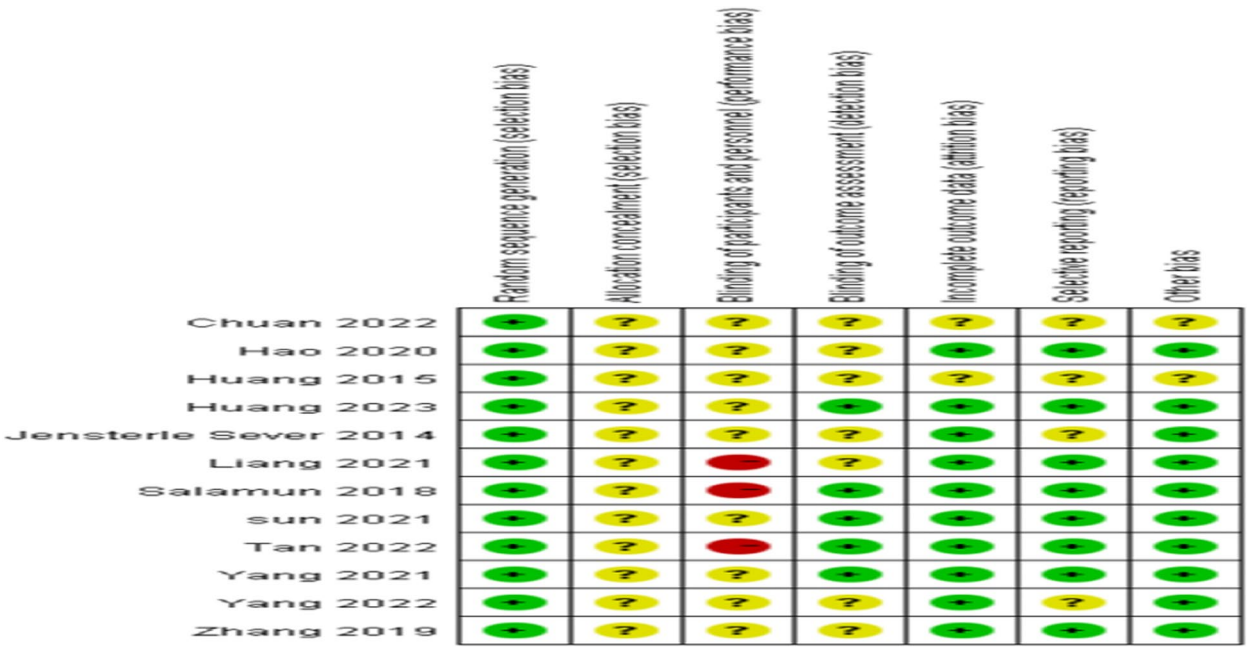

Fig. 3 Summary of risk of bias across included studies

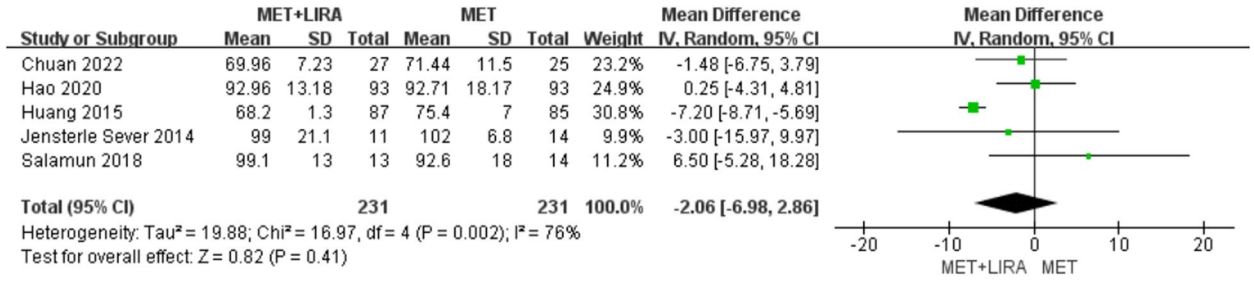

Fig. 4 Weight

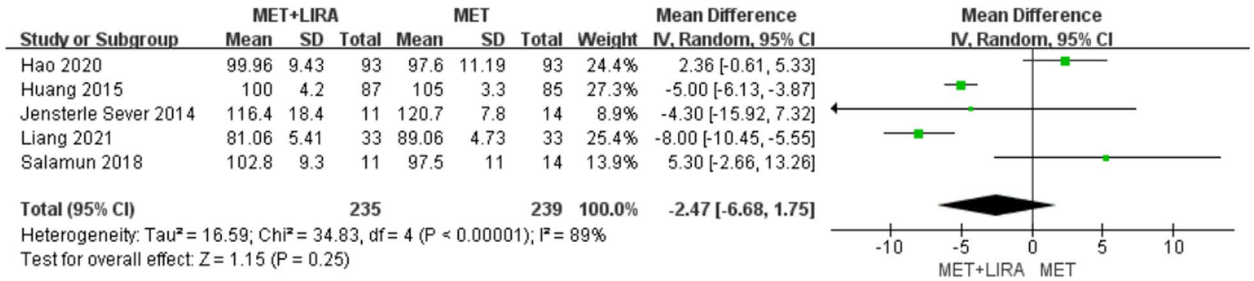

Fig. 5 Waist circumference

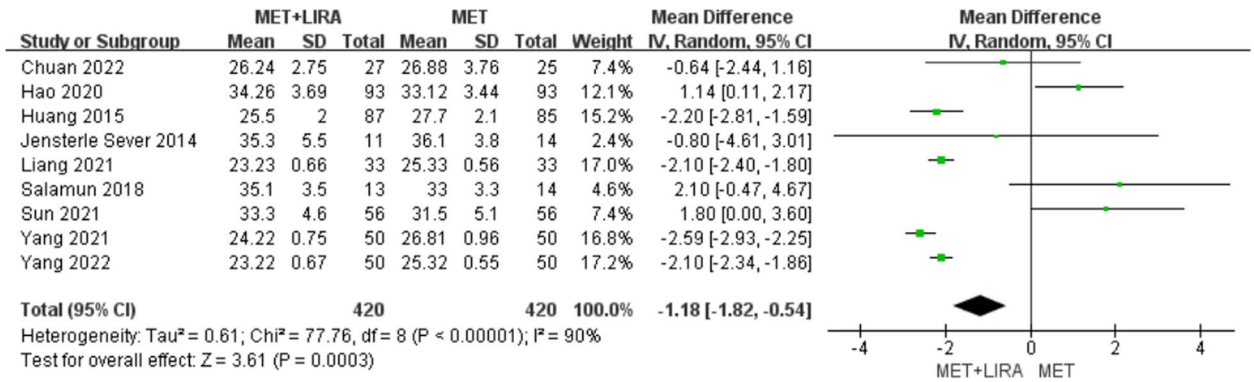

Fig. 6 Body mass index

pooled results indicated that TG levels were lower in the combination treatment group than in the treatment alone group (MD = −0.65, 95% CI: [−0.99,−0.31], $P < 0.00001$, Fig. 13).

Low-density lipoprotein

Five studies [16, 19–21, 24] involving a total of 453 patients provided LDL data, which we included in the meta-analysis. However, we observed significant heterogeneity among the studies ($P < 0.00001$; $I^2 = 97\%$), therefore, we used a random-effects model for analysis. The pooled results showed no significant difference in LDL levels between the combination therapy group and the group receiving treatment alone (MD = −0.31, 95% CI: [−0.99, 0.37], $P = 0.37$, Fig. 14).

High-density lipoprotein

Five studies [16, 19–21, 24] comprising 453 patients reported data on HDL, which we included in our meta-analysis. However, significant heterogeneity was observed between the studies ($P < 0.0001$; $I^2 = 84\%$), and therefore, a random-effects model was used for the analysis. The pooled results revealed no significant difference in HDL between the combination treatment group and the

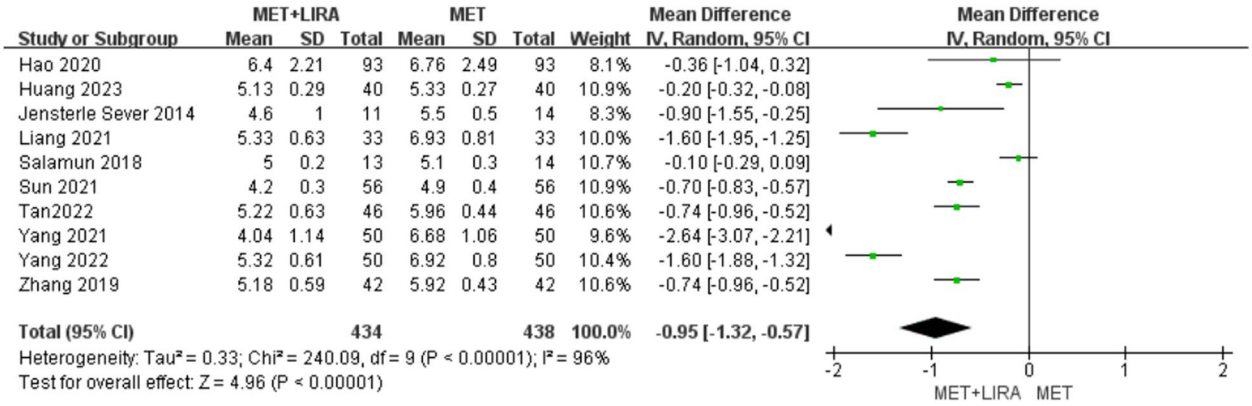

Fig. 7 Fasting blood glucose

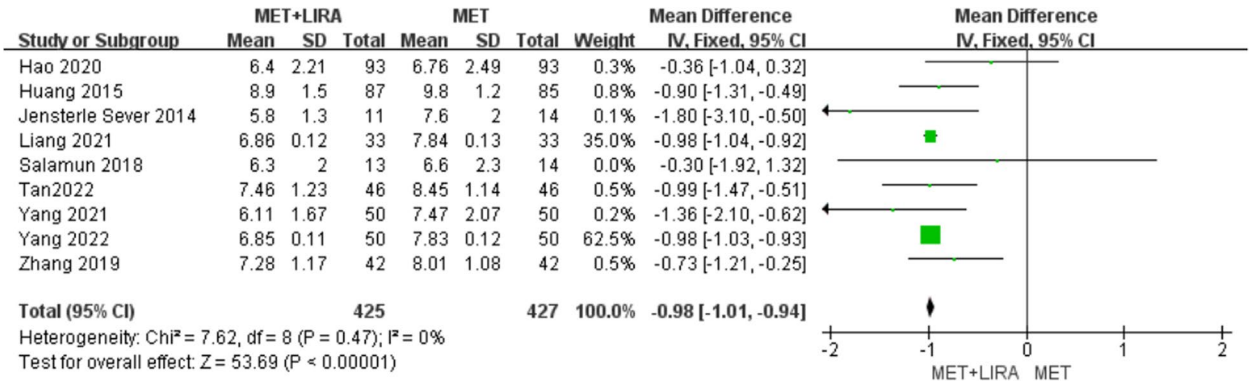

Fig. 8 Two-hour postprandial glucose

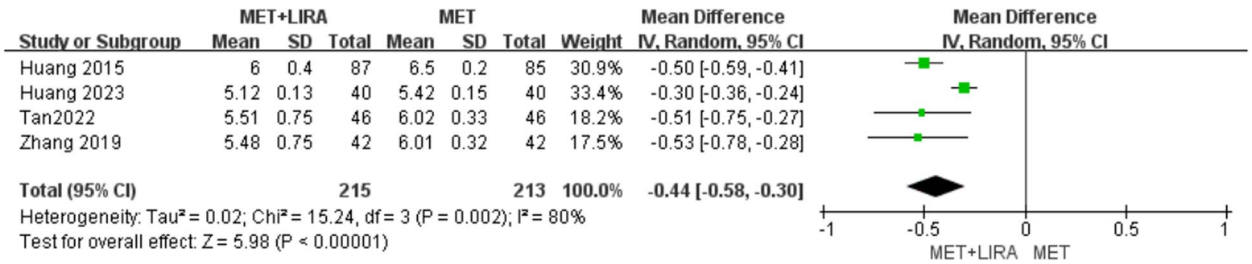

Fig. 9 Glycosylated hemoglobin A1c

treatment alone group (MD = 0.23, 95% CI: [−0.04,0.49], P = 0.09, Fig. 15).

Luteinizing hormone

Seven studies [12, 15–18, 20, 23], involving a total of 703 patients, reported data on LH levels. Therefore, we included them in the meta-analysis. Due to significant heterogeneity between the studies (P < 0.00001; I^2 = 92%), a random-effects model was used for analysis. The pooled results indicate that LH levels were lower in the combination treatment group compared to the treatment alone group (MD = −2.66, 95% CI: [−3.59,−1.73], P < 0.00001,16, Fig. 16).

Follicle stimulating hormone

Eight studies [12, 15–20, 23], comprising a total of 774 patients, have reported data on FSH. These studies were included in the meta-analysis. However, significant heterogeneity was observed among the studies (P = 0.004;

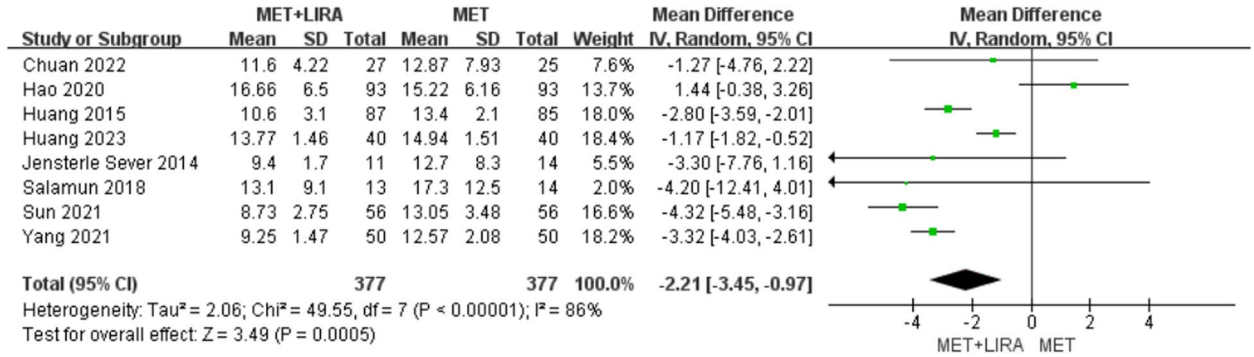

Fig. 10 Fasting insulin

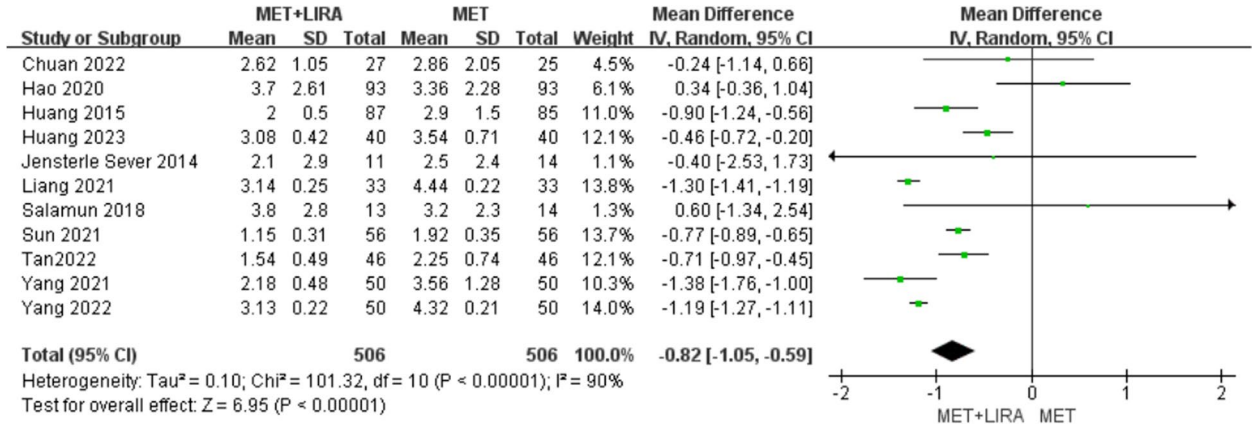

Fig. 11 Homeostasis model assessment of insulin resistance

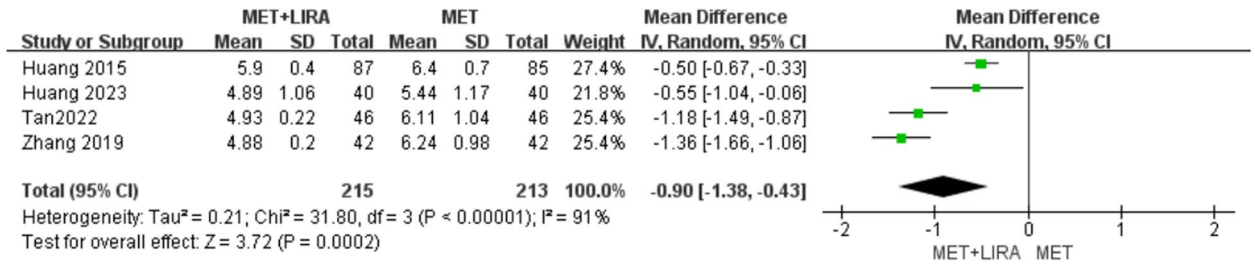

Fig. 12 Total cholesterol

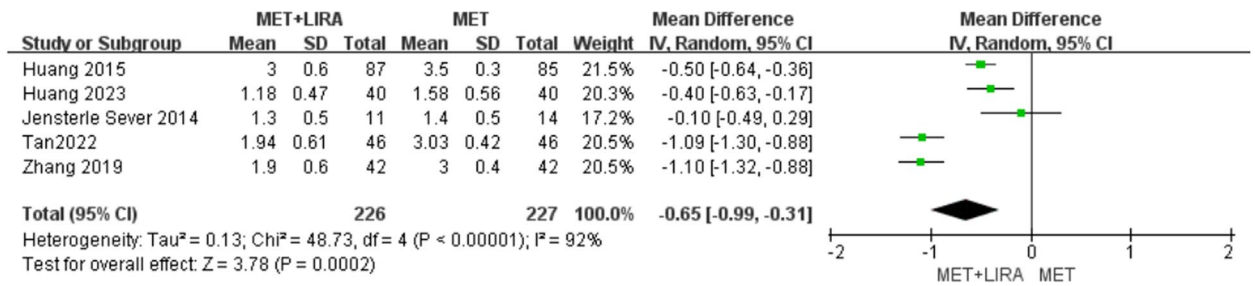

Fig. 13 Triglyceride

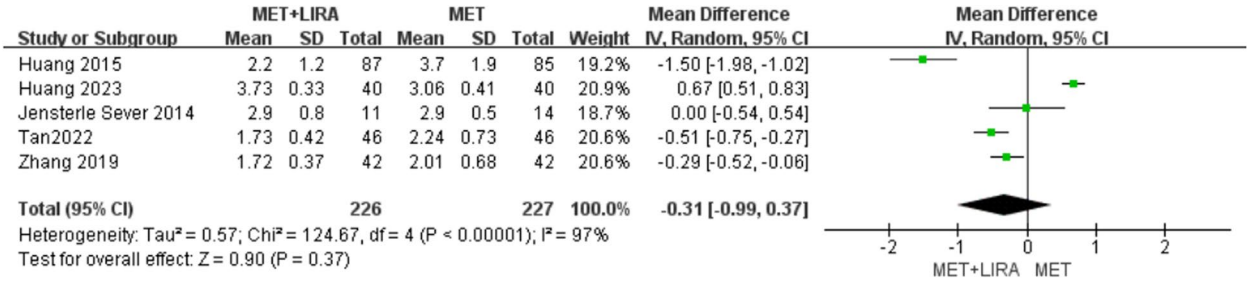

Fig. 14 Low-density lipoprotein

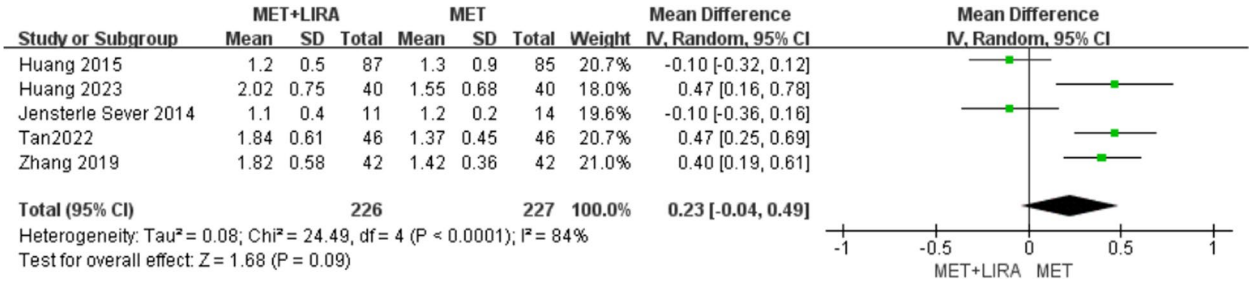

Fig. 15 High-density lipoprotein

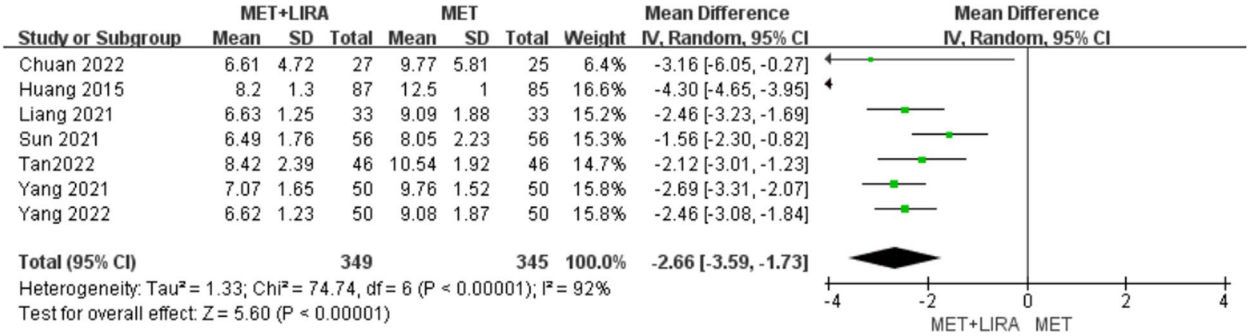

Fig. 16 Luteinizing hormone

I^2 = 74%), therefore a random-effects model was used for analysis. The pooled results indicate that the levels of FSH were lower in the combination treatment group compared to the treatment alone group (MD = −1.06, 95% CI: [−1.35,−0.76], P < 0.00001, Fig. 17).

Total testosterone

Eleven studies [12, 13, 15–20, 22–24], comprising a total of 1012 patients, were included in this meta-analysis as they provided data on TT levels. Significant heterogeneity was observed among the studies (P < 0.00001; I^2 = 98%), and therefore, a random-effects model was employed for analysis. The pooled results indicated that the combination treatment group had lower levels of TT compared to the treatment alone group (MD = −0.49, 95% CI: [−0.85,−0.13], P = 0.007, Fig. 18).

Anti-mullerian tubular hormone

Three studies [15, 17, 18] comprising a total of 278 patients provided data on AMH duct hormones, which were included in the meta-analysis. The inter-study heterogeneity was found to be low (P = 0.26; I^2 = 26%), and therefore, a fixed-effects model was used for analysis. The pooled results indicated that the levels of AMH duct hormones were lower in the combination treatment group compared to the treatment alone grou3.72p (MD = −1.38, 95% CI: [−1.66,−1.10], P < 0.00001, Fig. 19).

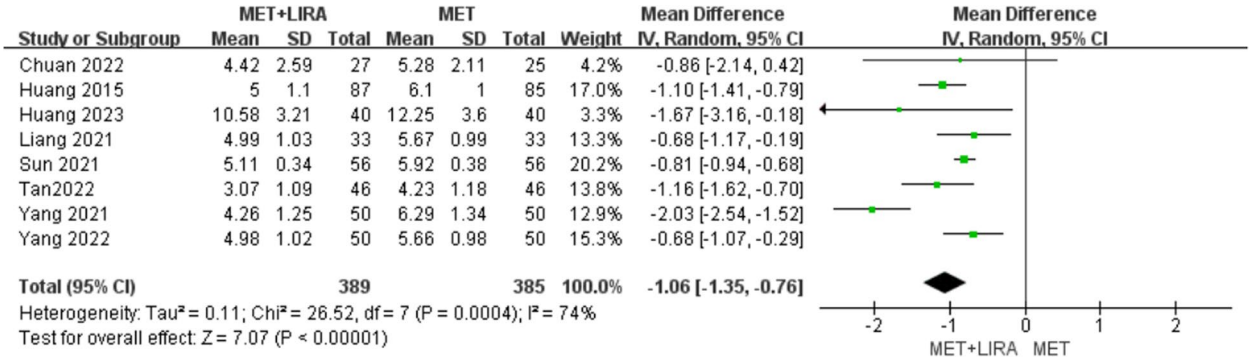

Fig. 17 Follicle stimulating hormone

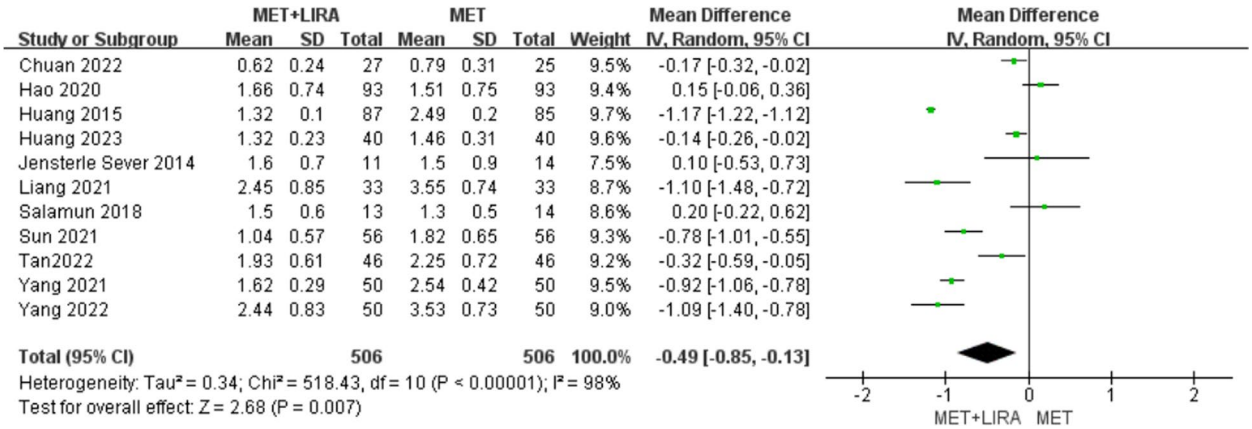

Fig. 18 Total testosterone

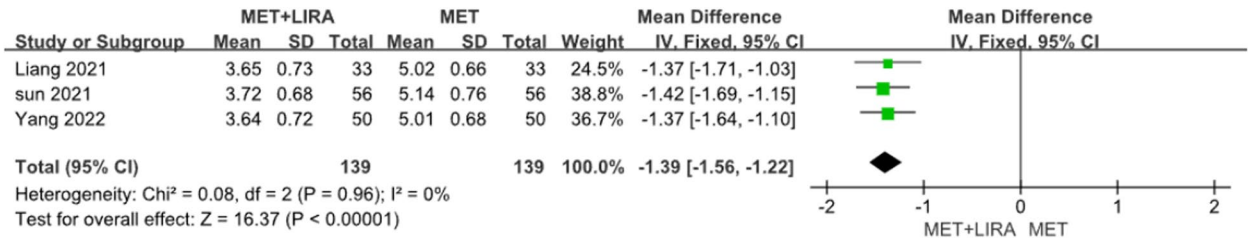

Fig. 19 Anti-mullerian tubular hormone

Establishing the rate of menstrual cycle

Three studies [16, 20, 23], comprising a total of 364 patients, reported data on the establishment the Rate of Menstrual Cycle, which we have included in our meta-analysis. The inter-study heterogeneity was found to be low ($P = 0.91$; $I^2 = 0\%$), thereby allowing for a fixed-effects model analysis. The pooled results indicated a significantly higher rate of establishing the Rate of Menstrual Cycle in the combination treatment group as compared to the treatment alone group (MD = 0.20, 95% CI: [0.11, 0.28], $P < 0.00001$, Fig. 20).

Normal ovulation rate

Four studies (478 patients) [16, 19, 20, 23] reported data on normal ovulation rates, and were included in the meta-analysis. The inter-study heterogeneity was low ($P = 0.69$; $I^2 = 0\%$), thus a fixed-effects model was used for analysis. The pooled results indicate that the normal ovulation rate was significantly higher in the combination treatment group compared to the treatment alone group (MD = 2.95, 95% CI: [2.00,4.34], $P < 0.00001$, Fig. 21).

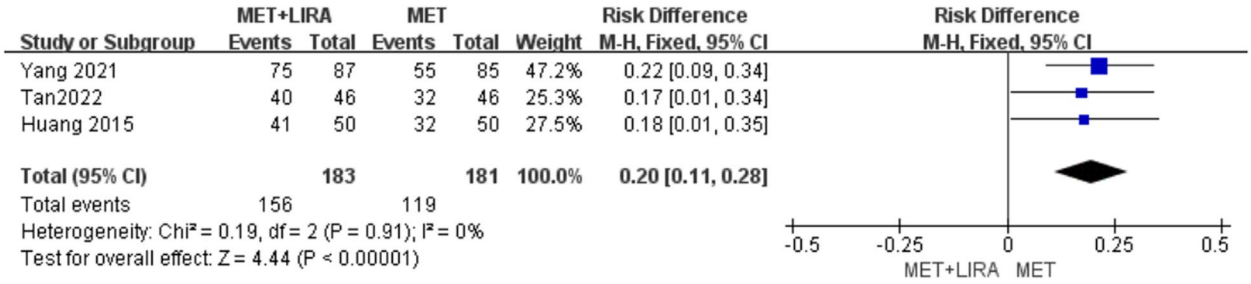

Fig. 20 Establishing the rate of menstrual cycle

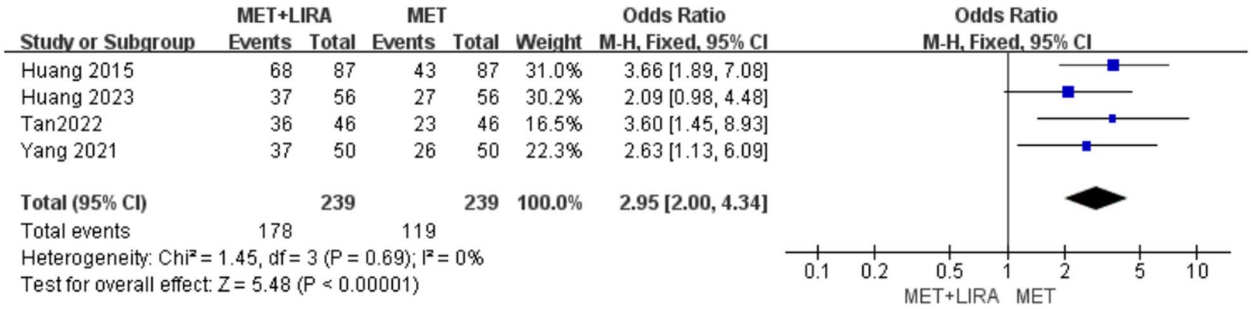

Fig. 21 Normal ovulation rate

Natural conception rate

Four studies [16, 19, 20, 23], comprising of 476 patients, reported data on natural conception rate. Therefore, we have included them in the meta-analysis. The inter-study heterogeneity was low ($P = 1.00$; $I^2 = 0\%$), leading to the use of a fixed-effects model for analysis. The pooled results indicate that the combination treatment group had a higher natural conception rate than the treatment alone group (MD = 2.54, 95% CI: [1.71,3.76], $P < 0.00001$, Fig. 22).

Incidence of gastrointestinal reactions

Nine studies [13, 15–17, 20–24] involving 864 patients reported data on the incidence of gastrointestinal reactions. These data were included in the meta-analysis. Inter-study heterogeneity was low ($P = 0.22$; $I^2 = 25\%$), so a fixed-effects model was used for analysis. The pooled results indicated that the incidence of gastrointestinal reactions was higher in the combination treatment group compared to the treatment alone group (MD = 1.95, 95% CI:[1.33,2.88], $P = 0.0007$, Fig. 23).

Incidence of hypoglycemic reactions

Four studies [16, 20, 21, 24] involving 373 patients reported data on the incidence of hypoglycemic reactions. These studies were included in the meta-analysis. The inter-study heterogeneity was low ($P = 0.28$; $I^2 = 22\%$), and therefore, a fixed-effects model was used for analysis. The pooled results indicated that there was no significant difference in the incidence of hypoglycemic reactions between the combination treatment group and the treatment alone group (MD = 0.76, 95% CI: [0.24,2.45], $P = 0.65$, Fig. 24).

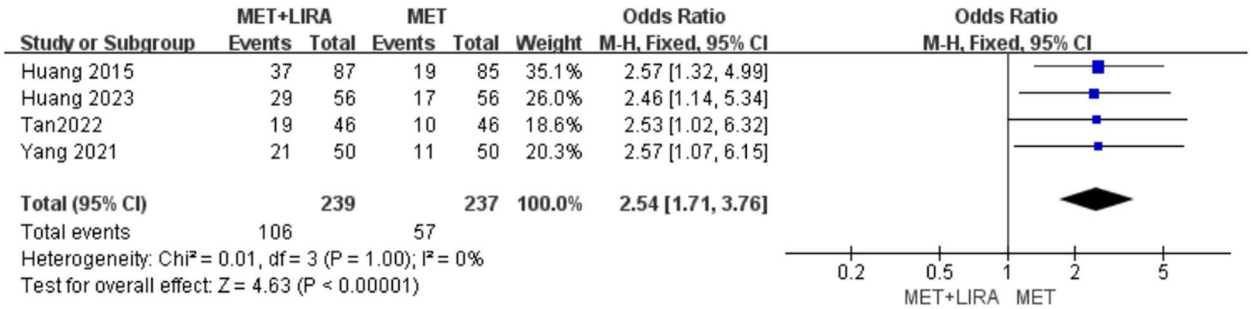

Fig. 22 Natural conception rate

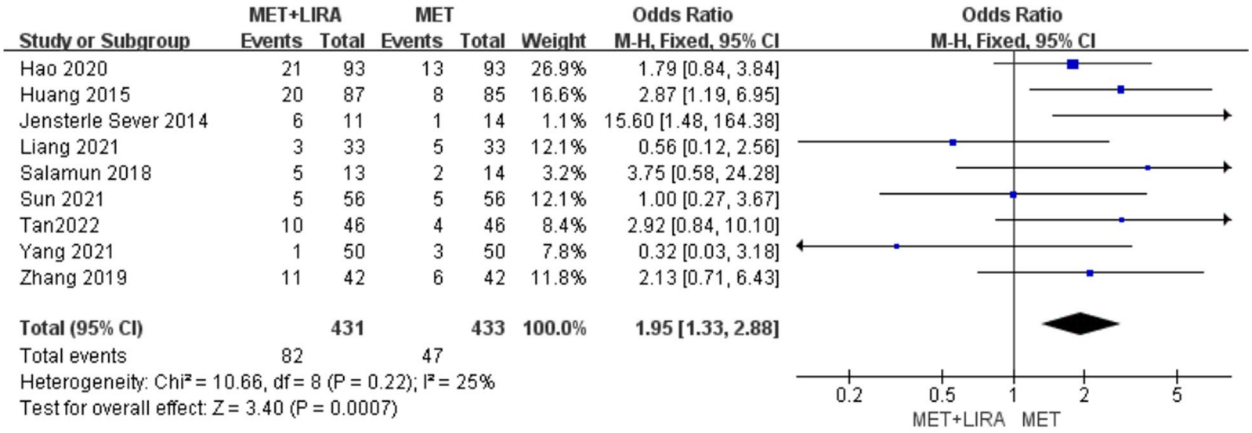

Fig. 23 Incidence of gastrointestinal reactions

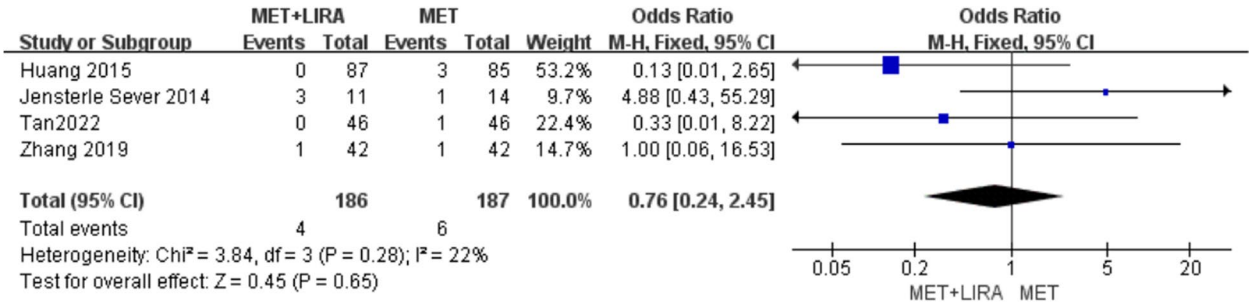

Fig. 24 Incidence of hypoglycemic reactions

Subgroup analysis

We conducted subgroup analyses based on LIRA dosages and geographic regions.

Comparison of Liraglutide (LIRA) Dosages(0.6 mg TID vs 1.2 mg QD) Liang2021, Yang et al. 2022 [18] (using 0.6 mg TID):T: MET + LIRA group showed significantly lower levels than MET group (2.45 ± 0.85 vs. 3.55 ± 0.74, $p < 0.05$, Fig. 25);AMH: MET + LIRA group had lower values (3.65 ± 0.73 vs. 5.02 ± 0.66, $p < 0.01$, Fig. 26); Huang 2015 [16], Huang 2023 (using 1.2 mg QD):FPG: Significant improvement in MET + LIRA group (6.0 ± 0.2 vs. 6.5 ± 0.9, $p < 0.05$, Fig. 27).

Subgroup analysis by geographic region

Geographic region (China vs no China)

Studies in China:HOMA-IR Reduction: Greater improvement (Δ1.2 vs Δ0.7, $p < 0.05$, Fig. 27).

Gastrointestinal Reactions: Lower incidence (average 15% vs 30% in non-Chinese studies, Fig. 28); No Chinese Studies:Weight Loss: Less pronounced (average 1.5 kg vs 3.2 kg in Chinese studies, Fig. 29).

Discussion

Our meta-analysis, based on available evidence, found that combining metformin with liraglutide had similar efficacy to metformin alone in terms of patient body weight, waist circumference, LDL, HDL, and incidence of hypoglycemic response. However, it was superior to metformin alone in terms of BMI, FBG, 2 hPG, HbA_{1c}, FINS, HOMA-IR, TC, TG, LH, FSH, TT, AMH, rate of establishing menstrual cycles, rate of normal ovulation, and rate of spontaneous conception. The only downside was that the incidence of gastrointestinal reactions was higher than that of the metformin-alone group.As a chronic endocrine disease commonly observed in women of reproductive age, PCOS is characterized by symptoms such as androgen excess, insulin resistance, and persistent anovulation. In some patients, it is accompanied by obesity, menstrual irregularities, and infertility [25, 26]. Relevant studies indicate that insulin resistance plays a crucial role in the development of PCOS, leading to hyperinsulinemia and metabolic abnormalities that further aggravate ovulation abnormality, ultimately causing a vicious cycle [27]. Metformin is one of the most commonly used drugs for

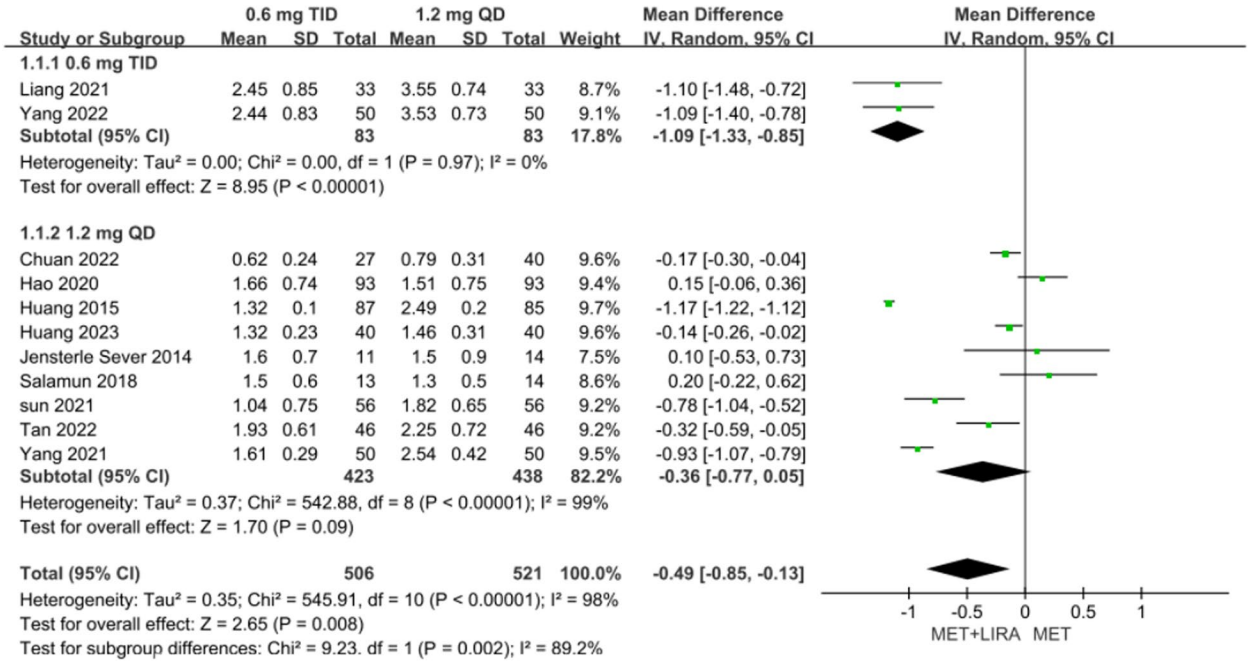

Fig. 25 Subgroup analysis of T

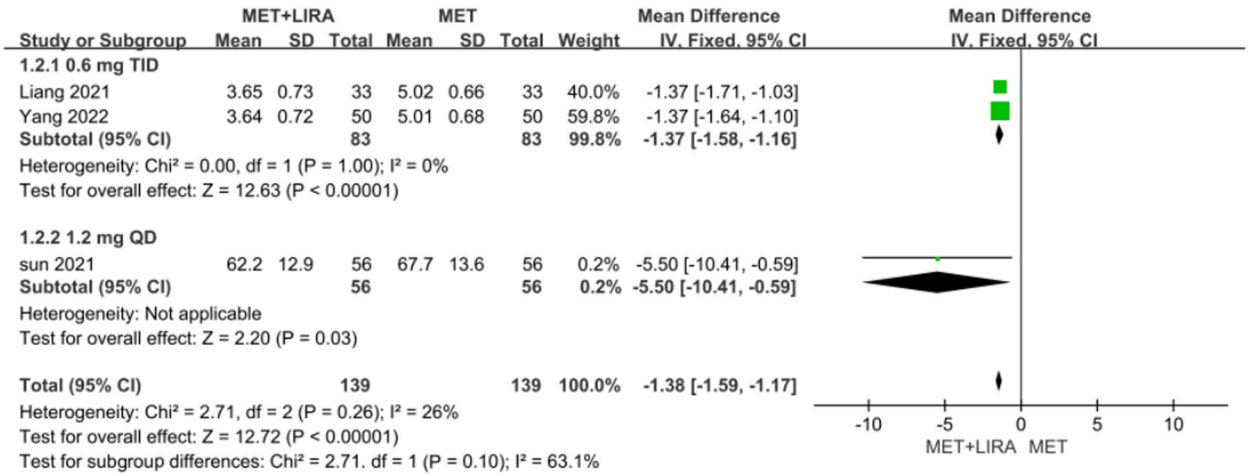

Fig. 26 Subgroup analysis of AMH

PCOS. It reduces insulin resistance by improving insulin sensitivity, which helps in improving metabolic disorders, ovarian steroid synthesis, and reducing the level of androgens in the body [28–30]. The mean BMI reduction of 1.18 kg/m^2, though statistically significant, may have modest clinical impact. However, even modest weight loss (5–10%) in PCOS is linked to improved ovulation and metabolic parameters, underscoring the therapeutic value of combined therapy. GLP-1 receptor agonists are also commonly used in treating PCOS by mimicking intestinal insulin, regulating ovulatory function, and improving the menstrual cycle. Liraglutide, a GLP-1 receptor agonist, reduces glucose-dependent insulin secretion and glucagon secretion, slows down gas emptying, and enhances the sense of satiety, thereby improving blood glucose, reducing body weight, and moderately improving low blood pressure and hyperlipidemia [31, 32]. Studies have shown that combining metformin with liraglutide can improve the ovulation effect in patients with PCOS better than a single drug [33, 34]

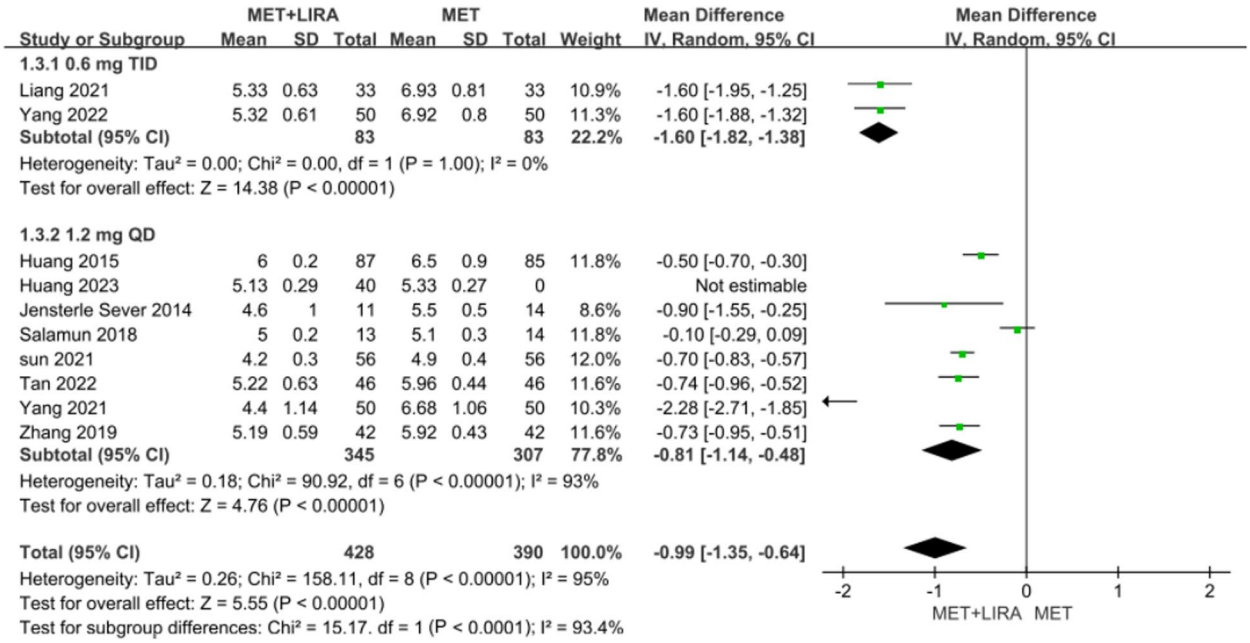

Fig. 27 Subgroup analysis of FPG

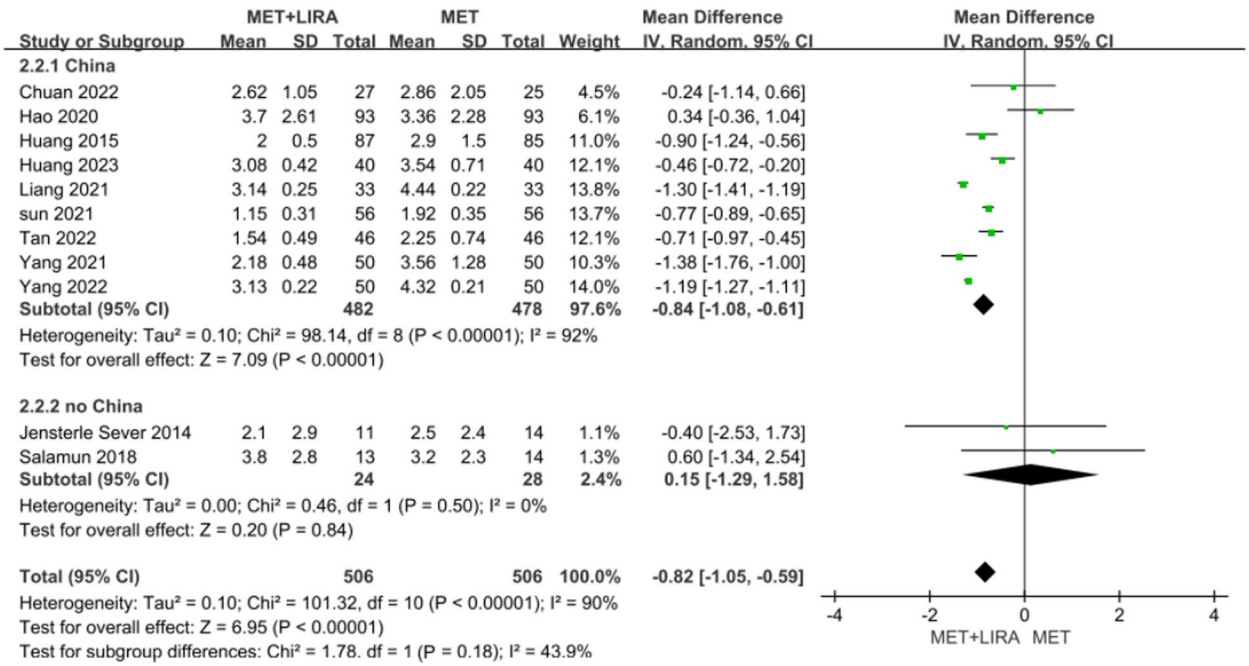

Fig. 28 Subgroup analysis of HOMA-IR

PCOS is often accompanied by metabolic syndromes, such as obesity, dyslipidemia, dysglycemia, and insulin resistance. Obesity, being the main initiating factor of metabolic syndrome, can induce insulin resistance, and insulin resistance, which is the core of metabolic syndrome, can further induce impaired glucose regulation, elevated blood pressure, and dyslipidemia, among other issues [27, 35]. Metformin is widely used for the treatment of metabolic and endocrine disorders in PCOS, as it reduces insulin resistance by improving insulin sensitivity in the liver and peripheral tissues. Liraglutide, a GLP-1 receptor agonist, pharmacologically increases

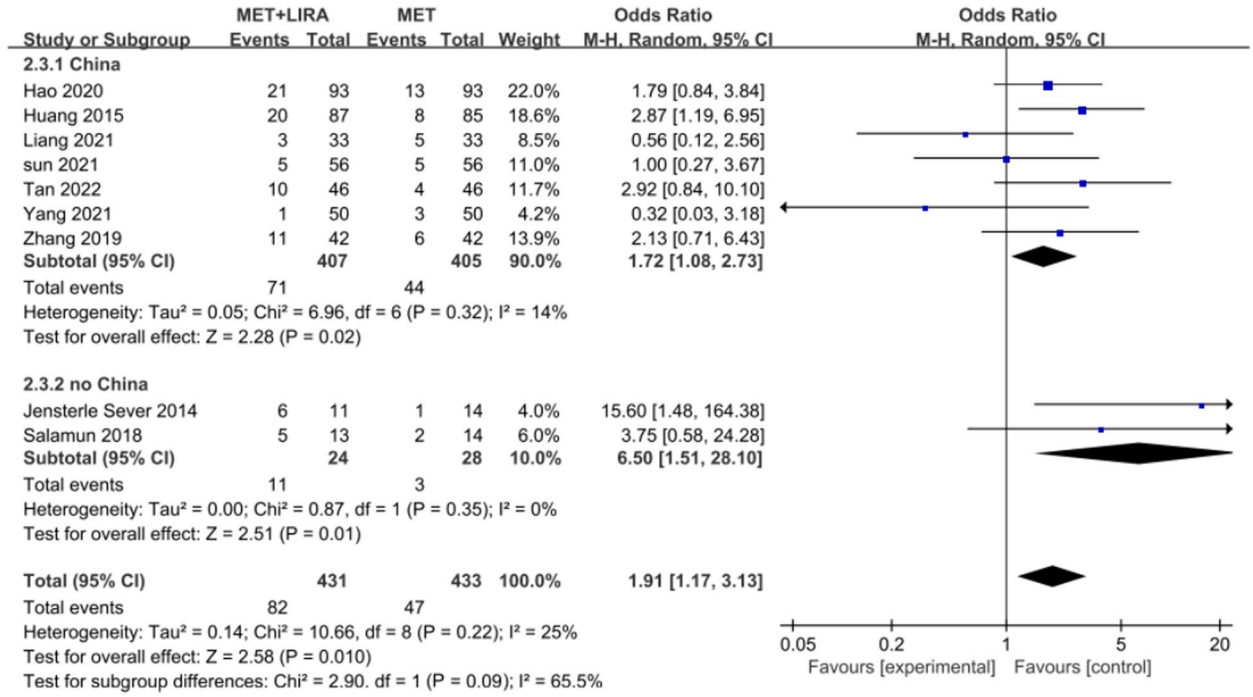

Fig. 29 Subgroup analysis of gastrointestinal reactions

glucose-dependent insulin secretion, decreases glucagon secretion, slows down gastric emptying, and increases the feeling of satiety. Consequently, it significantly improves blood glucose levels, reduces body mass, moderately lowers blood pressure, and improves hyperlipidemia [11, 36, 37].

AMH is a member of the TGF-β superfamily and is produced by granulosa cells. It is believed to play a crucial role in protecting ovarian reserve by inhibiting follicular recruitment and FSH-dependent follicular growth [38]. AMH is closely associated with ovarian function, and changes in its indices can reflect the state of ovarian function [39]. In patients with polycystic ovary syndrome (PCOS), AMH production is higher than in normal women, leading to increased follicle numbers [40, 41]. This high level of AMH secretion can cause cessation of follicular development and anovulation in the body [42]. LH and FSH are glycoproteins secreted by gonadotropin-releasing hormone (GnRH), which is stimulated by the hypothalamus. They are mainly distributed in the anterior pituitary gland and effectively respond to the ovarian reserve function of the body [43–45]. The results of this meta-analysis indicate that the levels of AMH, LH, FSH, and testosterone were reduced in both groups, with a more significant reduction in the combined treatment group. This suggests that metformin combined with liraglutide treatment could more effectively improve the hormone levels of patients (Fig. 30).

The study reveals that the group receiving liraglutide in combination with metformin exhibited higher rates of menstrual cycle, ovulation, and spontaneous conception compared to the group receiving metformin alone. These findings suggest that liraglutide-assisted treatment can effectively improve the ovulation and pregnancy rates of patients with polycystic ovary syndrome (PCOS) infertility, with significant efficacy. This can be attributed to the fact that the combined use of liraglutide and metformin can effectively address the internal environmental disorders of PCOS infertility patients, and promote the improvement of blood glucose, blood lipids, and sex hormone levels [46, 47]. Additionally, liraglutide, as a GLP-1 analog, can regulate the reproductive system through the hypothalamo-pituitary system, leading to a more regular menstrual cycle and an improvement in ovulatory disorders [28, 48]. With regard to safety, the most common adverse reactions were gastrointestinal reactions (such as nausea, stomach pain, vomiting, and diarrhea) and hypoglycemic reactions. Although the incidence of hypoglycemic reactions was similar in the group receiving metformin combined with liraglutide and the group receiving metformin alone, the incidence of gastrointestinal adverse events was higher in the former group. Therefore, it is important to administer liraglutide correctly. While odur findings are robust, the included studies predominantly featured small sample sizes and short follow-up periods (median 16 weeks). Larger, long-term RCTs

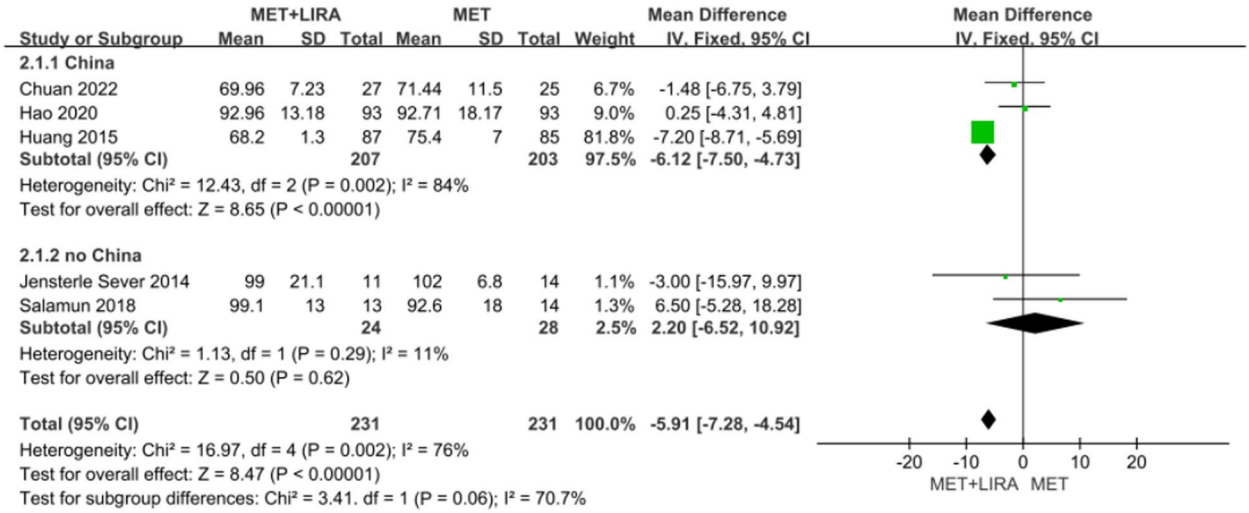

Fig. 30 Subgroup analysis of weigh

are needed to validate the durability of combined therapy and assess rare adverse events. Genome-wide association studies (GWAS) could further elucidate genetic factors influencing treatment response.Recent advances highlight the role of genetic and epigenetic factors in PCOS pathogenesis. For instance, vitamin D receptor (VDR) polymorphisms and dysregulated competing endogenous RNA (ceRNA) networks may influence insulin resistance and hyperandrogenism [49–51]. Future studies should explore whether liraglutide's efficacy varies with genetic profiles.

In subgroup analyses, we found that a dosing regimen of 0.6 mg TID of liraglutide was superior in improving hyperandrogenemia and in reducing side effects. Conversely, a dosage of 1.2 mg QD demonstrated greater efficacy in glycemic control and fertility outcomes albeit with an increased risk of gastrointestinal reactions.The metabolic and reproductive enhancements associated with MET + LIRA were more pronounced and better tolerated within the Chinese population. In contrast, non-Chinese populations may exhibit slightly diminished efficacy and safety, attributable to variations in genetic factors, dietary habits, or body mass index (predominantly among obese patients).

This meta-analysis has several limitations.(1)The inclusion of studies from diverse geographic regions and populations may have led to heterogeneity in the results. (2)The limited sample sizes and short study duration in both the control and experimental groups are also noteworthy limitations.(3)There is a big gap between the sample size of English document and other artile,which may lead to insufficient testing ability.(4)The heterogeneity of the pooled results may even be related to different doses of the drug.

Conclusions

Current data suggests that the combination of liraglutide and metformin has the potential to significantly improve glucose and lipid metabolism in patients with Polycystic Ovary Syndrome infertility. Furthermore, it may lower serum sex hormone levels, resulting in notable clinical benefits. This therapy also enhances pancreatic islet and ovarian function, ultimately boosting ovulation and pregnancy rates. It is crucial to adhere to proper administration methods to minimize adverse reactions.

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Authors' contributions
Rongmei Huang: Conceptualization、Methodology、Formal analysis and investigation、Writing—original draft preparation Rinan He: Writing—review and editing、Resources、Supervision.

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Data availability
Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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