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Comparative efficacy of pharmacological interventions on metabolic and hormonal outcomes in polycystic ovary syndrome: a Network Meta-Analysis of Randomized controlled trials

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Abstract

Background Polycystic ovary syndrome (PCOS) is a common endocrine disorder associated with metabolic and hormonal abnormalities. This study aimed to evaluate the comparative efficacy of pharmacological interventions on these outcomes.

Methods We conducted a systematic review and network meta-analysis of randomized controlled trials (RCTs) assessing pharmacological treatments for PCOS. Searches in PubMed, MEDLINE, Embase, and Web of Science were conducted up to October 20, 2023. Eligible studies were RCTs with at least 12 weeks of follow-up and outcomes including body weight (BW), body mass index (BMI), waist circumference (WC), testosterone, sex hormone-binding globulin (SHBG), lipid profiles, HOMA-IR, fasting blood glucose (FBG), and fasting insulin (FINS).

Results Twenty-nine RCTs with 1476 participants were included. The combination of standard therapy with GLP-1 receptor agonists significantly reduced BW (MD= -3.44; 95% CI= -6.20 to -0.67), BMI (MD= -2.05; 95% CI= -3.55 to -0.55), and WC (MD= -4.39; 95% CI= -6.75 to -2.02) compared to standard therapy alone. Orlistat significantly lowered testosterone (SMD= -2.16; 95% CI= -3.84 to -0.48) and increased HDL-C levels (SMD = 0.90; 95% CI = 0.02 to 1.79) compared to placebo. The combination therapy also reduced HOMA-IR (MD= -1.29; 95% CI= -2.38 to -0.21) and FBG (SMD= -1.80; 95% CI= -3.04 to -0.55) compared to placebo.

Conclusion Combining standard therapy with GLP-1 receptor agonists offers superior efficacy in improving metabolic and hormonal outcomes in women with PCOS. Orlistat effectively reduces androgen levels. These findings support the use of combination pharmacotherapy for comprehensive management of PCOS.

Keywords Polycystic ovary syndrome, Pharmacological interventions, GLP-1 receptor agonists, Metabolic outcomes, Network meta-analysis

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Introduction

Polycystic ovary syndrome (PCOS) is a multifaceted endocrine disorder characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology on ultrasonography [1]. It affects approximately 6–20% of women of reproductive age worldwide, depending on the diagnostic criteria used [2]. PCOS is not only the leading cause of anovulatory infertility but also is associated with a spectrum of metabolic disturbances, including insulin resistance, obesity, dyslipidemia, and an increased risk of type 2 diabetes mellitus and cardiovascular disease [3, 4]. The syndrome's complexity poses significant challenges to long-term health and quality of life, necessitating effective therapeutic strategies [5]. These challenges have led to the development and continual evolution of treatment options, including both traditional and emerging pharmacological interventions.

Current management of PCOS is individualized and often requires a combination of lifestyle modifications and pharmacotherapy [6]. Lifestyle interventions, such as dietary changes and increased physical activity, are first-line treatments aimed at weight reduction and improvement of insulin sensitivity [7]. Pharmacological therapies are employed to address specific symptoms and metabolic abnormalities. Metformin, an insulin sensitizer, is commonly prescribed to improve insulin resistance and promote ovulation [8]. Other agents, including thiazolidinediones like pioglitazone, anti-androgens such as flutamide, and weight-loss medications like orlistat [9], have been utilized with varying degrees of success. Recently, novel pharmacotherapies, such as glucagon-like peptide-1 (GLP-1) receptor agonists (e.g., exenatide, liraglutide, semaglutide) [10], sodium-glucose co-transporter 2 (SGLT-2) inhibitors (e.g., canagliflozin, empagliflozin) [11], and phosphodiesterase-4 inhibitors like roflumilast, have emerged as promising treatments due to their favorable effects on metabolic parameters, weight loss, and insulin sensitivity.

Despite the availability of multiple therapeutic options, there is no clear consensus on the most effective pharmacological interventions for improving metabolic and hormonal outcomes in PCOS. Previous studies and traditional meta-analyses have often focused on head-to-head comparisons between two treatments, limiting the ability to draw comprehensive conclusions across a broader spectrum of therapies [12, 13]. Moreover, inconsistencies in study designs, patient populations, and outcome measures have contributed to heterogeneous findings. These limitations highlight the need for a more integrative analytical approach to evaluate the relative efficacy of both established and novel pharmacotherapies in the management of PCOS.

Network meta-analysis (NMA) offers a robust methodological framework that allows for the simultaneous comparison of multiple interventions by integrating direct and indirect evidence across a network of randomized controlled trials [14]. NMA not only provides estimates of relative effectiveness among treatments that have not been directly compared but also ranks interventions based on their efficacy and safety profiles [15]. This approach enhances the evidence base for clinical decision-making and guideline development. Therefore, we conducted a systematic review and network meta-analysis to compare the efficacy of various pharmacological interventions—including standard treatments and emerging therapies—on metabolic and hormonal outcomes in women with PCOS. Our objective was to generate a hierarchical ranking of these interventions to inform clinical practice and guide future research, ultimately aiming to optimize therapeutic strategies for this complex syndrome.

Methods

This study is a pre-registered systematic review and network meta-analysis, conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16].

Data sources and searches

A comprehensive literature search was conducted across PubMed, MEDLINE, Embase, and Web of Science from inception through October 20, 2024, without language restrictions. The search strategy focused on identifying randomized controlled trials (RCTs) evaluating pharmacological interventions on metabolic and hormonal outcomes in patients with PCOS. Search terms included "Polycystic Ovary Syndrome" along with specific pharmacologic agents such as "Acarbose," "Canagliflozin," "Empagliflozin," "Exenatide," "Flutamide," "Liraglutide," "Metformin," "Orlistat," "Pioglitazone," "Placebo," "Roflumilast," "Rosiglitazone," and "Semaglutide." The complete search strategy, including specific terms and combinations, is available in Supplementary File 1. Manual searches of reference lists in relevant studies and reviews supplemented database searches. Two independent reviewers screened titles, abstracts, and full texts for eligibility, resolving discrepancies by discussion or consultation with a third reviewer as needed.

Study selection

Studies were included in this meta-analysis if they met the following criteria: (a) study design is RCT; (b) involved participants diagnosed with PCOS according to recognized criteria (e.g., Rotterdam or NIH); (c) included pharmacological interventions with one or more of the

following agents: Acarbose, Canagliflozin, Empagliflozin, Exenatide, Flutamide, Liraglutide, Metformin, combinations of Metformin with Canagliflozin, Exenatide, Flutamide, Liraglutide, Rosiglitazone, or Sitagliptin, as well as Orlistat, Pioglitazone, Roflumilast, Rosiglitazone, Semaglutide, and placebo as comparators; (d) reported on at least one primary outcome related to metabolic or hormonal indicators, including body weight (BW), body mass index (BMI), waist circumference (WC), testosterone, sex hormone-binding globulin (SHBG), total cholesterol (TC), HDL-C, LDL-C, triglycerides (TG), HOMA-IR, fasting blood glucose (FBG), or fasting insulin (FINS); and (e) had a minimum follow-up duration of 12 weeks to ensure outcome validity.

Studies were excluded if they met any of the following criteria: (a) included patients with conditions secondary to PCOS, such as Cushing's syndrome, non-classical 21-hydroxylase deficiency, or hyperprolactinemia; (b) involved patients with pre-existing comorbidities, including diabetes or significant renal or hepatic disorders; (c) included interventions using contraceptive agents, ovulation induction drugs, or other endocrine-modulating treatments within six weeks prior to study initiation; and (d) were non-randomized trials or case studies lacking comparative outcome data.

Data extraction

Eligible studies were managed using EndNote X9 to avoid redundancy. Two independent reviewers extracted data on study characteristics (author, publication year, location, sample size, interventions, treatment duration, and follow-up), participant demographics (age, gender, baseline measures), and outcomes (e.g., body weight, BMI, testosterone, cholesterol). Missing data were requested from study authors, with follow-up emails sent up to four times over six weeks to ensure data completeness. Discrepancies in data extraction were resolved by consensus or with input from a third reviewer.

Risk of Bias Assessment

The risk of bias in the included studies was assessed using the Cochrane Collaboration's tool, which evaluates six domains: (a) sequence generation, (b) allocation concealment, (c) blinding of participants and outcome assessors, (d) incomplete outcome data, (e) selective outcome reporting, and (f) other potential sources of bias. Two independent researchers performed the assessments, and any discrepancies were resolved through discussion with a third reviewer to reach consensus.

Data coding

Interventions were categorized by pharmacological class for analysis. Flutamide was classified as "Flutamide"; Exenatide, Liraglutide, and Semaglutide as "GLP-1 receptor agonists"; Orlistat as "Orlistat"; Canagliflozin and Empagliflozin as "SGLT-2 inhibitors"; Acarbose, Metformin, Pioglitazone, and Rosiglitazone as "Standard Treatments"; and placebo as a separate category. Combination therapies were coded by their respective dual-therapy groupings. This structured coding facilitated consistent comparisons across treatment groups, in line with network meta-analysis standards.

Data analysis

Data analysis was conducted using Stata software (version 17.0, StataCorp LLC, Texas, USA). A network meta-analysis was employed to compare the efficacy and safety of pharmacological interventions for PCOS across various metabolic and hormonal outcomes. A network plot was generated to depict the connections among treatment comparisons, ensuring the suitability of the network meta-analysis structure. Given the clinical heterogeneity anticipated across studies, a random-effects model was applied to account for both within-study and between-study variability.

For continuous outcomes where measurement methods and units were consistent—namely body weight, BMI, waist circumference, SHBG, and HOMA-IR—mean differences (MDs) with 95% confidence intervals (CIs) were calculated. For other continuous outcomes with variations in testing methods or measurement units (testosterone, cholesterol, HDL-C, LDL-C, triglycerides, FBG, and FINS), standardized mean differences (SMDs) with 95% CIs were utilized to standardize across studies. Binary outcomes were analyzed using odds ratios (ORs) with 95% CIs to assess dichotomous endpoints.

Heterogeneity was evaluated using the I^2 statistic, with thresholds of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. The Bayesian framework in Stata, utilizing the "network" and "mvmeta" packages, facilitated the network meta-analysis. Treatments were ranked based on surface under the cumulative ranking curve (SUCRA) values, with higher SUCRA values representing greater relative efficacy. To detect potential publication bias, adjusted funnel plots were generated, and Egger's test was conducted, with a p-value < 0.05 signaling potential bias [17]. Predictive interval plots were also used to further explore heterogeneity and account for effect size variability. All statistical tests were two-sided, with a p-value < 0.05 considered statistically significant.

Results

Characteristics of included studies

The initial electronic search identified 3011 records. After removing 1652 duplicates, 371 records were screened

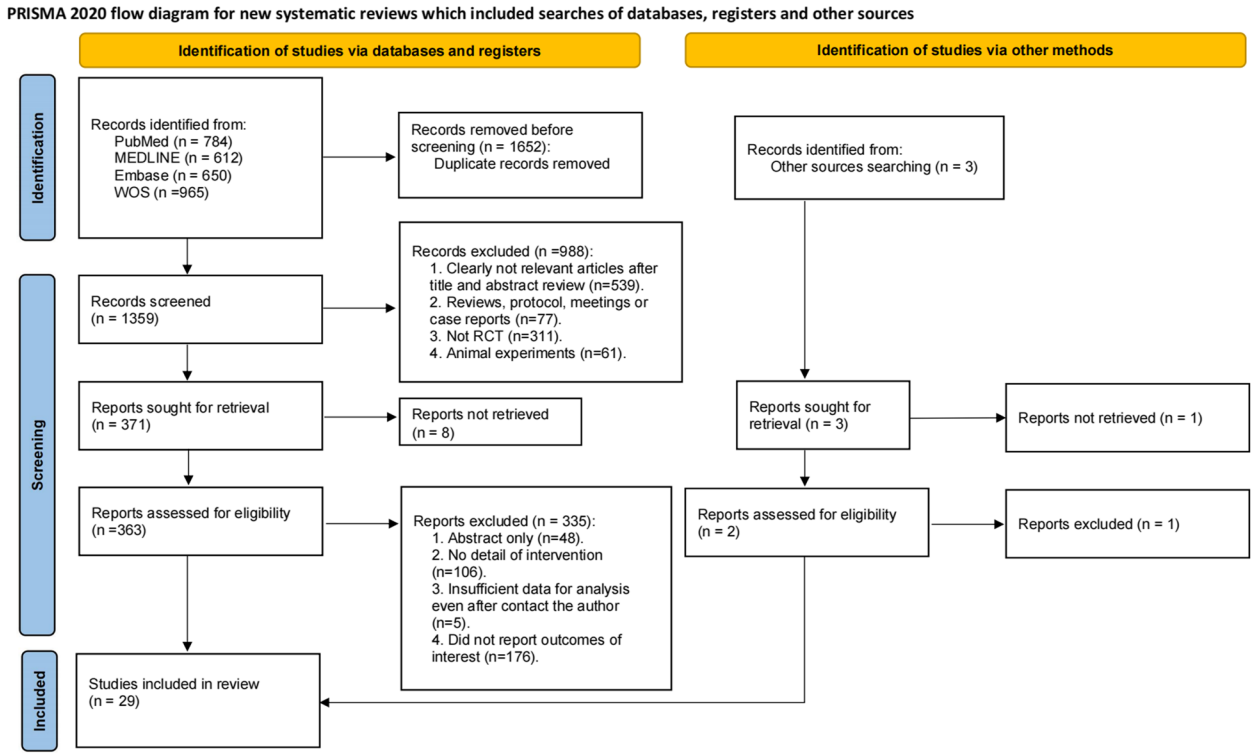

Fig. 1 PRISMA Flow diagram of the search process for studies

based on titles and abstracts. Subsequently, 363 full-text articles were assessed for eligibility, resulting in the inclusion of 29 studies comprising 1476 participants for the systematic review and network meta-analysis (Fig. 1) [18–43]. Detailed characteristics of the included studies are available in Supplementary File 2.

The included studies were published between 2000 and 2022, with a median publication year of 2014. Sample sizes varied from 20 to 143 participants, with a median of 40 participants per study. The mean age of participants ranged from 23.9 to 34.3 years, with a median of 27.9 years. Baseline BMI was reported in 27 studies, ranging from 27.1 to 40.8 kg/m², with a median of 35.9 kg/m². Baseline HOMA-IR levels were reported in 20 studies, providing valuable insights into the metabolic profile of the participants.

Regarding treatment strategies, 24 studies investigated Standard therapies (e.g., Metformin, Pioglitazone), 9 studies utilized GLP-1 receptor agonists, 6 studies examined Orlistat, and 4 studies assessed combinations of Standard + GLP-1 therapy. Additionally, Flutamide and SGLT-2 inhibitors were each evaluated in 2 studies, as were Standard + Flutamide regimens. Roflumilast, Standard + DPP-4 inhibitors, and Standard + SGLT-2 combinations were each examined in 1 study. Placebo was used as a control in 14 studies.

The results of network meta-analysis

Anthropometric outcomes

BW The network meta-analysis for BW included 19 studies with 1,091 patients. Direct comparisons and sample distributions are shown in Fig. 3.1 of Supplementary File 3. Based on SUCRA rankings (Fig. 2.1), the top three treatments for BW reduction were Standard + GLP-1 (81.6%), GLP-1 (75.2%), and Standard + Flutamide (58.7%). As shown in Table 1., Standard + GLP-1 (MD = −3.44, 95% CI: −6.20 to −0.67) and GLP-1 (MD = −2.91, 95% CI: −5.04 to −0.78) significantly reduced BW compared to Standard. Additionally, compared to Placebo, Standard + GLP-1 (MD = −6.18, 95% CI: −8.78 to −3.57), GLP-1 (MD = −5.65, 95% CI: −7.44 to −3.86), SGLT-2 (MD = −4.06, 95% CI: −6.82 to −1.29), Orlistat (MD = −3.41, 95% CI: −5.19 to −1.62), and Standard (MD = −2.74, 95% CI: −4.54 to −0.94) showed significant BW reductions.

BMI The BMI network meta-analysis included 26 studies with 1,393 patients. Direct comparisons and sample distributions are displayed in Fig. 3.2 of Supplementary File 3. According to SUCRA rankings (Fig. 2.2), the top treatments for BMI reduction were Standard + GLP-1 (72.3%), Orlistat (71.4%), and SGLT-2 (63.1%). Table 2 shows that Orlistat significantly reduced BMI compared

Table 1 BW

Standard + Glp-1									
−0.52 (−2.54,1.49)	Glp-1								
−1.30 (−11.03,8.44)	−0.77 (−10.33,8.79)	Standard + Flutamide							
−1.54 (−14.74,11.67)	−1.01 (−14.10,12.07)	−0.24 (−16.25,15.77)	Roflumilast						
−2.12 (−5.60,1.36)	−1.59 (−4.59,1.40)	−0.82 (−10.52,8.87)	−0.58 (−13.66,12.50)	Sglt-2					
−2.30 (−10.73,6.13)	−1.77 (−10.00,6.46)	−1.00 (−10.73,8.73)	−0.76 (−16.01,14.49)	−0.18 (−8.56,8.20)	Flutamide				
−2.69 (−6.95,1.58)	−2.16 (−6.05,1.72)	−1.39 (−11.40,8.61)	−1.15 (−14.46,12.16)	−0.57 (−4.44,3.30)	−0.39 (−9.13,8.35)	Standard + Sglt-2			
−2.77 (−5.77,0.23)	−2.24 (−4.61,0.13)	−1.47 (−11.01,8.07)	−1.23 (−14.28,11.82)	−0.65 (−3.49,2.19)	−0.47 (−8.68,7.73)	−0.08 (−3.85,3.69)	Orlistat		
−3.44 (−6.20,−0.67)	**−2.91 (−5.04,−0.78)**	−2.14 (−11.60,7.32)	−1.90 (−14.81,11.01)	−1.32 (−3.43,0.79)	−1.14 (−9.26,6.97)	−0.75 (−4.00,2.50)	−0.67 (−2.58,1.24)	Standard	
−6.18 (−8.78,−3.57)	**−5.65 (−7.44,−3.86)**	−4.88 (−14.31,4.55)	−4.64 (−17.67,8.39)	**−4.06 (−6.82,−1.29)**	−3.88 (−11.96,4.20)	−3.49 (−7.20,0.22)	**−3.41 (−5.19,−1.62)**	**−2.74 (−4.54,−0.94)**	Placebo

Table 2 BMI

Standard + Glp-1									
−0.03 (−1.80,1.75)	Orlistat								
−0.24 (−2.50,2.03)	−0.21 (−2.37,1.96)	Sglt-2							
−0.33 (−1.49,0.84)	−0.30 (−1.86,1.26)	−0.09 (−2.21,2.02)	Glp-1						
−0.54 (−2.85,1.77)	−0.52 (−2.72,1.69)	−0.31 (−2.94,2.33)	−0.22 (−2.36,1.93)	Standard + Flutamide					
−0.54 (−2.82,1.74)	−0.52 (−2.69,1.66)	−0.31 (−2.92,2.30)	−0.22 (−2.32,1.89)	0.00 (−2.08,2.08)	Flutamide				
−0.63 (−5.00,3.74)	−0.60 (−5.02,3.82)	−0.39 (−5.03,4.24)	−0.30 (−4.54,3.94)	−0.09 (−4.75,4.57)	−0.09 (−4.73,4.56)	Roflumilast			
−1.04 (−3.79,1.70)	−1.02 (−3.67,1.64)	−0.81 (−3.80,2.18)	−0.72 (−3.33,1.90)	−0.50 (−3.56,2.56)	−0.50 (−3.54,2.53)	−0.41 (−5.30,4.47)	Standard + Sglt-2		
−1.33 (−2.70,0.03)	**−1.31 (−2.49,−0.12)**	−1.10 (−2.91,0.71)	−1.01 (−2.10,0.09)	−0.79 (−2.72,1.13)	−0.79 (−2.68,1.09)	−0.70 (−4.97,3.56)	−0.29 (−2.67,2.09)	Standard	
−2.05 (−3.55,−0.55)	**−2.02 (−3.35,−0.69)**	−1.81 (−3.83,0.20)	**−1.72 (−2.91,−0.53)**	−1.51 (−3.41,0.40)	−1.51 (−3.38,0.36)	−1.42 (−5.74,2.90)	−1.00 (−3.55,1.54)	−0.71 (−1.62,0.19)	Placebo

to Standard (MD = −1.31, 95% CI: −2.49 to −0.12). Furthermore, Standard + GLP-1 (MD = −2.05, 95% CI: −3.55 to −0.55), Orlistat (MD = −2.02, 95% CI: −3.35 to −0.69), and GLP-1 (MD = −1.72, 95% CI: −2.91 to −0.53) significantly reduced BMI compared to Placebo.

WC The WC network meta-analysis included 17 studies with 942 patients. Direct comparisons and sample distributions are presented in Fig. 3.3 of Supplementary File 3. Based on SUCRA rankings (Fig. 2.3), the top treatments for WC reduction were Standard + GLP-1 (88.9%), GLP-1 (86.0%), and Flutamide (64.9%). As detailed in Table 3, Standard + GLP-1 significantly reduced WC compared to SGLT-2 (MD = −2.85, 95% CI: −5.54 to −0.16), Orlistat (MD = −3.74, 95% CI: −5.98 to −1.49), Standard (MD = −4.39, 95% CI: −6.75 to −2.02), Standard + Flutamide (MD = −4.88, 95% CI: −8.46 to −1.31), and Placebo (MD = −5.34, 95% CI: −7.49 to −3.19). GLP-1 also showed a significant reduction in WC compared to SGLT-2 (MD = −2.50, 95% CI: −4.75 to −0.25), Orlistat (MD = −3.39, 95% CI: −4.96 to −1.82), Standard (MD = −4.04, 95% CI: −5.99 to −2.09), Standard + Flutamide (MD = −4.54,

Table 3 WC

Standard + Glp-1								
−0.35 (−2.56,1.86)	Glp-1							
−2.09 (−5.87,1.70)	−1.74 (−5.18,1.71)	Flutamide						
−2.85 (−5.54,−0.16)	**−2.50 (−4.75,−0.25)**	−0.76 (−4.17,2.65)	Sglt-2					
−2.31 (−12.30,7.68)	−1.96 (−11.77,7.85)	−0.22 (−10.49,10.04)	0.54 (−9.38,10.45)	Roflumilast				
−3.74 (−5.98,−1.49)	**−3.39 (−4.96,−1.82)**	−1.65 (−4.77,1.46)	−0.89 (−2.46,0.67)	−1.43 (−11.24,8.38)	Orlistat			
−4.39 (−6.75,−2.02)	**−4.04 (−5.99,−2.09)**	−2.30 (−5.42,0.81)	**−1.54 (−3.01,−0.08)**	−2.08 (−11.91,7.75)	−0.65 (−1.39,0.09)	Standard		
−4.88 (−8.46,−1.31)	**−4.54−7.75,−1.32)**	−2.80 (−6.14,0.54)	−2.04 (−5.21,1.14)	−2.57 (−12.77,7.62)	−1.14 (−4.00,1.71)	−0.50 (−3.35,2.35)	Standard + Flutamide	
−5.34 (−7.49,−3.19)	**−4.99 (−6.17,−3.82)**	**−3.26 (−6.38,−0.14)**	**−2.50 (−4.16,−0.83)**	−3.03 (−12.82,6.75)	**−1.60 (−2.30,−0.90)**	−0.95 (−1.99,0.08)	−0.46 (−3.32,2.40)	Placebo

95% CI: −7.75 to −1.32), and Placebo (MD = −4.99, 95% CI: −6.17 to −3.82). Flutamide significantly reduced WC compared to Placebo (MD = −3.26, 95% CI: −6.38 to −0.14).

Hormonal outcomes

Testosterone The network meta-analysis for testosterone included 22 studies with 1198 patients, evaluating the effects of various treatments. Direct comparisons and sample distributions are shown in Fig. 3.4 of Supplementary File 3. According to SUCRA rankings (Fig. 3.1), the top three treatments for reducing testosterone were Orlistat (91.7%), Standard + GLP-1 (58.3%), and Standard + Flutamide (55.9%). As shown in Table 4, Orlistat significantly reduced testosterone levels compared to Placebo (SMD = −2.16, 95% CI: −3.84 to −0.48) and Standard (SMD = −2.32, 95% CI: −3.94 to −0.71).

SHBG The SHBG network meta-analysis included 21 studies with 948 patients, assessing the impact of different treatments. Direct comparisons and sample distributions are provided in Fig. 3.5 of Supplementary File 3. Based on SUCRA rankings (Fig. 3.2), the top treatments for increasing SHBG were Standard + GLP-1 (76.8%), SGLT-2 (65.2%), and Standard + Flutamide (56.6%). However, as indicated in Table 5, there were no statistically significant differences in SHBG levels across all treatment comparisons.

Lipid outcomes

TC The network meta-analysis for TC included 20 studies with 1053 patients. Direct comparisons and sample distributions are shown in Fig. 3.6 of Supplementary File 3. Based on SUCRA rankings (Fig. 4.1), the top treatments for reducing TC were Standard + GLP-1 (95.0%), Orlistat (90.6%), and GLP-1 (60.2%). As indicated in Table 6, Standard + GLP-1 significantly reduced TC compared to GLP-1 (SMD = −1.36, 95% CI: −2.28 to −0.44), Standard + Flutamide (SMD = −1.64, 95% CI: −3.08 to −0.20), Flutamide (SMD = −1.76, 95% CI: −3.20 to −0.32), Standard (SMD = −1.77, 95% CI: −2.78 to −0.76), SGLT-2 (SMD = −2.04, 95% CI: −3.90 to −0.18), and Placebo (SMD = −2.14, 95% CI: −3.25 to −1.04). Orlistat significantly reduced TC compared to Standard + Flutamide (SMD = −1.38, 95% CI: −2.75 to −0.02), Flutamide (SMD = −1.50, 95% CI: −2.87 to −0.13), Standard (SMD = −1.51, 95% CI: −2.42 to −0.60), and Placebo (SMD = −1.88, 95% CI: −2.88 to −0.89).

HDL-C The network meta-analysis for HDL-C included 19 studies with 918 patients. Direct comparisons and sample distributions are illustrated in Fig. 3.7 of Supplementary File 3. According to SUCRA rankings (Fig. 4.2), the top treatments for increasing HDL-C were Orlistat (85.0%), Standard + DPP-4 (74.5%), and Standard + Flutamide (73.6%). As shown in Table 7, Orlistat significantly increased HDL-C compared to Placebo (SMD = 0.90, 95% CI: 0.02 to 1.79) and GLP-1 (SMD = 1.29, 95% CI: 0.18 to 2.41).

LDL-C The network meta-analysis for LDL-C included 19 studies with 918 patients. Direct comparisons and sample distributions are provided in Fig. 3.8 of Supplementary File 3. Based on SUCRA rankings (Fig. 4.3), the top treatments for reducing LDL-C were Standard + GLP-1 (87.0%), Standard + DPP-4 (56.3%), and GLP-1 (54.1%). However, as shown in Table 8, no statistically significant differences were observed among the treatments.

Table 4 Testosterone

Orlistat										
−1.51 (−4.23,1.21)	Standard + Glp-1									
−1.65 (−4.18,0.88)	−0.14 (−3.14,2.86)	Standard + Flutamide								
−1.61 (−5.20,1.98)	−0.10 (−3.99,3.78)	0.04 (−3.77,3.84)	Standard + Sglt-2							
−1.75 (−4.28,0.77)	−0.25 (−3.24,2.75)	−0.10 (−2.39,2.19)	−0.14 (−3.95,3.66)	Flutamide						
−1.76 (−4.55,1.02)	−0.26 (−3.41,2.89)	−0.11 (−3.17,2.94)	−0.15 (−4.08,3.77)	−0.01 (−3.07,3.04)	Sglt-2					
−2.13 (−5.46,1.21)	−0.62 (−3.98,2.74)	−0.48 (−4.04,3.09)	−0.52 (−4.85,3.82)	−0.37 (−3.94,3.19)	−0.36 (−4.06,3.33)	Roflumilast				
−2.16 (−3.84,−0.48)	−0.65 (−3.08,1.77)	−0.51 (−2.56,1.54)	−0.55 (−3.92,2.82)	−0.41 (−2.46,1.64)	−0.40 (−2.89,2.10)	−0.03 (−3.13,3.06)	Placebo			
−2.17 (−4.42,0.09)	−0.66 (−2.47,1.15)	−0.52 (−3.11,2.07)	−0.56 (−4.13,3.02)	−0.42 (−3.00,2.17)	−0.40 (−3.17,2.36)	−0.04 (−2.96,2.87)	−0.01 (−1.90,1.88)	Glp-1		
−2.60 (−6.23,1.04)	−1.09 (−5.01,2.83)	−0.95 (−4.79,2.90)	−0.99 (−5.55,3.58)	−0.84 (−4.69,3.00)	−0.83 (−4.80,3.14)	−0.47 (−4.84,3.90)	−0.44 (−3.85,2.98)	−0.43 (−4.05,3.19)	Standard + Dpp4	
−2.32 (−3.94,−0.71)	−0.82 (−3.01,1.37)	−0.67 (−2.73,1.38)	−0.71 (−3.92,2.49)	−0.57 (−2.62,1.48)	−0.56 (−2.83,1.71)	−0.20 (−3.11,2.72)	−0.16 (−1.20,0.87)	−0.16 (−1.73,1.42)	0.27 (−2.98,3.53)	Standard

Table 5 SHBG

Standard + Glp-1										
0.14 (−0.96,1.23)	Sglt-2									
0.27 (−0.80,1.34)	0.13 (−1.01,1.28)	Standard + Flutamide								
0.31 (−0.41,1.03)	0.17 (−0.66,1.00)	0.04 (−0.76,0.83)	Standard							
0.33 (−0.68,1.33)	0.19 (−0.89,1.27)	0.06 (−0.98,1.09)	0.02 (−0.68,0.72)	Orlistat						
0.42 (−1.07,1.91)	0.29 (−1.26,1.83)	0.15 (−1.38,1.68)	0.11 (−1.19,1.42)	0.10 (−1.38,1.57)	Standard + Dpp4					
0.40 (−0.86,1.66)	0.26 (−1.14,1.67)	0.13 (−1.26,1.51)	0.09 (−1.04,1.23)	0.07 (−1.26,1.40)	−0.02 (−1.75,1.71)	Roflumilast				
0.40 (−0.21,1.02)	0.27 (−0.72,1.25)	0.13 (−0.83,1.09)	0.10 (−0.44,0.63)	0.08 (−0.80,0.96)	−0.02 (−1.43,1.39)	0.00 (−1.13,1.14)	Glp-1			
0.41 (−0.43,1.25)	0.27 (−0.66,1.21)	0.14 (−0.66,0.93)	0.10 (−0.33,0.53)	0.08 (−0.68,0.85)	−0.01 (−1.39,1.36)	0.01 (−1.20,1.22)	0.01 (−0.68,0.69)	Placebo		
0.58 (−0.50,1.65)	0.44 (−0.71,1.59)	0.31 (−0.58,1.19)	0.27 (−0.53,1.06)	0.25 (−0.79,1.28)	0.15 (−1.37,1.68)	0.18 (−1.21,1.56)	0.17 (−0.79,1.13)	0.17 (−0.63,0.96)	Flutamide	
0.66 (−0.71,2.04)	0.53 (−0.91,1.96)	0.39 (−1.02,1.81)	0.35 (−0.82,1.52)	0.33 (−1.03,1.70)	0.24 (−1.51,1.99)	0.26 (−1.37,1.89)	0.26 (−1.03,1.54)	0.25 (−0.99,1.50)	0.09 (−1.33,1.50)	Standard + Sglt-2

Table 6 TC

Standard + Glp-1									
−0.26 (−1.61,1.09)	Orlistat								
−1.36 (−2.28,−0.44)	−1.10 (−2.26,0.05)	Glp-1							
−1.64 (−3.08,−0.20)	**−1.38 (−2.75,−0.02)**	−0.28 (−1.53,0.97)	Standard + Flutamide						
−1.77 (−3.73,0.20)	−1.51 (−3.42,0.41)	−0.41 (−2.24,1.43)	−0.13 (−2.11,1.86)	Standard + Dpp4					
−1.76 (−3.20,−0.32)	**−1.50 (−2.87,−0.13)**	−0.40 (−1.65,0.85)	−0.12 (−1.28,1.05)	0.01 (−1.98,1.99)	Flutamide				
−1.77 (−2.78,−0.76)	**−1.51 (−2.42,−0.60)**	−0.41 (−1.13,0.32)	−0.13 (−1.17,0.92)	−0.00 (−1.69,1.69)	−0.01 (−1.05,1.04)	Standard			
−1.88 (−3.75,0.00)	−1.62 (−3.44,0.21)	−0.52 (−2.26,1.23)	−0.23 (−2.13,1.66)	−0.11 (−2.42,2.21)	−0.12 (−2.01,1.78)	−0.11 (−1.69,1.48)	Standard + Sglt-2		
−2.04 (−3.90,−0.18)	−1.78 (−3.59,0.02)	−0.68 (−2.40,1.04)	−0.40 (−2.28,1.48)	−0.28 (−2.57,2.02)	−0.28 (−2.16,1.59)	−0.28 (−1.84,1.29)	−0.17 (−2.39,2.06)	Sglt-2	
−2.14 (−3.25,−1.04)	**−1.88 (−2.88,−0.89)**	−0.78 (−1.62,0.05)	−0.50 (−1.54,0.54)	−0.38 (−2.14,1.39)	−0.38 (−1.43,0.66)	−0.38 (−0.89,0.14)	−0.27 (−1.93,1.40)	−0.10 (−1.74,1.54)	Placebo

TG The TG network meta-analysis included 22 studies with 1192 patients. Direct comparisons and sample distributions are presented in Fig. 3.9 of Supplementary File 3. According to SUCRA rankings (Fig. 4.4), the top treatments for reducing TG were Standard + GLP-1 (97.7%), Orlistat (85.7%), and GLP-1 (60.0%). Table 9 shows that Standard + GLP-1 significantly reduced TG compared to GLP-1 (SMD = −1.30, 95% CI: −2.05 to −0.56), Flutamide (SMD = −1.62, 95% CI: −2.77 to −0.46), SGLT-2 (SMD = −1.64, 95% CI: −2.84 to −0.45), Standard + Flutamide (SMD = −1.73, 95% CI: −2.89 to −0.58), Standard (SMD = −1.75, 95% CI: −2.56 to −0.93), and Placebo (SMD = −2.29, 95% CI: −3.19 to −1.39). Orlistat also significantly reduced TG compared to Standard + Flutamide (SMD = −1.13, 95% CI: −2.13 to −0.12), Standard (SMD = −1.14, 95% CI: −1.77 to −0.51), and Placebo (SMD = −1.68, 95% CI: −2.34 to −1.02). Additionally, GLP-1 significantly reduced TG compared to Placebo (SMD = −0.99, 95% CI: −1.66 to −0.32), and Standard also showed a significant reduction compared to Placebo (SMD = −0.54, 95% CI: −0.96 to −0.12).

Glucose and insulin metabolism outcomes

HOMA-IR The network meta-analysis for HOMA-IR included 22 studies with 975 patients. Direct comparisons and sample distributions are shown in Fig. 3.10 of Supplementary File 3. According to SUCRA rankings (Fig. 5.1), the top treatments for reducing HOMA-IR were Standard + Flutamide (65.6%), Standard + GLP-1 (65.6%), and SGLT-2 (60.7%). However, as shown in Table 10, only Standard significantly reduced HOMA-IR compared to Orlistat (MD = −3.36, 95% CI: −6.61 to −0.12).

FBG The network meta-analysis for FBG included 17 studies with 736 patients. Direct comparisons and sample distributions are presented in Fig. 3.11 of Supplementary File 3. Based on SUCRA rankings (Fig. 5.2), the top treatments for lowering FBG were Standard + GLP-1 (94.8%), GLP-1 (70.0%), and Standard + SGLT-2 (63.4%). As indicated in Table 11, Standard + GLP-1 significantly reduced FBG compared to Standard (SMD = −1.29, 95% CI: −2.38 to −0.21), Placebo (SMD = −1.80, 95% CI: −3.04 to −0.55), and Flutamide (SMD = −2.10, 95% CI: −3.91 to −0.30).

FINS The network meta-analysis for FINS included 19 studies with 861 patients. Direct comparisons and sample distributions are displayed in Fig. 3.12 of Supplementary File 3. Based on SUCRA rankings (Fig. 5.3), the top treatments for reducing FINS were Standard + GLP-1 (87.5%), Standard + SGLT-2 (71.4%), and GLP-1 (66.7%). As shown in Table 12, Standard + GLP-1 significantly reduced FINS compared to Standard + Flutamide (SMD = −1.26, 95% CI: −2.30 to −0.21).

Risk of Bias and Publication Bias

In the 29 included trials, all studies were rated as low risk for bias in random sequence generation, selective reporting, and other potential biases. For allocation concealment, 8 studies were assessed as unclear risk, while the remaining 21 were rated as low risk. Blinding of participants and personnel was rated as high risk in 5 studies,

Table 7 HDL-C

Orlistat								
0.07 (−1.80,1.94)	Standard + Dpp4							
0.27 (−1.02,1.56)	0.20 (−1.73,2.13)	Standard + Flutamide						
0.68 (−0.21,1.57)	0.61 (−1.03,2.25)	0.41 (−0.60,1.42)	Standard					
0.67 (−0.73,2.07)	0.60 (−1.37,2.56)	0.40 (−1.08,1.88)	−0.01 (−1.09,1.07)	Sglt-2				
0.91 (−0.38,2.20)	0.84 (−1.09,2.77)	0.64 (−0.48,1.77)	0.23 (−0.78,1.24)	0.24 (−1.24,1.72)	Flutamide			
0.90 (0.02,1.79)	0.83 (−0.89,2.56)	0.64 (−0.37,1.65)	0.23 (−0.30,0.75)	0.24 (−0.97,1.44)	−0.01 (−1.01,1.00)	Placebo		
1.22 (−0.08,2.51)	1.15 (−0.76,3.05)	0.95 (−0.43,2.33)	0.54 (−0.42,1.50)	0.55 (−0.90,1.99)	0.31 (−1.07,1.69)	0.31 (−0.75,1.38)	Standard + Glp-1	
1.29 (0.18,2.41)	1.22 (−0.56,3.01)	1.03 (−0.18,2.24)	0.62 (−0.09,1.32)	0.63 (−0.66,1.91)	0.38 (−0.82,1.59)	0.39 (−0.43,1.21)	0.08 (−0.81,0.96)	Glp-1

Table 8 LDL-C

Standard + Glp-1								
−1.24 (−5.60,3.13)	Standard + Dpp4							
−1.45 (−3.50,0.60)	−0.21 (−4.31,3.89)	Glp-1						
−1.48 (−4.71,1.75)	−0.24 (−4.68,4.20)	−0.03 (−2.87,2.81)	Standard + Flutamide					
−1.62 (−3.85,0.61)	−0.38 (−4.13,3.38)	−0.17 (−1.82,1.49)	−0.14 (−2.51,2.24)	Standard				
−1.78 (−5.00,1.45)	−0.54 (−4.98,3.90)	−0.33 (−3.17,2.51)	−0.30 (−2.94,2.35)	−0.16 (−2.53,2.21)	Flutamide			
−1.96 (−5.40,1.48)	−0.72 (−5.30,3.86)	−0.51 (−3.61,2.59)	−0.48 (−4.01,3.06)	−0.34 (−2.96,2.28)	−0.18 (−3.71,3.35)	Sglt-2		
−1.96 (−5.03,1.11)	−0.72 (−5.05,3.60)	−0.51 (−3.17,2.15)	−0.48 (−3.56,2.60)	−0.34 (−2.49,1.81)	−0.18 (−3.26,2.89)	−0.00 (−3.39,3.39)	Orlistat	
−2.38 (−4.85,0.10)	−1.14 (−5.09,2.81)	−0.93 (−2.85,0.99)	−0.90 (−3.27,1.48)	−0.76 (−2.00,0.48)	−0.60 (−2.97,1.77)	−0.42 (−3.32,2.48)	−0.42 (−2.57,1.73)	Placebo

unclear in 14, and low risk in 10. Blinding of outcome assessment showed high risk in 4 studies, unclear in 14, and low risk in the remaining 11 studies. For incomplete outcome data, 9 studies were rated as unclear risk, and 20 as low risk (Supplementary File 5) .

Potential publication bias was evaluated using funnel plots (Supplementary File 4). Scatter plot distributions around the vertical axis varied in symmetry, suggesting possible publication bias. Specifically, Fig. 4.1 and 4.3 showed relatively uniform distributions, while the remaining funnel plots indicated some asymmetry. Egger's test results revealed potential publication bias for TG (Supplementary File 4, Fig. 4.9) and FBG (Fig. 4.11) with p-values < 0.05, suggesting caution in interpreting these outcomes. Egger's test for all other outcomes indicated no significant publication bias, supporting the robustness of the overall analysis across included studies (Figs. 2, 3, 4, 5).

Discussion

This comprehensive network meta-analysis included 29 randomized controlled trials involving 1476 patients diagnosed with PCOS. We evaluated the effects of various pharmacological interventions on metabolic and hormonal outcomes associated with PCOS, yielding several key findings. First, the combination of standard treatment with GLP-1 receptor agonists, such as Liraglutide and Semaglutide, significantly reduced BW, BMI, and WC, outperforming standard treatment alone and placebo. This highlights the potential of combinatory therapies in managing obesity in PCOS. Second, Orlistat demonstrated superior efficacy in lowering testosterone levels, indicating its clinical value for managing

Table 9 TG

Standard + Glp-1									
−0.61 (−1.63,0.41)	Orlistat								
−1.30 (−2.05,−0.56)	−0.69 (−1.53,0.14)	Glp-1							
−1.36 (−2.84,0.12)	−0.75 (−2.13,0.64)	−0.05 (−1.41,1.31)	Standard + Sglt-2						
−1.48 (−3.07,0.11)	−0.87 (−2.37,0.63)	−0.17 (−1.65,1.31)	−0.12 (−1.96,1.72)	Standard + Dpp4					
−1.62 (−2.77,−0.46)	−1.01 (−2.01,0.00)	−0.31 (−1.31,0.68)	−0.26 (−1.75,1.23)	−0.14 (−1.74,1.46)	Flutamide				
−1.64 (−2.84,−0.45)	−1.03 (−2.11,0.04)	−0.34 (−1.39,0.71)	−0.29 (−1.80,1.22)	−0.17 (−1.79,1.45)	−0.03 (−1.23,1.18)	Sglt-2			
−1.73 (−2.89,−0.58)	**−1.13 (−2.13,−0.12)**	−0.43 (−1.43,0.57)	−0.38 (−1.87,1.11)	−0.26 (−1.86,1.34)	−0.12 (−1.04,0.81)	−0.09 (−1.30,1.11)	Standard + Flutamide		
−1.75 (−2.56,−0.93)	**−1.14 (−1.77,−0.51)**	−0.45 (−1.02,0.13)	−0.39 (−1.63,0.84)	−0.27 (−1.64,1.09)	−0.13 (−0.97,0.70)	−0.11 (−0.98,0.77)	−0.01 (−0.85,0.82)	Standard	
−2.29 (−3.19,−1.39)	**−1.68 (−2.34,−1.02)**	**−0.99 (−1.66,−0.32)**	−0.94 (−2.24,0.37)	−0.81 (−2.24,0.61)	−0.68 (−1.51,0.15)	−0.65 (−1.62,0.32)	−0.56 (−1.39,0.27)	−0.54 (−0.96,−0.12)	Placebo

hyperandrogenism. While the combination of standard treatment and GLP-1 receptor agonists also improved hormonal levels, their effects were less pronounced. Third, our analysis showed that combining standard treatment with GLP-1 receptor agonists effectively reduced total cholesterol and LDL-C, important markers for cardiovascular risk in PCOS patients. Finally, this combination therapy exhibited significant advantages in improving insulin resistance and glucose metabolism, particularly in reducing HOMA-IR and FBG. Overall, our findings support a multifaceted therapeutic approach for managing PCOS, potentially enhancing outcomes across metabolic and hormonal dimensions.

Our network meta-analysis provides compelling evidence that combining standard treatments with GLP-1 receptor agonists yields significant advantages across multiple metabolic and hormonal parameters in women with PCOS. Specifically, the combination therapy was superior in reducing body weight, BMI, and waist circumference compared to standard treatment alone or placebo. This is consistent with several RCTs that have demonstrated the additive or synergistic effects of GLP-1 receptor agonists when used alongside metformin, a first-line therapy for PCOS management [44, 45]. For instance, a study by Jensterle et al. found that the addition of liraglutide to metformin resulted in a significantly greater reduction in body weight and waist circumference compared to metformin monotherapy in obese women with PCOS [44]. Similarly, our analysis revealed that the combination therapy not only improved anthropometric measures but also had favorable effects on lipid profiles, including significant reductions in total cholesterol and triglycerides, which are critical risk factors for cardiovascular disease in this population.

The significant advantages observed with the combination of standard treatment and GLP-1 receptor agonists may be attributed to their complementary mechanisms of action targeting the multifaceted pathophysiology of PCOS. Metformin improves insulin sensitivity by activating AMP-activated protein kinase (AMPK), leading to decreased hepatic gluconeogenesis and increased peripheral glucose uptake. GLP-1 receptor agonists, such as liraglutide and semaglutide, enhance glucose-dependent insulin secretion, inhibit glucagon secretion, slow gastric emptying, and promote satiety via central nervous system pathways [46]. The synergistic effect of these agents results in a more pronounced improvement in insulin resistance, as evidenced by significant reductions in HOMA-IR and fasting insulin levels in our analysis. Moreover, the combination therapy's impact on weight loss is particularly noteworthy, as obesity exacerbates insulin resistance and hyperandrogenism in PCOS [47, 48]. The dual action of reducing caloric intake through appetite suppression and improving metabolic parameters positions the combination therapy as a potent intervention for PCOS management.

Additionally, GLP-1 receptor agonists have been shown to exert direct effects on the reproductive axis. Emerging evidence suggests that GLP-1 receptors are expressed in the hypothalamus and pituitary gland, indicating a potential role in modulating gonadotropin secretion [49, 50]. Animal studies have demonstrated that GLP-1

Table 10 HOMA-IR

Standard + Flutamide										
−0.34 (−6.67,6.00)	Standard + Glp-1									
−0.44 (−8.49,7.61)	−0.10 (−6.80,6.60)	SgIt-2								
−0.75 (−6.69,5.19)	−0.41 (−3.25,2.43)	−0.31 (−6.65,6.03)	Glp-1							
−0.60 (−7.15,5.95)	−0.26 (−6.86,6.33)	−0.16 (−8.42,8.09)	0.15 (−6.06,6.36)	Flutamide						
−0.74 (−8.79,7.32)	−0.40 (−7.10,6.31)	−0.30 (−8.61,8.01)	0.01 (−6.34,6.36)	−0.14 (−8.39,8.12)	Standard + SgIt-2					
−1.28 (−6.78,4.23)	−0.94 (−4.16,2.28)	−0.84 (−6.71,5.03)	−0.53 (−2.92,1.86)	−0.68 (−6.47,5.12)	−0.54 (−6.42,5.34)	Standard				
−1.32 (−6.83,4.18)	−0.98 (−4.73,2.76)	−0.88 (−7.14,5.38)	−0.57 (−3.56,2.41)	−0.72 (−6.52,5.08)	−0.58 (−6.85,5.68)	−0.04 (−2.21,2.12)	Placebo			
−1.82 (−9.45,5.81)	−1.49 (−7.38,4.40)	−1.39 (−9.30,6.53)	−1.08 (−6.40,4.25)	−1.22 (−9.06,6.62)	−1.09 (−9.01,6.84)	−0.55 (−5.86,4.77)	−0.50 (−6.18,5.17)	Roflumilast		
−4.28 (−13.48,4.93)	−3.94 (−11.99,4.11)	−3.84 (−13.27,5.59)	−3.53 (−11.28,4.22)	−3.68 (−13.06,5.70)	−3.54 (−12.97,5.89)	−3.00 (−10.37,4.37)	−2.96 (−10.64,4.73)	−2.45 (−11.54,6.63)	Standard + Dpp4	
−4.64 (−10.87,1.59)	−4.30 (−8.83,0.22)	−4.20 (−10.91,2.50)	−3.89 (−7.84,0.05)	−4.04 (−10.53,2.45)	−3.90 (−10.62,2.81)	**−3.36 (−6.61,−0.12)**	−3.32 (−6.67,0.03)	−2.82 (−9.02,3.38)	−0.36 (−8.42,7.69)	Orlistat

Table 11 FBG

Standard + Glp-1										
−0.87 (−1.75,0.02)	Glp-1									
−0.91 (−2.76,0.93)	−0.05 (−1.73,1.64)	Standard + Sglt-2								
−1.07 (−2.87,0.74)	−0.20 (−1.83,1.43)	−0.15 (−2.24,1.94)	Standard + Flutamide							
−1.29 (−2.38,−0.21)	−0.43 (−1.20,0.35)	−0.38 (−1.87,1.11)	−0.23 (−1.70,1.24)	Standard						
−1.29 (−3.23,0.64)	−0.43 (−2.20,1.35)	−0.38 (−2.57,1.81)	−0.23 (−2.40,1.94)	−0.00 (−1.60,1.60)	Standard + Dpp4					
−1.37 (−3.01,0.26)	−0.50 (−1.92,0.91)	−0.46 (−2.52,1.60)	−0.31 (−2.34,1.72)	−0.08 (−1.50,1.34)	−0.08 (−2.22,2.06)	Roflumilast				
−1.40 (−2.91,0.12)	−0.53 (−1.84,0.78)	−0.48 (−2.31,1.35)	−0.33 (−2.14,1.48)	−0.10 (−1.16,0.95)	−0.10 (−2.02,1.82)	−0.02 (−1.79,1.75)	Sglt-2			
−1.55 (−3.10,0.00)	−0.68 (−2.03,0.66)	−0.63 (−2.52,1.25)	−0.48 (−2.27,1.30)	−0.25 (−1.40,0.89)	−0.25 (−2.22,1.71)	−0.18 (−1.98,1.63)	−0.15 (−1.71,1.40)	Orlistat		
−1.80 (−3.04,−0.55)	−0.93 (−1.89,0.04)	−0.88 (−2.54,0.77)	−0.73 (−2.20,0.74)	−0.50 (−1.22,0.22)	−0.50 (−2.25,1.25)	−0.42 (−1.98,1.14)	−0.40 (−1.67,0.87)	−0.25 (−1.38,0.88)	Placebo	
−2.10 (−3.91,−0.30)	−1.24 (−2.87,0.40)	−1.19 (−3.28,0.90)	−1.04 (−2.70,0.62)	−0.81 (−2.28,0.66)	−0.81 (−2.98,1.36)	−0.73 (−2.76,1.30)	−0.71 (−2.52,1.10)	−0.56 (−2.34,1.23)	−0.31 (−1.78,1.16)	Flutamide

Table 12 FINS

Standard + Glp-1										
−0.26 (−1.55,1.04)	Standard + Sglt-2									
−0.40 (−1.04,0.25)	−0.14 (−1.31,1.02)	Glp-1								
−0.42 (−1.44,0.60)	−0.16 (−1.39,1.06)	−0.02 (−0.87,0.83)	Orlistat							
−0.44 (−1.52,0.63)	−0.18 (−1.44,1.07)	−0.04 (−0.95,0.87)	−0.02 (−1.01,0.97)	Sglt-2						
−0.69 (−1.75,0.36)	−0.44 (−1.68,0.81)	−0.29 (−1.17,0.58)	−0.28 (−1.22,0.67)	−0.25 (−1.27,0.76)	Flutamide					
−0.68 (−1.47,0.11)	−0.43 (−1.45,0.60)	−0.28 (−0.83,0.27)	−0.26 (−0.94,0.41)	−0.24 (−0.96,0.48)	0.01 (−0.70,0.72)	Standard				
−0.79 (−1.99,0.40)	−0.54 (−1.99,0.91)	−0.39 (−1.42,0.63)	−0.38 (−1.60,0.85)	−0.35 (−1.61,0.90)	−0.10 (−1.34,1.14)	−0.11 (−1.14,0.91)	Roflumilast			
−0.78 (−1.64,0.08)	−0.52 (−1.63,0.58)	−0.38 (−1.01,0.25)	−0.36 (−1.05,0.33)	−0.34 (−1.17,0.50)	−0.08 (−0.79,0.62)	−0.10 (−0.51,0.31)	0.02 (−1.07,1.11)	Placebo		
−1.21 (−2.64,0.22)	−0.95 (−2.52,0.62)	−0.81 (−2.12,0.50)	−0.79 (−2.16,0.57)	−0.77 (−2.16,0.62)	−0.52 (−1.90,0.87)	−0.53 (−1.72,0.66)	−0.42 (−1.99,1.15)	−0.43 (−1.69,0.82)	Standard + Dpp4	
−1.26 (−2.30,−0.21)	−1.00 (−2.25,0.25)	−0.86 (−1.74,0.02)	−0.84 (−1.78,0.10)	−0.82 (−1.83,0.20)	−0.56 (−1.35,0.23)	−0.58 (−1.29,0.14)	−0.46 (−1.71,0.78)	−0.48 (−1.19,0.24)	−0.05 (−1.43,1.34)	Standard + Flutamide

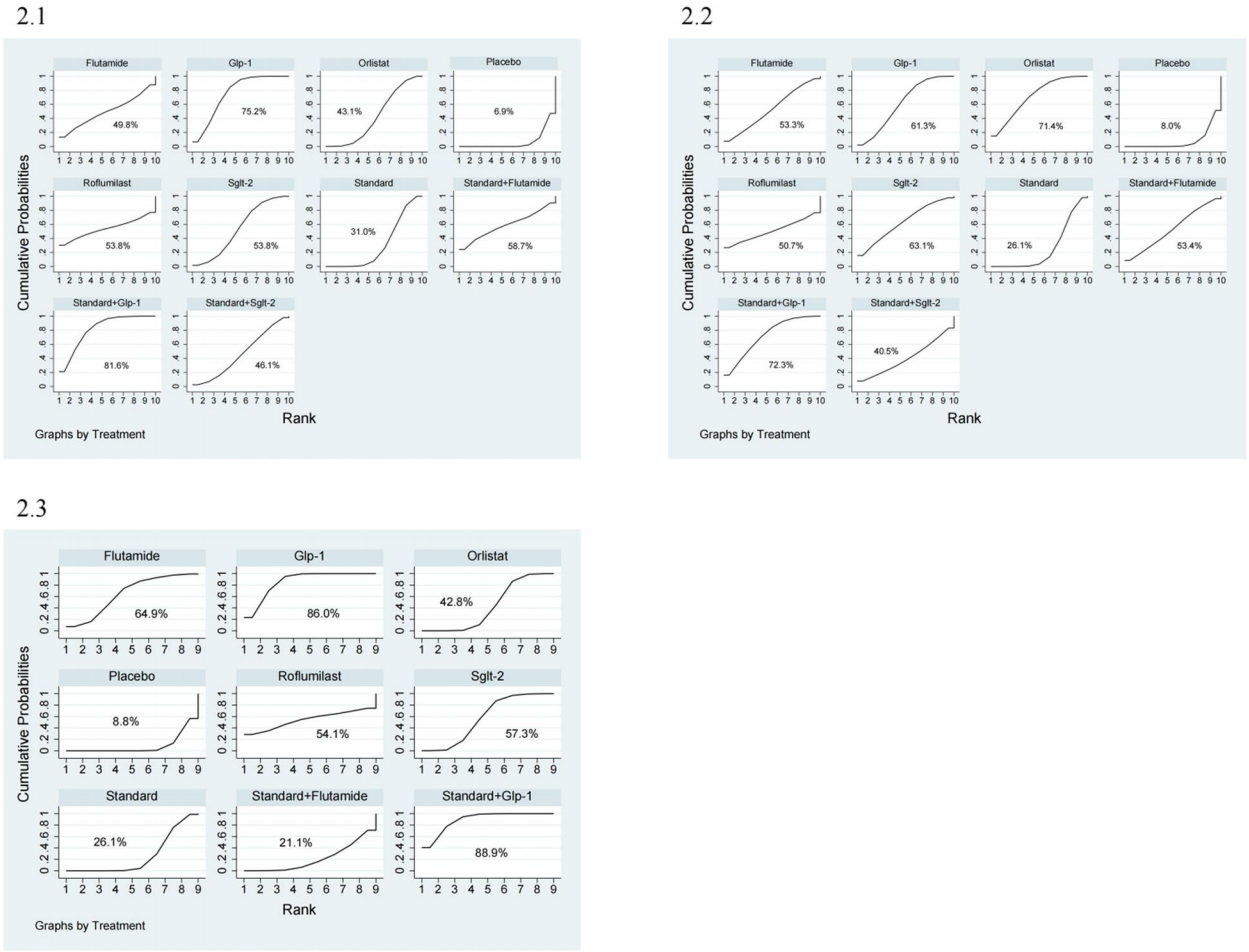

Fig. 2 Ranking of treatment strategies based on probability of their effects for Anthropometric Outcomes. 1: BW 2: BMI, 3: WC

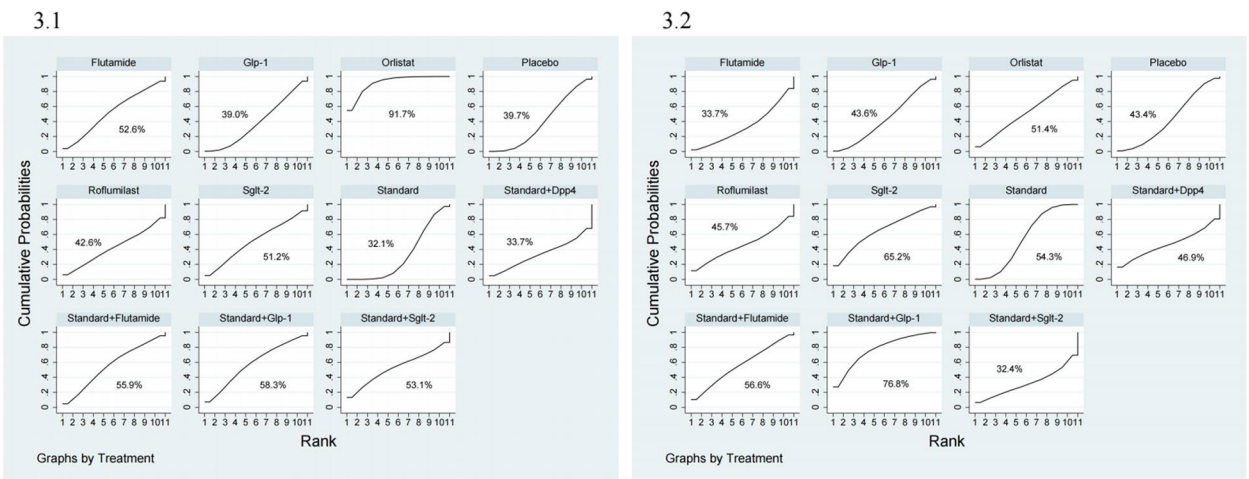

Fig. 3 Ranking of treatment strategies based on probability of their effects for Hormonal Outcomes. 1: Testosterone, 2: SHBG

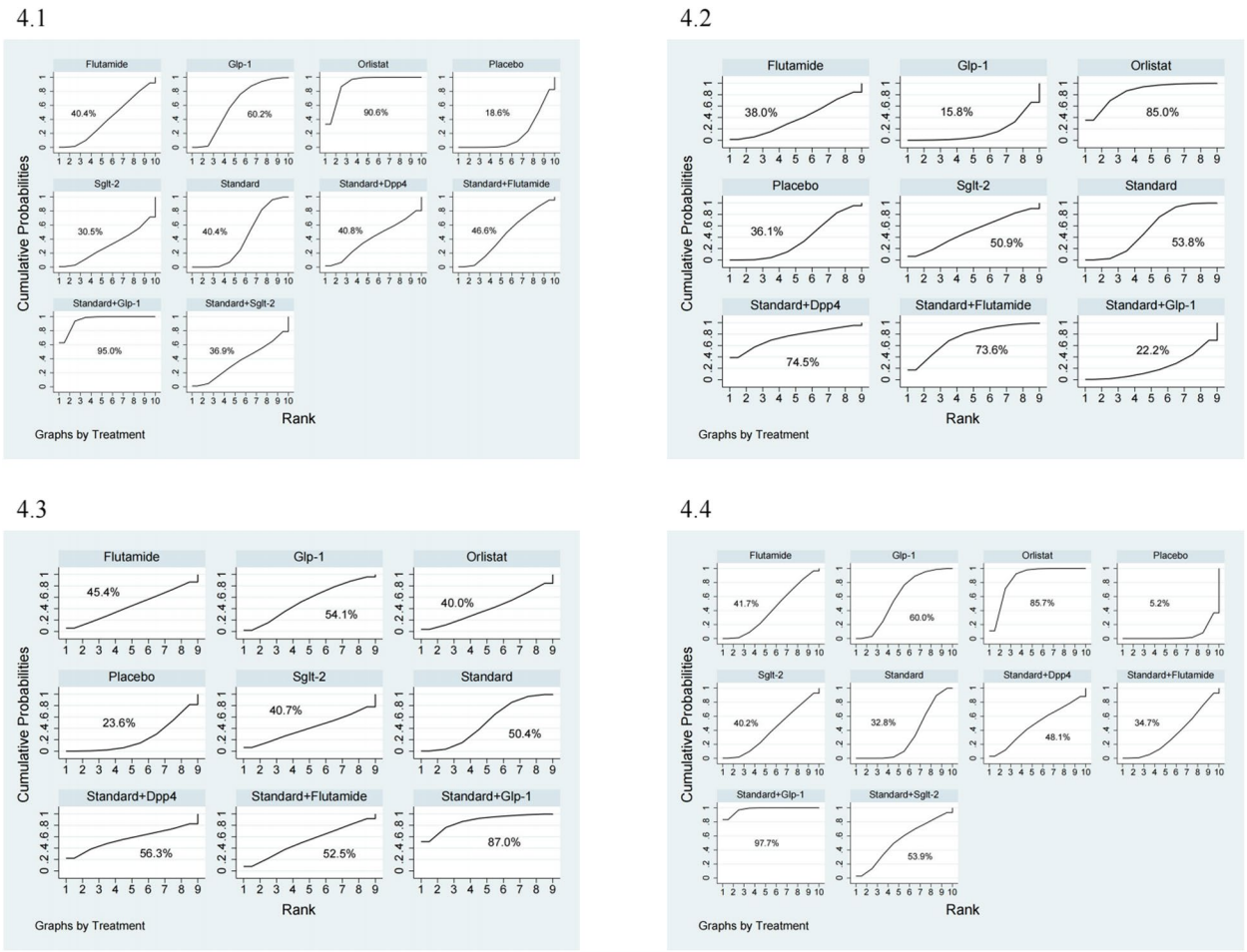

Fig. 4 Ranking of treatment strategies based on probability of their effects for Lipid Outcomes. 1: TC, 2: SCr, 3: HDL-C, 4: LDL-C, 5: TG

receptor activation can influence the hypothalamic-pituitary-gonadal axis, potentially normalizing menstrual irregularities associated with PCOS [49]. Although our analysis did not show a statistically significant impact on SHBG levels, the trend towards hormonal improvement may reflect the multifactorial benefits of GLP-1 receptor agonists beyond metabolic regulation.

Our findings also highlight Orlistat's efficacy in significantly reducing testosterone levels, which is of particular clinical relevance given the central role of hyperandrogenism in PCOS pathogenesis. Orlistat's effect on lowering androgen levels aligns with previous studies that have reported improvements in hyperandrogenic symptoms following Orlistat-induced weight loss [51, 52]. For example, a randomized controlled trial by Colak et al. demonstrated that Orlistat treatment led to significant reductions in serum total testosterone and free androgen index in obese women with PCOS [52]. These findings suggest that Orlistat may offer a targeted therapeutic option for managing hyperandrogenism in PCOS patients, particularly those who are overweight or obese.

The mechanisms by which Orlistat reduces testosterone levels are multifaceted. Primarily, Orlistat induces weight loss by inhibiting gastrointestinal lipases, leading to decreased fat absorption and caloric intake [51, 53]. Weight loss is known to ameliorate insulin resistance and hyperinsulinemia, key drivers of excessive ovarian androgen production in PCOS [53]. Hyperinsulinemia stimulates the theca cells in the ovaries to produce androgens and suppresses hepatic production of SHBG, resulting in elevated free testosterone levels [54]. By reducing body weight and improving insulin sensitivity, Orlistat indirectly decreases ovarian androgen synthesis and increases SHBG levels, thereby lowering circulating free testosterone [55]. Furthermore, there is some evidence to suggest that Orlistat may exert direct inhibitory effects on steroidogenic enzymes involved in androgen biosynthesis, such as 17β-hydroxysteroid dehydrogenase and

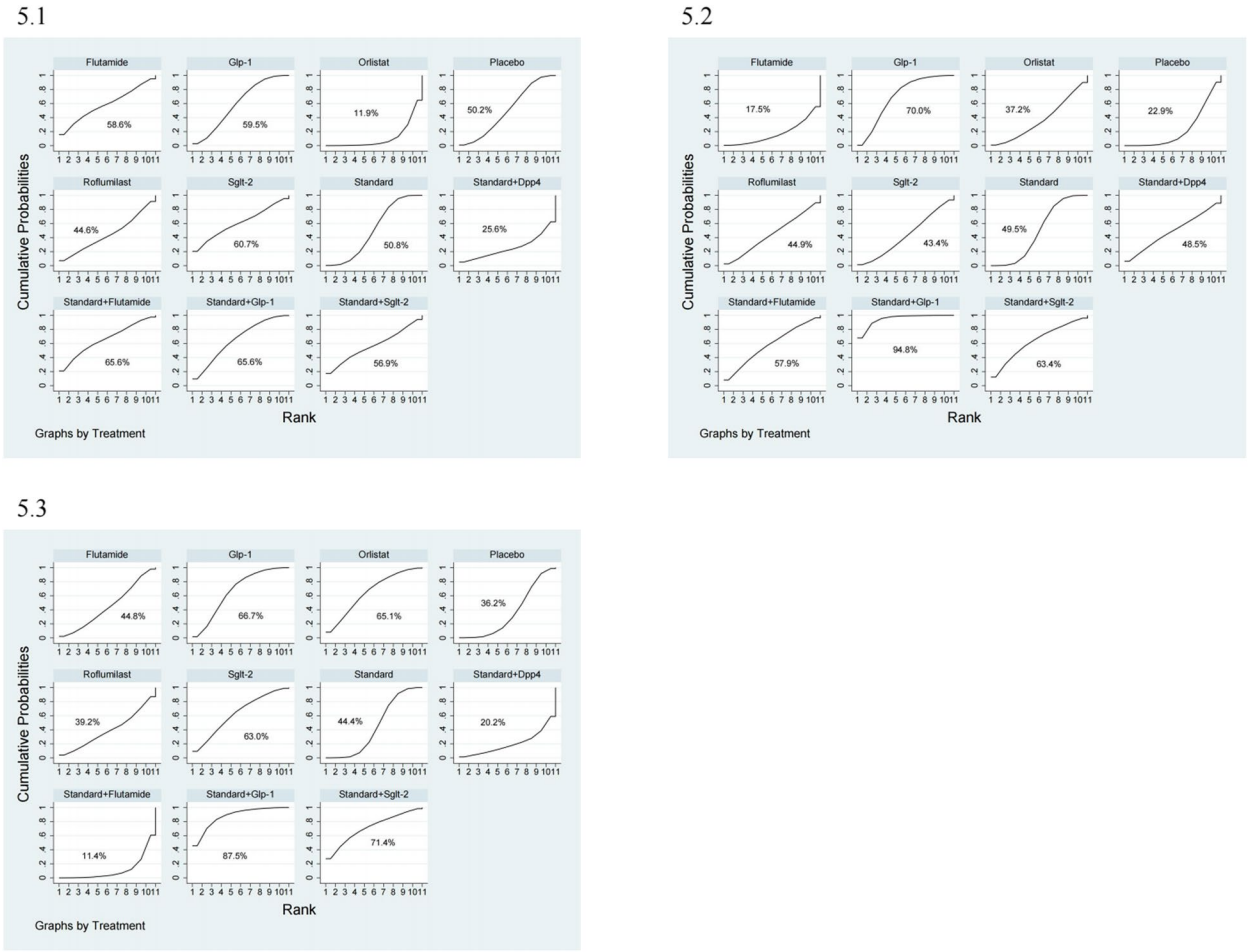

Fig. 5 Ranking of treatment strategies based on probability of their effects for Glucose and Insulin Metabolism Outcomes. 1: HOMA-IR, 2: FBG, 3: FINS

5α-reductase [56]. This weight-independent mechanism may contribute to the significant reduction in testosterone levels observed with Orlistat therapy, although further research is needed to elucidate these pathways fully.

While our network meta-analysis offers valuable insights into the comparative efficacy of pharmacological interventions for PCOS, it is essential to acknowledge certain limitations inherent in our study. First, the heterogeneity among included studies regarding diagnostic criteria, intervention protocols, and patient characteristics may affect the robustness of our conclusions. Despite using random-effects models to mitigate between-study variability, residual confounding factors may persist. Second, the potential for publication bias exists, as indicated by asymmetrical funnel plots for some outcomes. This bias may result from the underreporting of negative or non-significant findings in the literature. Third, the relatively short duration of most included studies (minimum of 12 weeks) limits our ability to assess the long-term efficacy and safety of the interventions. Longitudinal studies with extended follow-up periods are necessary to evaluate the sustainability of therapeutic benefits and to monitor potential adverse effects. Lastly, our analysis focused on surrogate metabolic and hormonal outcomes without incorporating patient-centered endpoints such as quality of life, ovulation rates, or pregnancy outcomes. Future research should aim to include these clinically relevant outcomes to provide a more comprehensive assessment of treatment efficacy.

Conclusion

Our comprehensive network meta-analysis underscores the superior efficacy of combining standard therapy with GLP-1 receptor agonists in improving a spectrum of metabolic and hormonal outcomes in women with PCOS. The combination therapy significantly enhances weight loss, insulin sensitivity, and lipid profiles, addressing key components of PCOS pathophysiology. Orlistat

emerges as a particularly effective agent for reducing androgen levels, offering an additional therapeutic avenue for patients with pronounced hyperandrogenism. These findings advocate for a personalized, multifaceted treatment approach in PCOS management, tailored to individual patient profiles and clinical manifestations. Clinicians should weigh the benefits of combination therapies against potential side effects and patient preferences, aiming to optimize both metabolic and reproductive health outcomes.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Authors' contributions
Yali Bo: Data curation, Formal Analysis, Methodology, Software, Writing – original draft. Jie Zhao: Data curation, Software, Writing – original draft. Chengjiang Liu, Ting Yu: Conceptualization, Supervision, Validation, Visualization, Writing – review & editing. All authors contributed to the manuscript and approved the final version for submission.

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Data availability
All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate
This is a systematic review and meta-analysis, ethics approval and consent to participate are not applicable.

Consent for publication
Not applicable. This study does not involve human participants.

Competing interests
The authors declare no competing interests.

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