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Obesity Pharmacotherapy

Pharmacologic therapy to induce weight loss in women who have obesity/overweight with polycystic ovary syndrome: a systematic review and network meta-analysis

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Summary

Background: Women with polycystic ovary syndrome (PCOS) are almost three times more likely to be obese than those without PCOS. However, we have no specific interventions to induce weight loss so far and rely on drugs used to treat other symptoms of the syndrome or obesity in the general population.

Objective: The objective of this study is to compare the effectiveness of metformin, inositol, liraglutide and orlistat to induce weight loss in women with PCOS and overweight/obesity.

Methods: A search was conducted using the MEDLINE, EMBASE, PubMed and CENTRAL databases. Individually randomized, parallel group trials that evaluated the effects of these pharmacological treatments among adults or adolescents with PCOS and overweight/obesity, compared with a placebo or metformin group, were considered eligible. Registration number: PROSPERO CRD 42017076625.

Results: Twenty-three trials reporting on 941 women were included in the network meta-analysis. The amount of weight lost differed significantly among the drugs (in descending order): liraglutide, orlistat and metformin. Liraglutide alone, liraglutide/metformin and metformin alone significantly reduced waist circumference, but no change was found with orlistat. Data for waist-to-hip ratio were only available for metformin, which had no significant effect.

Conclusion: Liraglutide appears superior to the other drugs in reducing weight and waist circumference.

Keywords: Obesity, overweight, pharmacologic therapy, polycystic ovary syndrome.

Introduction

The World Health Organization has declared 'obesity is one of the greatest public health challenges of the 21st century' (1). Obesity is particularly a problem for women with polycystic ovary syndrome (PCOS) as they have a 2.8-fold increased prevalence (50–80%) compared with women who do not have the syndrome (2,3). In the original description of the syndrome by Stein and Leventhal in 1935, 60% (three of the five women for whom habitus was reported) were obese (4).

Unfortunately, this obesity, which is so common in women with PCOS, exacerbates symptoms of the syndrome (5). Hyperinsulinaemia reduces circulating levels of sex hormone-binding globulin, increasing free testosterone, which inhibits follicular maturation with consequent menstrual irregularity and infertility. Insulin also augments the thecal androgen production responsible for acne and hirsutism (6). In the longer term, hyperinsulinaemia increases the risks of diabetes (type II and gestational), coronary heart disease and endometrial cancer (7–11).

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Weight loss is therefore fundamental to the management of women with PCOS (2,12). Aside from increasing the severity of the symptoms of PCOS, obesity reduces the effectiveness of fertility treatment (ovulation induction and *in vitro* fertilization) and increases the risk of pregnancy complications (10,13). For these reasons, fertility treatment is withheld by the National Health Service for those with a body mass index (BMI) > 30 kg m^{-1} (2). Although lifestyle management is the first line therapy in PCOS for prevention of weight gain and for weight loss (14), the efficacy of lifestyle management for established obesity has been limited in PCOS in the general population (15), and new approaches are needed (16). Moreover, for some women with PCOS and obesity, lifestyle modifications are not effective, or for the women who cannot or are not willing to modify their lifestyle, the pharmacologic therapy to induce weight loss is also very important. Bariatric surgery can also effectively attenuates PCOS and its clinical symptomatology including hirsutism and menstrual irregularity in severely women with obesity (17). The goal for weight reduction in women with PCOS is to improve insulin resistance, reduce hyperandrogenism and alleviate PCOS clinical severity (15,18,19). However, because we do not understand the mechanisms responsible for obesity in women with this condition, we are forced to rely on drugs used to treat other symptoms of the syndrome or those licensed to treat obesity in the general population (7). Based on familiarity and cost, metformin is widely used for this purpose in women with PCOS (20). Other drugs used include orlistat, inositol and liraglutide (21–23); however, their comparative efficacy in women with PCOS is unknown. We have conducted the first systematic review and meta-analysis to compare the effects of these drugs on weight loss in women with PCOS and overweight/obesity.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement to conduct our systematic review (24).

Study eligibility criteria

We included studies that (i) used a randomized, parallel group trial design; (ii) were conducted in the following settings: clinic, hospital, medical centre or community; (iii) recruited adults/adolescents who have obesity/overweight with PCOS; and (iv) included placebo or metformin as the control arm. Where studies reported similar or overlapping data, only the latest or those with a larger sample size were considered for this review. The outcomes of interest included BMI, weight, waist circumference and waist-to-hip ratio (WHR).

Literature search methodology

We searched the following databases for published articles and conference abstracts and proceedings in consultation with a search methodologist: MEDLINE (Ovid), EMBASE (Ovid), PubMed and the Cochrane Central Register of Controlled trials (CENTRAL). The search was performed in July 2017. No language or date restrictions were employed. Qualified librarians were consulted for the search strategy. Medical Subject Heading terms included keywords defining PCOS ('polycystic ovary syndrome', 'Stein-Leventhal syndrome') and the relevant treatments of interest ('metformin', 'liraglutide', 'orlistat', 'inositol'). The full review protocol was registered with PROSPERO under registration number CRD 42017076625.

Study selection

After a primary screening of titles and abstracts (by F. W., Y. W., Y. Z and F. Q.), the full texts of all potentially eligible studies were retrieved. Three review authors (F. W., Y. W. and Y. Z.) independently examined and selected the eligible articles in compliance with the inclusion criteria for the current review. Study investigators were contacted if clarification regarding details of the study was needed. Disagreement with respect to study eligibility was resolved via discussion with the other reviewer (F. Q.). The selection process is presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram.

Data extraction

Two review authors (F. W. and Y. W.) independently extracted the data from each eligible study. Any disagreements were resolved by discussion with a third review author (F. Q.). Data retrieved included characteristics of study, subjects and interventions, as well as outcome measures. Authors were contacted for additional or missing information as required.

Risk of bias

The risk of bias of the included studies was assessed independently by two authors (F. W. and Y. Z.) using the Cochrane Risk of Bias Tool 2.0 with respect to the following aspects: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported results. Any discrepancies were resolved among the authors to reach a consensus.

Statistical analysis

We extracted point estimates of relevant means and standard deviations (SDs) from individual studies. This includes mean difference and its associated SD between the

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comparison groups after the experiment. If the SD associated with the mean difference was not reported, then a 95% confidence interval was used for the computation of SD. Moreover, if the mean difference and associated SD between the comparison groups was not reported, we extracted the arm-specific mean and SD both before and after the treatment to calculate these quantities. The formula for computing the mean change and its associated SD for a specific arm referred to Dias *et al*. (25). The mean of the comparison groups was assumed to follow a normal distribution, and, therefore, the calculation of mean difference (and associated SD) was based on the subtraction of two independent normal distributions (26). If the equal variance assumption is valid (i.e. the variances of the pairwise groups were comparable), the pooled SD was calculated as $S_{pooled} = \sqrt{\frac{S_1^2(n_1-1)+S_2^2(n_2-1)}{n_1+n_2-2}}$, where n_1, n_2 are the sample size for the two arms and S_1, S_2 are the arm-specific SDs; if the equal variance assumption does not hold, the following formula was applied to compute the pooled SD: $S_{pooled} = \sqrt{\frac{S_1^2}{n_1}+\frac{S_2^2}{n_2}}$.

A network meta-analysis (25) was performed to simultaneously compare the efficacy of different treatment options for managing weight (i.e. BMI and absolute weight change) and waist circumference (i.e. absolute waist change). The purpose of a network meta-analysis is to combine results from direct and indirect comparisons of treatment effect in a single analysis. For example, an estimated difference of treatment effect between drug A and drug C can be obtained by comparing trials of drug A versus B with that of drug B versus C. The network was graphed to illustrate the pairwise comparisons between different treatment options. We assessed both the heterogeneity within the trial and the inconsistency between trials using the I^2 statistic and p-value. A standard random-effects meta-analysis was conducted to compare the efficacy of metformin and placebo in terms of change in WHR as the number of eligible studies for this outcome of interest is not enough to construct a network.

We used standard meta-analyses with a random-effects model to examine any heterogeneity that may exist in each of the pairwise treatment comparisons (e.g. metformin versus placebo and orlistat versus metformin). The statistical heterogeneity was assessed with the I^2 statistic and p-value. In terms of inconsistency, heat plots were provided to visualize whether there was disagreement between direct and indirect comparisons (27,28).

Subgroup analysis was performed for studies that reported an outcome of interest (i.e. BMI, and weight and waist circumference) with the same treatment duration (12 or 24 weeks). A network meta-analysis was used for outcomes reported at 12 weeks (because more than two treatments were compared), whereas a standard meta-analysis was applied for outcomes reported at 24 weeks (only metformin and placebo were compared).

A funnel plot and a regression test that detected any asymmetry of the funnel plot were used to examine publication bias for standard meta-analysis. The p-value associated with the Egger's test statistic was also reported.

Sensitivity analysis was conducted to explore the effect of the summary estimate by excluding studies that were considered to result in high heterogeneity (i.e. $I^2 > 50\%$) in the pairwise standard meta-analysis.

All the analyses were performed in R using the packages 'netmeta' (used for network meta-analysis) (29) and 'metafor' (used for standard meta-analysis) (30).

Results

Search results

The search strategy yielded 4,307 studies; however, 3,848 studies were excluded because it was clear from the title or abstract that they did not fulfil the selection criteria. After full-text review of 459 potential studies, we further excluded 15 duplicates, 318 studies not meeting the selection criteria and 100 studies due to lack of essential data (e.g. mean and SD of the change of BMI, body weight, waist circumference or WHR between before and after interventions cannot be retrieved or computed). A total number of 26 studies were included for the systemic review, among which three studies were excluded because different preparations of inositol were examined. This resulted in 23 eligible studies for the meta-analysis. Details of the literature search and selection process are shown in Fig. 1.

Characteristics of included studies

Table 1 presents characteristics of included studies. Trials were performed in European (31–46), American (47–52) and Asian (53–56) countries. Participants in these trials were recruited from outpatient clinics, hospitals or medical centres and were diagnosed with PCOS according to either the National Institutes of Health or Rotterdam criteria. Participants aged 18 years to menopause were included in 24 studies, and two studies examined the effect of metformin on weight reduction in adolescent women (49,50). Apart from two studies where liraglutide 1.8 mg d^{-1} for 26 weeks and 3.0 mg d^{-1} for 12 weeks were applied (40,41), 1.2 mg d^{-1} was used for 12 weeks in the remaining five studies examining the efficacy of liraglutide. The use of liraglutide1.2 mg d^{-1} in combination with metformin 2.0 g d^{-1} was identified in four trials (36,39,40,42). Participants received a dosage of metformin ranging from 1.5 to 2.0 g d^{-1} for 12 or 24 weeks. The dose of orlistat was 360 mg d^{-1}, and the duration of treatment was 12 weeks in all relevant studies. In addition, over 50% of the trials examining metformin and orlistat recommended lifestyle modifications such as dieting and exercise, whereas the

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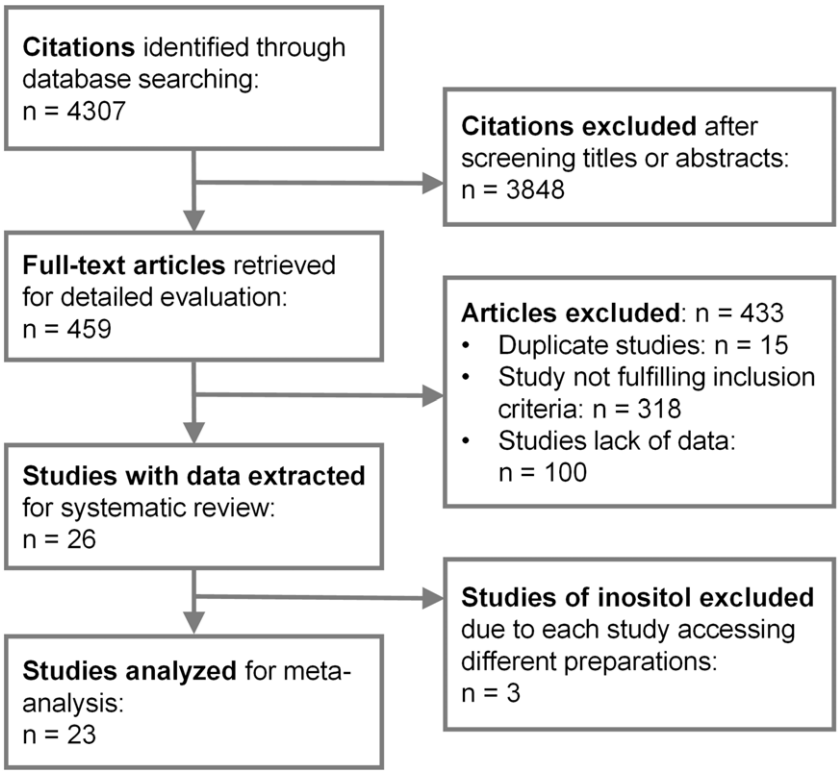


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection. Full-text articles included abstract only publications.

corresponding figure was only 28.6% for trials examining liraglutide. For studies included in the meta-analysis, the dropout rate was 9.2% (12/130) for liraglutide alone, 6.0% (3/50) for liraglutide + metformin, 12.8% (47/366) for metformin alone, 5.4% (7/130) for orlistat and 9.5% (30/315) for placebo. Two studies did not report the dropout rate in each arm. Three studies compared the effects of inositol; however, Nestler *et al.* (52) studied D-chiro-inositol, Gerli *et al.* (45) studied myo-inositol and Nordio and Proietti (46) studied myo-inositol alone or in combination with D-chiro-inositol. The results of these studies could therefore not be combined for meta-analysis. None of the trials assessing inositol included lifestyle modification.

Results from risk of bias assessment

Using the RoB 2.0 tool (57), of 26 randomized controlled trials (RCTs), there were 16 (61.5%) RCTs with low risk of bias arising from the randomization process, 23 (88.5%) RCTs with low risk of bias due to deviations from intended interventions and 19 (73.1%) RCTs with low risk of bias due to missing outcome data; all assessed RCTs had low risk of bias in measurement of the outcome, and 24 (92.3%) RCTs had low risk of bias in selection of the reported results. RoB could not be assessed for Jensterle *et al.* (42) because of insufficient information. Low risk, some concerns and high risk of allover bias were found in 9 (34.6%) (33–35,41,43,44,47,52,56), 10 (38.5%) (32,36,38–40,46,48,49,53,55) and 6 (23.1%) (31,37,45,50,51,54) RCTs. The high risk of allover bias originated from missing outcome data (31,37,45,50,51) and selection of the reported results (54). Table 2 shows results from the risk of bias assessment.

Efficacy outcomes

The network of eligible comparison for efficacy is presented in Fig. 2. While metformin was directly compared with all the other treatments, the comparisons between the remaining four treatments (i.e. liraglutide alone, the combination of liraglutide and metformin, orlistat and placebo) were connected either directly or indirectly by at least one trial.

Our network meta-analysis included 23 RCTs with a total number of 941 participants. Apart from four trials where a combination of liraglutide and metformin (60 women) was evaluated, the remaining trials offered a single drug as an intervention, including liraglutide (6 trials, of which 5 used a dose below the 3-mg licensed dose for obesity treatment, 118 women), metformin (19 trials, 338 women), orlistat (5 trials, 123 women) and placebo (14 trials, 302 women).

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Table 1 Characteristics of the studies included in the systematic review

Study	Country	Study setting	PCOS diagnostic criteria	Inclusion criteria (e.g. age [year], BMI [kg m^{-2}])	Exclusion criteria
Pasquali *et al.* (31)	Italy	Outpatient clinic (endocrine and gastroenterology)	NIH	BMI ≥ 28, WHR ≥ 0.80, normal cortisol suppression, 17-hydroxyprogesterone and PRL	Thyroid dysfunction, type II diabetes, concomitant cardiovascular, renal and liver dysfunction, other causes of hyperandrogenism, medication or dieting for previous 3 months
Chou *et al.* (47)	Brazil	Gynaecology service of hospital	NIH	Age: 16–42, BMI ≥ 30	Smoking, kidney or liver disease, medication in previous 3 months, pregnancy, hyperprolactinaemia, thyroid dysfunction, androgen-producing neoplasms and late-onset congenital adrenal hyperplasia
Gambineri *et al.* (32)	Italy	Outpatient clinic	NIH and Rotterdam	BMI ≥ 28, WHR ≥ 0.80	Thyroid, cardiovascular, renal or liver dysfunction, Cushing's syndrome, congenital adrenal hyperplasia, medication or significant modification in body weight for previous 3 months, dieting
Maciel *et al.* (48)	Brazil	Division of Endocrine Gynaecology	NIH	Age: 17–32, no secondary causes of anovulation, no lipid-lowering drugs, antidiabetic medications, hormonal contraception in previous 3 months	Cushing's syndrome, late-onset 21-hydroxylase deficiency, thyroid dysfunction, hyperprolactinaemia, androgen-secreting tumours, diabetes, chronic renal or hepatic disease
Onalan *et al.* (53)	Turkey	Reproductive endocrinology clinic	NIH	Oligomenorrhea	Other causes of hyperandrogenism, medications altering insulin secretion or action, Cushing's syndrome, non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency, hyperprolactinaemia, thyroid dysfunction, type II diabetes
Gambineri *et al.* (33)	Italy	University medical centre, endocrine division	Rotterdam	Age: 18–45, BMI ≥ 28, waist circumference ≥ 88 cm	Medication or significant modification in body weight in the previous 3 months or dieting, hyperprolactinaemia, Cushing's syndrome, late-onset congenital adrenal hyperplasia, thyroid dysfunction, diabetes, cardiovascular, renal or liver diseases

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Table 1 (Continued)

Study	Country	Study setting	PCOS diagnostic criteria	Inclusion criteria (e.g. age [year], BMI [kg m^{-2}])	Exclusion criteria
Tang *et al.* (34)	UK	Infertility clinic	Rotterdam	Anovulatory PCOS, age: 18–39, BMI > 30, desire to conceive, not pregnant	Hypercortisolism, congenital adrenal hyperplasia, hormone therapy in previous 6 weeks, chronic disease that could interfere with the absorption, distribution, metabolism or excretion of metformin, renal or liver disease, significant systemic disease or diabetes, pathology of the genital tract
Hoeger *et al.* (49)	USA	Community or local physician referral	NIH	Age: 12–18, BMI > 95th percentile	Other causes of hyperandrogenism and menstrual irregularity
Ladson *et al.* (50)	USA	Medical college	NIH	Age: 13–18, BMI > 27, generally healthy	Confounding medications
Sova *et al.* (35)	Finland	University hospital	Rotterdam	BMI ≥ 27	Diabetes, hormone-preparation, smoker, drinker, active liver disease, cardiac failure, liver or renal failure, pregnancy, lactation
Amiri *et al.* (54)	Iran	PCOS clinic	Rotterdam	Age: 18–40, 19 < BMI < 35, infertile, overweight and obese, waist circumference ≥ 88 cm	Hormonal and metformin treatment, attempt to lose weight in 3 recent months, hyperprolactinaemia, Cushing's syndrome, late-onset congenital adrenal hyperplasia, thyroid dysfunction, diabetes, cardiovascular, renal and liver diseases, pregnancy and athletes
Jensterle Sever *et al.* (36)	Slovenia	Outpatient clinic, department of endocrinology, diabetes and metabolic diseases, university medical centre	NIH	Age: >18, premenopausal, BMI ≥ 30, body weight loss <5% with 2 g d^{-1} metformin in previous 6 months	Diabetes, carcinoma, personal or family history of MEN2, significant cardiovascular, kidney or liver disease, medications other than metformin affecting reproductive or metabolic functions or statins in previous 3 months
Jensterle *et al.* (37)	Slovenia	University medical centre	NIH	Age: 18 to menopause, BMI ≥ 30, normal PRL and thyroid function	Cushing's syndrome, congenital (non-classic) adrenal hyperplasia, diabetes, carcinoma, personal or family history of MEN2, significant cardiovascular, kidney or hepatic disease, medications affecting reproductive or metabolic functions, statins in previous 3 months, insulin-sensitizing drugs ever

(*Continues*)

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Table 1 (Continued)

Study	Country	Study setting	PCOS diagnostic criteria	Inclusion criteria (e.g. age [year], BMI [kg m^{-2}])	Exclusion criteria
Jensterle *et al.* (38)	Slovenia	University medical centre	Rotterdam	Age: 18 to menopause, BMI ≥ 30	Carcinoma or neuropsychiatric events, personal or familial history of multiple endocrine, neoplasia 2, significant cardiovascular, kidney or hepatic disease, medications affecting reproductive or metabolic functions in previous 6 months
Jensterle *et al.* (39)	Slovenia	University medical centre	Rotterdam	Age: 18 to menopause, BMI ≥ 30	Carcinoma, significant cardiovascular, kidney or hepatic disease, medications affecting reproductive or metabolic functions
Jensterle *et al.* (40)	Slovenia	Outpatient clinic, department of endocrinology, diabetes and metabolic diseases, university medical centre	Rotterdam	Age: 18 to menopause, BMI ≥ 30	Carcinoma, significant cardiovascular, kidney or hepatic disease, medications affecting reproductive or metabolic functions
Nylander *et al.* (41)	Denmark	Social media, private practising gynaecologists, outpatient PCOS clinic	Rotterdam	Age: 18 to menopause, BMI ≥ 25 and/or insulin resistance	Pregnancy, breastfeeding, smoking >10 cigarettes/day, type II diabetes, hypertension, overt inflammatory disease, herbal medicine or medications affecting \haemostatic system, hormonal contraceptives in previous 6 months, antidiabetic or antihypertensive drugs in previous 3 months
Jensterle *et al.* (42)	Slovenia	University medical centre	Rotterdam	Infertile obese, poor response to lifestyle intervention regarding weight loss	N/A
Jayagopal *et al.* (43)	UK	Gynaecology outpatient clinic	NIH	No concurrent illness, no medication in previous 6 months, no previous pregnancy and no plan to conceive	Non-classical 21-hydroxylase deficiency, hyperprolactinaemia, Cushing's disease, androgen-secreting tumours, inability to comply, impaired fasting glycaemia, oestrogen therapy, untreated hypothyroidism, drug or alcohol abuse, breast or uterine cancer
Cho *et al.* (44)	UK	Endocrinology clinic	Rotterdam	Obese, hyperandrogenic, anovulatory Caucasian	Medications altering insulin resistance in previous 3 months, diabetes

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Table 1 (Continued)

Study	Country	Study setting	PCOS diagnostic criteria	Inclusion criteria (e.g. age [year], BMI [kg m^{-2}])	Exclusion criteria
Metwally *et al.* (51)	UK	Hospital	Rotterdam	Age: 18–40, BMI ≥ 30, anovulation	Contraindications for medications: renal or hepatic impairment, malabsorption syndrome, cholestasis, type II diabetes, pregnancy, breastfeeding
Ghandi *et al.* (55)	Iran	Gynaecology outpatient clinic	Rotterdam	Age: 18–40, BMI ≥ 30, no medication, not dieting in previous 3 months	Eumenorrheic PCOS, impaired fasting glycaemia, untreated hypothyroidism, renal or hepatic impairment, hyperprolactinaemia and non-classical 21-hydroxylase deficiency
Moini *et al.* (56)	Iran	Clinic	Rotterdam	Age: 19–38, BMI ≥ 25, no hormonal medications, not dieting in previous 6 months	Cholestasis, liver or renal disease, malabsorption, hypothyroidism
Nestler *et al.* (52)	Venezuela	Hospital clinic	NIH	Age: 18–40, BMI ≥ 28, normal thyroid function and PRL	Type II diabetes or medications in previous 2 months
Gerli *et al.* (45)	Italy	Gynaecology, endocrine, and infertility outpatient clinics	Rotterdam	Age: <35	Hyperprolactinaemia, abnormal thyroid function, congenital adrenal hyperplasia
Nordio and Proietti (46)	Italy	N/A	Rotterdam	Age: 18–41, BMI > 27	Type II diabetes, smoking or drinking

Source	Intervention group	Lifestyle modification	Design, duration	Sample size	Mean age (year)	Outcomes extracted
Pasquali *et al.* (31)	MET: 850 mg BID PO PBO	Yes	RCT 24 weeks	MET: 10; PBO: 8	MET: 30.8; PBO: 32.3	Baseline, follow-up in BMI, weight, waist circumference and WHR
Chou *et al.* (47)	MET: 500 mg TID PO PBO	N/A	RCT 12 weeks	MET: 14; PBO: 16	MET: 24; PBO: 24.5	Baseline, follow-up BMI and WHR
Gambineri *et al.* (32)	MET: 850 mg BID PO PBO	Yes	RCT 24 weeks	MET: 10; PBO: 10	MET: 26.1; PBO: 27.1	Baseline, follow-up and change in BMI, weight
Maciel *et al.* (48)	MET: 1,500 mg d^{-1} PO PBO	N/A	RCT 24 weeks	MET: 8; PBO: 6	MET: 20.5; PBO: 21.1	Baseline, follow-up BMI
Onalan *et al.* (53)	MET: 500 mg for 5 d QD PO, 850 mg BID for 6 months PBO	No	RCT 24 weeks	MET: 27; PBO: 31	MET: 27.2; PBO: 25.5	Baseline and change in BMI, weight and WHR

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Source	Intervention group	Lifestyle modification	Design, duration	Sample size	Mean age (year)	Outcomes extracted
Gambineri *et al.* (33)	MET: 850 mg BID PO PBO	Yes	RCT 24 weeks	MET: 20; PBO: 19	MET: 28; PBO: 26	Baseline, follow-up BMI, weight, waist circumference
Tang *et al.* (34)	MET: 850 mg Q12H PO PBO	Yes	RCT 24 weeks	MET: 56; PBO: 66	MET: 29.7; PBO: 29.8	Baseline, follow-up and change in BMI, weight, waist circumference and WHR
Hoeger *et al.* (49)	MET: 425 mg QD PO, gradually to 850 mg BID PBO	No	RCT 24 weeks	MET: 6; PBO: 10	MET: 16; PBO: 15.4	Baseline, follow-up BMI, waist circumference
Ladson *et al.* (50)	MET: 500 mg d^{-1} PO, increased 500 mg every 5 d up to 2,000 mg d^{-1} PBO	Yes	RCT 24 weeks	MET: 10; PBO: 8	MET: 16.1; PBO: 15.4	Baseline BMI, weight, waist circumference and waist circumference change
Sova *et al.* (35)	MET: 1,000 mg BID PO PBO	N/A	RCT 12 weeks	MET: 23; PBO: 27	MET: 29.2; PBO: 27.4	Baseline, follow-up BMI, weight, waist circumference and WHR
Amiri *et al.* (54)	MET: 500 mg TID PO PBO	Yes	RCT 24 weeks	MET: 25; PBO: 26	25.6	Follow-up and change in BMI, waist circumference and WHR
Jensterle Sever *et al.* (36)	LIRA: 0.6 mg QD SC, gradually increased to 1.2 mg QD after 1 week MET: 1,000 mg BID PO LIRA + MET	No	RCT 12 weeks	LIRA: 11; MET: 14; LIRA + MET: 11	LIRA: 31.5; MET: 31.3; MET + LIRA: 31.1	Baseline and follow-up BMI, weight, waist circumference
Jensterle *et al.* (37)	LIRA: 0.6 mg QD SC., gradually increased to 1.2 mg QD after 1 week MET: 500 mg QD PO, increased by 500 mg every 3 d, up to 1,000 mg BID PO	No	RCT 12 weeks	LIRA: 14; MET: 14	LIRA: 29.5; MET: 25.3	Baseline and follow-up BMI, weight, waist circumference
Jensterle *et al.* (38)	LIRA: 0.6 mg QD SC, gradually increased to 1.2 mg QD after 1 week	No	RCT 12 weeks	LIRA: 14; MET: 13	30.7	Baseline and follow-up BMI, weight, waist circumference

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Source	Intervention group	Lifestyle modification	Design, duration	Sample size	Mean age (year)	Outcomes extracted
	MET: 500 mg QD PO, increased by 500 mg every 3 d, up to 1,000 mg BID					
Jensterle *et al.* (39)	LIRA: 0.6 mg QD SC, gradually increased to 1.2 mg QD after 1 week MET + LIRA: MET 500 mg QD PO, increased by 500 mg every 3 d, up to 1,000 mg BID, ≥1,000 mg BID metformin for 14 d prior to treatment with 1.2 mg LIRA QD SC	Yes	RCT 12 weeks	LIRA: 21; MET + LIRA: 22	LIRA: 30.3; MET + LIRA: 30.4	Baseline and follow-up BMI, weight, waist circumference
Jensterle *et al.* (40)	LIRA: 0.6 mg QD SC gradually increased to 3 mg QD MET + LIRA: MET 500 mg QD PO, increased by 500 mg every 3 d, up to 1,000 mg BID, LIRA 0.6 mg QD SC, gradually increased to 1.2 mg QD	Yes	RCT 12 weeks	LIRA: 14; MET + LIRA: 14	LIRA: 34.6; MET + LIRA: 31.6	Baseline, follow-up and change in BMI, weight, waist circumference
Nylander *et al.* (41)	LIRA: 0.6 mg QD SC for 1 week, 1.2 mg for next week and 1.8 mg for the rest period PBO	N/A	RCT 26 weeks	LIRA: 44; PBO: 21	31.4	Baseline, change in BMI, weight, waist circumference and WHR
Jensterle *et al.* (42)	MET + LIRA: MET 1,000 mg BID PO and LIRA 1.2 mg QD SC MET: 1000 mgBID PO PBO	N/A	RCT 12 weeks	MET + LIRA: 13; MET: 11; PBO: 11	30.8	Baseline BMI and weight change

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Source	Intervention group	Lifestyle modification	Design, duration	Sample size	Mean age (year)	Outcomes extracted
Jayagopal *et al.* (43)	ORL: 120 mg TID PO MET: 500 mg QD PO for 1 week, 500 mg BID for 1 week, 500 mg TID for the rest period	No	RCT 12 weeks	ORL: 10; MET: 11	27	Baseline, follow-up and change in weight
Cho *et al.* (44)	ORL: 120 mg TID PO MET: 500 mg QD PO for 1 week, 500 mg BID for 1 week, 500 mg TID for the rest period	Yes	RCT 12 weeks	ORL: 10; MET: 10	26.4	Baseline, follow-up and change in BMI
Metwally *et al.* (51)	ORL: 120 mg TID PO MET: 500 mg QD PO for 1 week, 500 mg BID for 4 weeks, increased in 500 mg increments every 4 weeks to 2,000 mg d^{-1}	Yes	RCT 12 weeks	ORL: 20; MET: 16	ORL: 30.6; MET: 28.8	Baseline, follow-up BMI, waist circumference
Ghandi *et al.* (55)	ORL: 120 mg TID PO MET: 500 mg QD PO for 1 week, 500 mg BID for 1 week, 500 mg TID for the rest period	N/A	RCT 12 weeks	ORL: 40; MET: 40	27	Baseline, follow-up and change in BMI, weight, waist circumference
Moini *et al.* (56)	ORL: 120 mg TID PO PBO	Yes	RCT 12 weeks	ORL: 43; PBO: 43	ORL: 26.8; PBO: 27.4	Baseline, follow-up BMI, weight, WHR
Nestler *et al.* (52)	DCI: 1,200 mg QD PO PBO	No	RCT 6–8 weeks	DCI: 22; PBO: 22	DCI: 29; PBO: 26	Baseline, follow-up BMI, WHR
Gerli *et al.* (45)	MI: 100 mg BID PO PBO	N/A	RCT 14 weeks	MI: 121; PBO: 142	MI: 28.6; PBO: 29.2	Baseline, follow-up BMI, WHR
Nordio and Proietti (46)	MI: 2 g MI BID PO MI + DCI: 550 mg MI, 13.8 mg DCI BID PO	No	RCT 24 weeks	MI: 24; MI + DCI: 26	MI: 28.2; MI + DCI: 27.9	Baseline, follow-up BMI, WHR

BID, twice a day; BMI, body mass index; DCI, D-chiro-inositol; LIRA, liraglutide; MEN2, multiple endocrine neoplasia type 2; MET, metformin; MI, myo-inositol; N/A, not applicable; NIH, the National Institutes of Health; ORL, orlistat; PBO, placebo; PCOS, polycystic ovary syndrome; PO, oral administration; PRL, prolactin; Q12H, every 12 h; QD, once a day; RCT, randomized controlled trial; SC, subcutaneous injection; TID, three times a day; WHR, waist-to-hip ratio.

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Table 2 Risk of bias assessment using RoB 2.0 tool

Study	Bias domain						
	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall bias	Setting of randomized trials
Pasquali *et al.* (31)	Low risk	Low risk	High risk	Low risk	Low risk	High risk	Double-blind, placebo-controlled trial
Chou *et al.* (47)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Double-blind, placebo-controlled trial
Gambineri *et al.* (32)	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns	Single-blind, placebo-controlled trial
Maciel *et al.* (48)	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns	Double-blind, placebo-controlled trial
Onalan *et al.* (53)	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns	Double-blind, placebo-controlled trial
Gambineri *et al.* (33)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Single-blind, placebo-controlled trial
Tang *et al.* (34)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Double blind, placebo-controlled trial
Hoeger *et al.* (49)	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns	Double-blind, placebo-controlled trial
Ladson *et al.* (50)	Low risk	Low risk	High risk	Low risk	Low risk	High risk	Double-blind, placebo-controlled trial
Sova *et al.* (35)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Double-blind, placebo-controlled trial
Amiri *et al.* (54)	Low risk	Low risk	Low risk	Low risk	High risk	High risk	Single-blind, placebo-controlled trial
Jensterle Sever *et al.* (36)	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns	Open-label parallel trial
Jensterle *et al.* (37)	Some concerns	Low risk	High risk	Low risk	Low risk	High risk	Open-label parallel trial
Jensterle *et al.* (38)	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns	Open-label parallel trial
Jensterle *et al.* (39)	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns	Open-label parallel trial
Jensterle *et al.* (40)	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns	Open-label parallel trial
Nylander *et al.* (41)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Double-blind, placebo-controlled trial
Jayagopal *et al.* (43)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Open-label, parallel trial
Cho *et al.* (44)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Open-label, parallel trial
Metwally *et al.* (51)	Low risk	Low risk	High risk	Low risk	Low risk	High risk	Open-label parallel trial
Ghandi *et al.* (55)	Some concerns	Some concerns	Low risk	Low risk	Low risk	Some concerns	Open-label parallel trial
Moini *et al.* (56)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Double-blind, placebo-controlled trial
Nestler *et al.* (52)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Double-blind, placebo-controlled trial
Gerli *et al.* (45)	Low risk	Low risk	High risk	Low risk	Low risk	High risk	Double-blind, placebo-controlled trial
Nordio and Proietti (46)	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns	Open-label parallel trial

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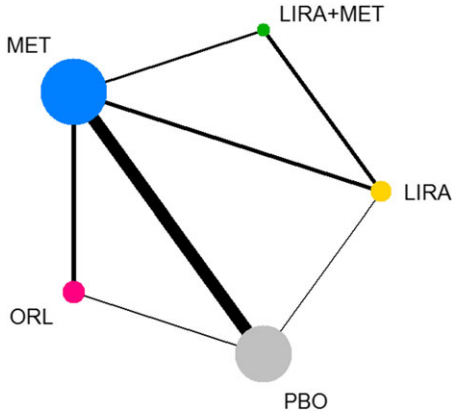


Figure 2 Network of eligible comparisons for efficacy. The size of the circles is proportional to sample size, and the width of lines is proportional to the number of trials. LIRA, liraglutide; MET, metformin; ORL: orlistat; PBO, placebo. [Colour figure can be viewed at wileyonlinelibrary.com]

Compared with the placebo, all the interventions (liraglutide, metformin, orlistat and liraglutide in combination with metformin) resulted in a significant reduction in BMI in women with PCOS and overweight/obesity (Fig. 3A). The efficacy of all the treatments was compared pairwise (Table 3). Using subgroup analysis, only orlistat significantly reduced BMI after 12 weeks of treatment (Fig. 3B and Table 3). Similarly, there was no significant impact of metformin on BMI reduction after 24 weeks of treatment (Fig. 3C). The funnel plot showed minor asymmetry (Fig. S1A).

Compared with the placebo, all the interventions, liraglutide, metformin, orlistat and the combination of liraglutide and metformin led to a significant decrease in weight (Fig. 4A). The magnitude of weight reduction differed significantly among drugs (in descending order): liraglutide alone, orlistat and metformin alone (Table 4). Liraglutide alone was more effective than liraglutide and metformin combined. This may reflect the higher liraglutide dose in studies of monotherapy than in those where it was used with metformin. At 12 weeks, only orlistat had a significant impact on BMI, while liraglutide alone and orlistat had a significant effect on weight (Fig. 4B and Table 4). The results from 24 weeks suggested that metformin was superior to the placebo (Fig. 4C). Funnel plot analysis indicated no publication bias (Fig. S1B).

The results for waist circumference (Fig. 5 and Table 5) were mainly consistent with those for BMI and weight: liraglutide alone, liraglutide in combination with metformin and metformin alone led to a significant decrease in the waist circumference of women with PCOS and overweight/obesity (Fig. 5A). Liraglutide alone was more effective than metformin (Table 5). The reduction in waist circumference was not significant compared with the placebo for all treatments at 12 weeks (Fig. 5B and Table 5). Waist circumference was significantly reduced after 24 weeks of metformin therapy (Fig. 5C). There was minor publication bias (Fig. S1C).

Data for WHR were only available for metformin; metformin was not found to be superior to the placebo, based on results of all included studies (Fig. 6A) or only 24-week studies (Fig. 6B). Again, minor publication bias was present (Fig. S1D and E).

Pairwise meta-analysis showed significant heterogeneity (I^2 = 71%) for the direct comparison between metformin and the placebo (results for waist circumference based on all the included studies), but there was no heterogeneity (I^2 = 0) or moderate heterogeneity ($I^2 < 25\%$) for all the remaining comparisons. No significant inconsistency was identified from our assessment based on the heat plots (Fig. S2).

Sensitivity analysis

One study (49) was excluded from the sensitivity analysis for waist circumference because it was the leading contributor to heterogeneity in the direct comparison between metformin and placebo. The results of the network meta-analysis after removing this study (Fig. S3 and Table S1) were consistent with the previous results for waist circumference (Fig. 5A).

Four trials (31,48–50) were excluded in the sensitivity analysis for BMI, weight and waist circumference because the sample size was less than 10 per arm. The results of the network meta-analysis after removing these trials (Fig. S4A–C and Table S2A–C) were consistent with the previous results for BMI, weight and waist circumference (Figs 3A, 4A and 5A).

Two studies (49,50) were excluded from the sensitivity analysis for BMI and waist circumference because they included adolescents. However, none of these studies assessed weight loss. The results of the network meta-analysis after removing these studies (Fig. S5A and B; Table S3A and B) were consistent with the previous results for BMI and waist circumference (Figs 3A and 5A).

Discussion

As far as we are aware, this is the first meta-analysis to compare the effects of the treatments currently used to induce weight loss in women with PCOS and overweight/obesity. The findings have important implications for clinical practice. We used network meta-analysis to simultaneously compare the efficacy of a range of interventions because a network allows for indirect comparisons of treatments, which are not studied in a head-to-head fashion. The findings for the different treatments were consistent for all anthropometric measures: BMI, weight, waist circumference and WHR.

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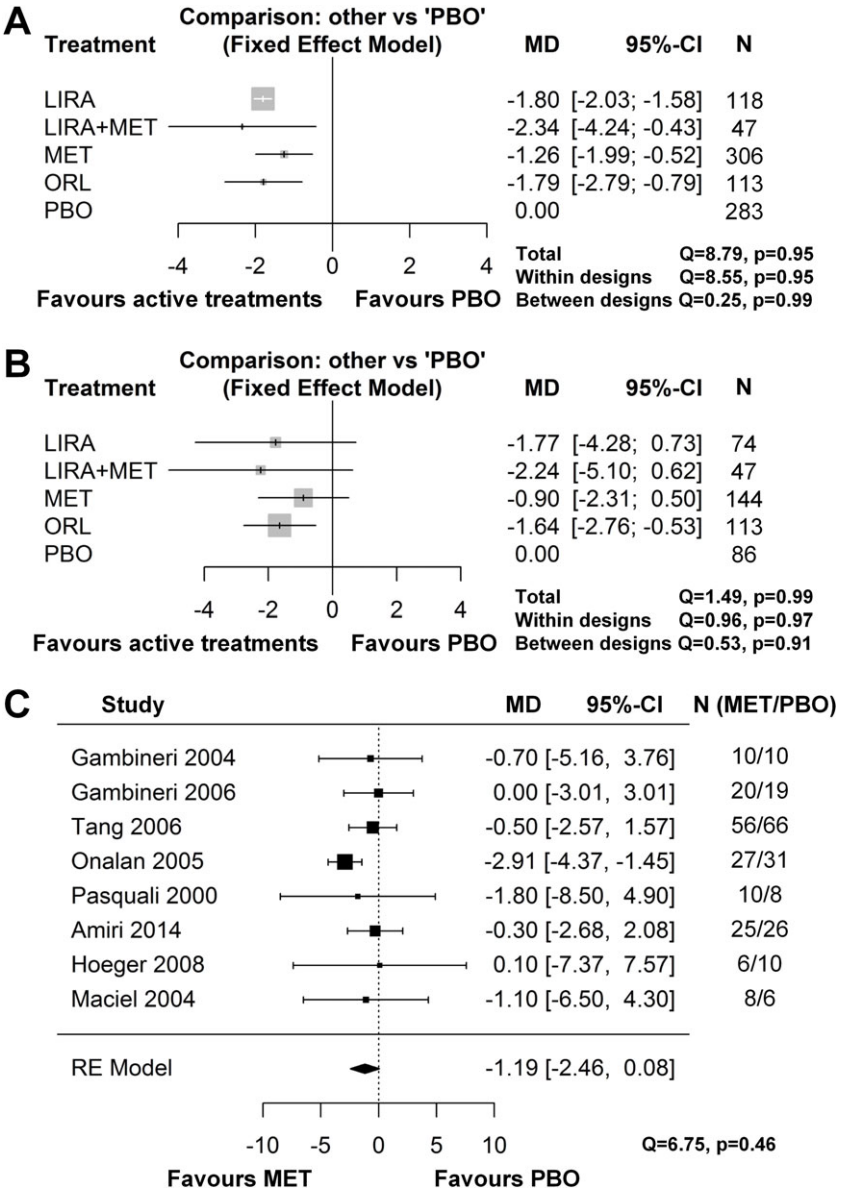


Figure 3 Meta-analysis of efficacy of treatment options on body mass index (BMI) change compared with placebo. (A) Network meta-analysis of drug efficacy on the change in BMI (results based on combining all the included studies, i.e. 12 weeks and 24/26 weeks); (B) network meta-analysis of drug efficacy on change in BMI (results for 12 weeks); (C) standard meta-analysis comparing the efficacy of metformin with placebo on the change in BMI at 24 weeks. CI, confidence interval; LIRA, liraglutide; MD, mean difference; MET, metformin; N, sample size; ORL, orlistat; PBO, placebo; RE, random effects.

Table 3 Network meta-analysis of efficacy of intervention options on body mass index change

		Using data from 12-week studies		
LIRA	−0.47 (−2.41 to 1.47)	0.87 (−1.20 to 2.94)	0.13 (−2.29 to 2.55)	1.77 (−0.73 to 4.28)
0.53 (−1.36 to 2.43)	**LIRA + MET**	1.33 (−1.16 to 3.83)	0.59 (−2.20 to 3.38)	2.24 (−0.62 to 5.10)
−0.55 (−1.31 to 0.21)	−1.08 (−3.06 to 0.90)	**MET**	−0.74 (−1.58 to 0.52)	0.9 (−0.50 to 2.31)
−0.01 (−1.03 to 1.01)	−0.55 (−2.67 to 1.58)	0.54 (−0.51 to 1.58)	**ORL**	**1.64 (0.53 to 2.76)**
−1.8 (−2.03 to −1.58)	**−2.34 (−4.24 to −0.43)**	**−1.26 (−1.99 to −0.52)**	**−1.79 (−2.79 to −0.79)**	**PBO**
		Using data from all included studies		

The efficacy estimate is located at the intersection of the column-defining treatment and the row-defining treatment. A mean difference below zero favours the column-defining treatment. Bold and underlined results are statistically significant. LIRA, liraglutide; MET, metformin; ORL, orlistat; PBO, placebo.

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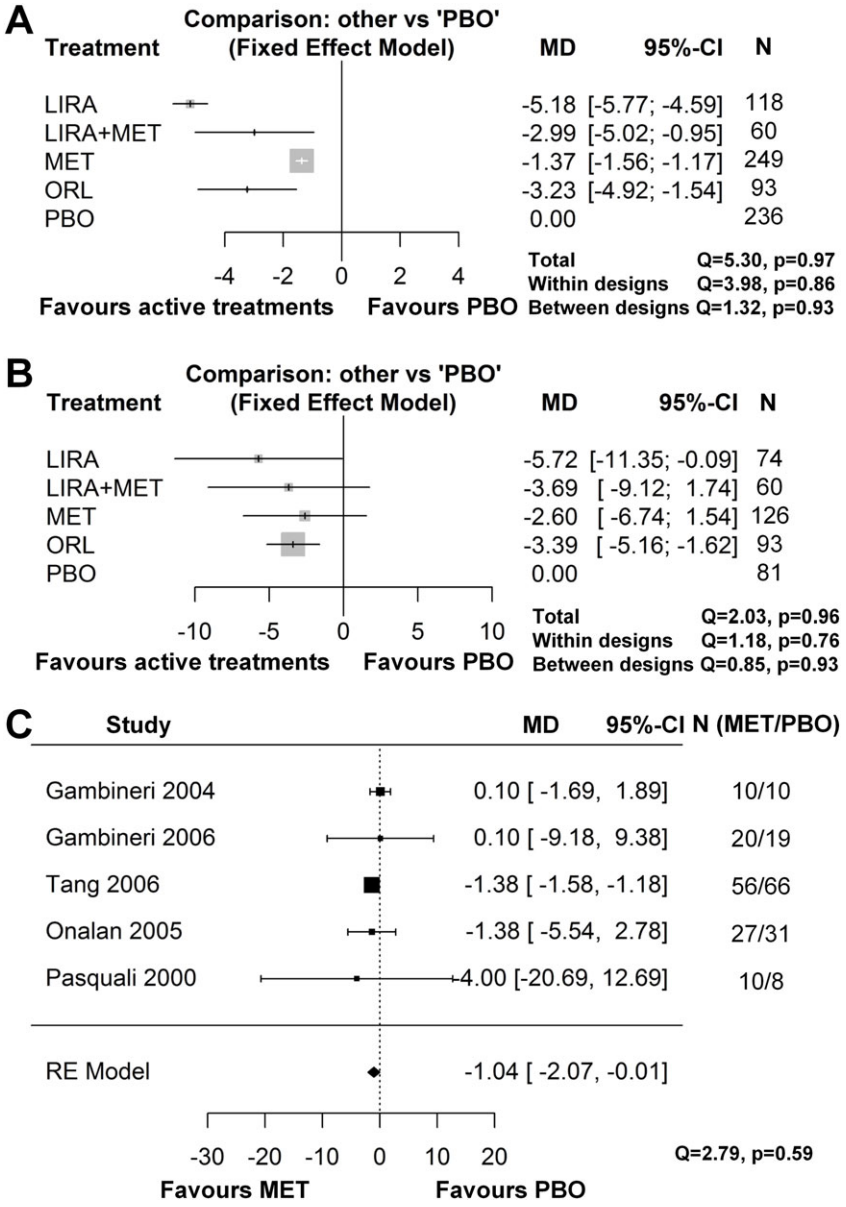


Figure 4 Network meta-analysis of efficacy of treatment options on weight loss compared with the placebo. (A) Network meta-analysis of drug efficacy on weight loss (results based on combining all the included studies, i.e. 12/14 weeks and 24/26 weeks); (B) network meta-analysis of drug efficacy on weight loss (results for 12 weeks); (C) standard meta-analysis comparing the efficacy of metformin with placebo on weight loss at 24 weeks. CI, confidence interval; LIRA, liraglutide; MD, mean difference; MET, metformin; N, sample size; ORL, orlistat; PBO, placebo; RE, random effects.

Table 4 Network meta-analysis of efficacy of intervention options on weight change

	Using data from 12-week studies			
LIRA	2.03 (−0.15 to 4.21)	3.12 (−0.70 to 6.94)	2.33 (−3.19 to 7.85)	**5.72 (0.09 to 11.35)**
−2.20 (−4.18 to −0.21)	**LIRA + MET**	1.09 (−2.42 to 4.60)	0.30 (−5.01 to 5.61)	3.69 (−1.74 to 9.12)
−3.82 (−4.44 to −3.20)	−1.62 (−3.65 to 0.42)	**MET**	−0.79 (−4.77 to 3.19)	2.60 (−1.54 to 6.74)
−1.95 (−3.74 to −0.16)	0.25 (−2.39 to 2.89)	**1.87 (0.17 to 3.56)**	**ORL**	**3.39 (1.62 to 5.16)**
−5.18 (−5.77 to −4.59)	**−2.99 (−5.02 to −0.95)**	**−1.37 (−1.56 to −1.17)**	**−3.23 (−4.92 to −1.54)**	**PBO**
Using data from all included studies				

The efficacy estimate is located at the intersection of the column-defining treatment and the row-defining treatment. A mean difference below zero favours the column-defining treatment. Bold and underlined results are statistically significant. LIRA, liraglutide; MET, metformin; ORL, orlistat; PBO, placebo.

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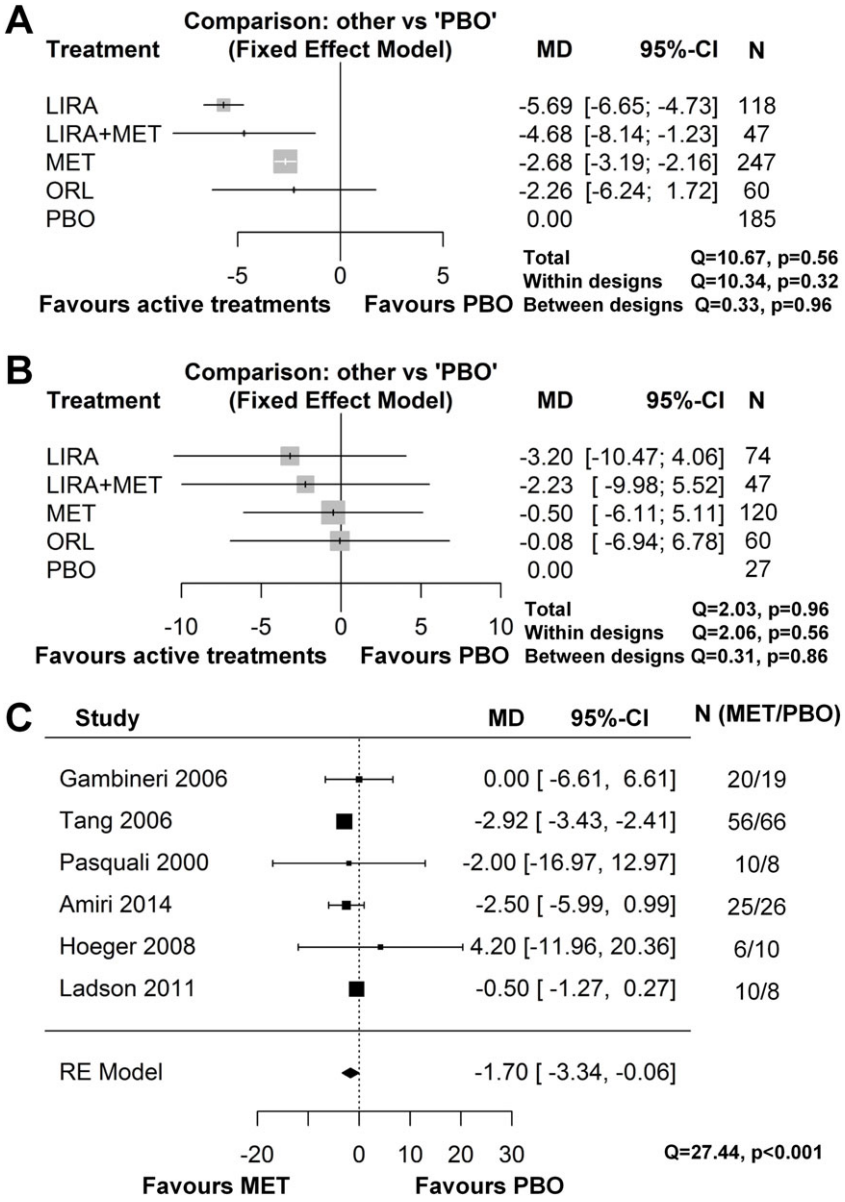


Figure 5 Network meta-analysis of efficacy of treatment options on waist circumference change compared with placebo. (A) Network meta-analysis of drug efficacy on the change in waist circumference (results based on combining all the included studies, i.e. 12 weeks and 24/26 weeks); (B) network meta-analysis of drug efficacy on change in waist circumference (results for 12 weeks); (C) standard meta-analysis comparing the efficacy of metformin with placebo on the change in waist circumference at 24 weeks. CI, confidence interval; LIRA, liraglutide; MD, mean difference; MET, metformin; N, sample size; ORL, orlistat; PBO, placebo; RE, random effects.

Table 5 Network meta-analysis of efficacy of intervention options on waist circumference change

		Using data from 12-week studies		
LIRA	0.97 (−2.40 to 4.35)	2.7 (−1.91 to 7.32)	3.12 (−2.95 to 9.20)	3.2 (−4.06 to 10.47)
−1 (−4.35 to 2.34)	**LIRA + MET**	1.73 (−3.61 to 7.08)	2.15 (−4.49 to 8.80)	2.23 (−5.52 to 9.98)
−3.01 (−4.09 to −1.93)	−2.01 (−5.49 to 1.48)	**MET**	0.42 (−3.53 to 4.37)	0.5 (−5.11 to 6.11)
−3.43 (−7.52 to 0.66)	−2.43 (−7.69 to 2.84)	−0.42 (−4.37 to 3.53)	**ORL**	0.08 (−6.78 to 6.94)
−5.69 (−6.65 to −4.73)	**−4.68 (−8.14 to −1.23)**	**−2.68 (−3.19 to −2.16)**	−2.26 (−6.24 to 1.72)	**PBO**
		Using data from all included studies		

The efficacy estimate is located at the intersection of the column-defining treatment and the row-defining treatment. A mean difference below zero favours the column-defining treatment. Bold and underlined results are statistically significant. LIRA, liraglutide; MET, metformin; ORL, orlistat; PBO, placebo.

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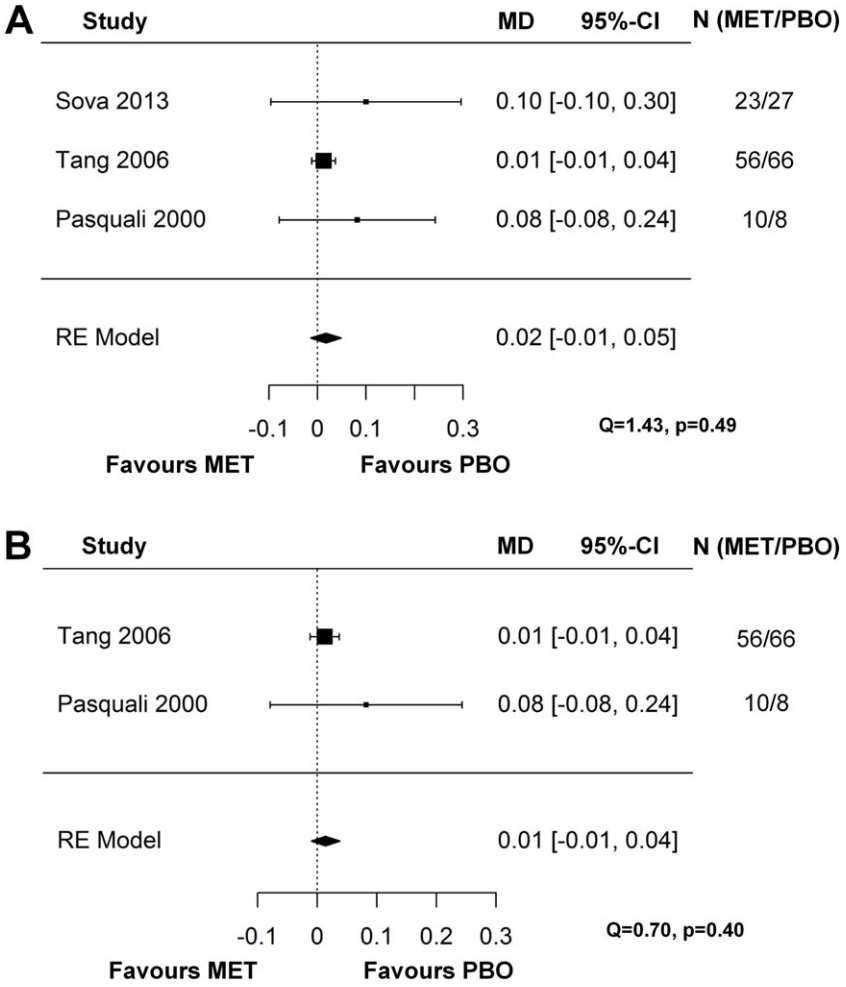


Figure 6 Role of metformin in waist-to-hip ratio change. (A) Standard meta-analysis of efficacy of metformin on waist-to-hip ratio change compared with placebo (results based on combining all the included studies, i.e. 12 and 24 weeks). (B) Standard meta-analysis of metformin efficacy on change in WHR (results for 24 weeks). CI, confidence interval; MD, mean difference; MET, metformin; N, sample size; PBO, placebo; RE, random effects.

Although this analysis was directed at pharmacological treatment, a hypocaloric diet and physical activity remain the first line treatments for weight loss in women with PCOS (58). Aerobic physical activity of moderate intensity for 90 min week^{-1} is recommended for patients with PCOS (59), and 5% to 15% weight loss or more is considered to improve clinical symptoms (60). However, lifestyle interventions seem not to be effective in providing lasting weight loss success (61). In addition, there is heterogeneity in the responsiveness to long-term lifestyle intervention in women with overweight/obesity and PCOS (62). Thus, more aggressive treatments, such as weight-loss medication, should be added to patients who fail to respond to lifestyle intervention (63).

For change in BMI and weight, all the drugs that qualified be evaluated in meta-analysis (liraglutide, metformin [alone and in combination] and orlistat) were superior to the placebo. There were, however, significant differences in the efficacy of these drugs; for weight loss, treatment with liraglutide was superior to all other treatments, and orlistat was superior to metformin based on the data of all the included studies.

It was not possible to calculate the mean percentage weight loss for the three drugs, but the results from the included studies show a relatively modest effect: after 12 weeks of therapy, orlistat (360 mg) −1.02% ± 0.9% (43) to −6.37% (56) and metformin (1.5 g) −4.69% ± 1.3% (43) to −5.04% ± 0.67% (55). With liraglutide monotherapy, 16%, 42% and 57% of patients achieved weight loss of at least 5% in doses of 1.2, 1.2 and 3 mg daily, respectively (36,39,40).

With the exception of a few outcomes confined to orlistat and liraglutide, 12 weeks of treatment is ineffective, so treatment should be continued for at least 24 weeks and

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probably much longer as the available evidence suggests that lost weight is regained when treatment is stopped. However, orlistat is only licenced for 3 years use.

Liraglutide, a glucagon-like peptide-1 receptor agonist, was developed to treat type II diabetes (15), but weight loss has been well described as an additional benefit, which prompted the manufacturer to develop a higher dose formulation specifically for this indication (15). Liraglutide is also used by some doctors to treat women who have obesity/overweight with PCOS. Orlistat, which has an established safety profile (64), is a reversible inhibitor of gastric and pancreatic lipases. As it is generally well tolerated, orlistat is an option for treatment of patients affected by obesity with or without type II diabetes and also has a role in the management of patients with metabolic syndrome and obesity, associated comorbidities or concomitant disorders (65). Myo-inositol and D-chiro-inositol are increasingly used by doctors and by self-medication to treat the symptoms of PCOS. These compounds improve insulin resistance, reduce serum androgen levels and ameliorate many features of metabolic syndrome (66). Unfortunately, we found only single studies of each isomer, so these drugs could not be evaluated in this meta-analysis.

Some other drugs, such as bupropion/naltrexone, lorcaserin and topiramate/phentermine, are also widely used in the treatment of obesity. They aid in weight loss mainly by reducing food intake through different mechanisms (60). Topiramate/phentermine seems to have a higher percentage of weight loss when compared with the other two, and there is no difference between lorcaserin and bupropion/naltrexone (63). However, topiramate/phentermine has shown risks of teratogenicity and psychiatric disturbances (67), while the other two have more acceptable safety profiles. Unfortunately, these anti-obesity drugs have not been reported in women with PCOS.

Although BMI is the most widely used measure of obesity, there is increasing evidence that waist circumference is more closely associated with insulin resistance (2,68). Because waist circumference is positively correlated with the visceral adiposity index (69) and 98% of women with PCOS and metabolic syndrome have an abnormal waist circumference (70), this measurement is particularly relevant to the present study. In support of this, waist circumference was found to be the simplest method of clinical screening for insulin resistance in women with hirsutism (68). None of the drugs evaluated had a significant effect on waist circumference after 12 weeks. However, based on data of all the included studies, liraglutide and metformin (alone or in combination) were superior to the placebo. Data were not available for 24 weeks of therapy with the other treatments, but network analysis showed that liraglutide was superior to metformin after combining all the included studies.

The results of this analysis provide the first comparison of the drugs currently used to induce weight loss in women with PCOS and overweight/obesity. Effective therapy is urgently needed in view of the high prevalence of obesity in women with this syndrome and its adverse effects on symptoms (including infertility) and increased risk of long-term morbidity (e.g. diabetes and coronary heart disease) (2,12). Although all the drugs were superior to the placebo to induce weight loss, liraglutide was the most effective. Liraglutide and metformin (alone or in combination) reduced waist circumference, but, again, liraglutide was superior. Orlistat was superior to metformin in terms of weight loss but may be seen as inferior as it was not shown to reduce waist circumference. Our results also suggest that 12 weeks of treatment was not effective. Finally, the relative efficacy of the three drugs must be judged against their cost, with liraglutide being 100-fold and orlistat 10-fold more expensive than metformin. As the indication of anti-obesity drugs is obesity, rather than overweight or symptoms of PCOS, lifestyle modifications should be recalled and replaced in the therapeutic arsenal.

The present study has some limitations. Firstly, publication bias may exist given that studies with significant results are more likely to be published, although we have attempted to address this issue by retrieving all the available studies and a funnel plot was used to assess any bias that may have arisen from this source. Secondly, we could not perform an analysis for the different inositol isomers. Data for the effects of 24 weeks of treatment were only available for metformin. Two studies (49,50) were confined to treating adolescent patients with PCOS. Finally, there was high heterogeneity for the comparison between metformin and placebo with respect to waist circumference, which was considered to be caused by one study (49) where an increase in waist circumference was observed after 24 weeks. This may reflect the sample size as only six participants were included in the intervention arm. Sample size may also explain the wide confidence intervals for all the anthropometric measures for the liraglutide/metformin combination. As our initiative is to compare more than two drugs simultaneously (can only be achieved through constructing a network meta-analysis) to give clinicians a clue of medication options to induce weight loss in women with PCOS and overweight/obesity, in our meta-analysis, we included all the studies that met the inclusion criteria. Admittedly, small studies are likely to contribute to significant amount of bias as there is more uncertainty in estimates and the results are more likely to be spontaneous. Moreover, adolescents may have different hormonal and metabolic profile as well as behaviour compared with adults. To deal with this issue, we have conducted sensitivity analysis by removing the studies with small sample size (less than 10 in each arm) and the studies with adolescents. We did not find any significant changes

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on the conclusions of our findings (shown as Supporting Information).

This study focused on the effects of the currently available drugs that are most commonly used to treat women with PCOS and obesity. However, new and possibly more effective anti-obesity drugs such as semaglutide (a once weekly GLP-1 agonist that induces weight loss of around 13.8%) (71), bupropion/naltrexone and lorcaserin are now available, and these may have an important role in treating women with PCOS.

Conclusion

The results of this study provide evidence that the three treatments with data suitable for analysis (liraglutide, metformin and orlistat) reduce BMI and weight in women with PCOS and overweight/obesity. Although effective, they are adjunct to, not a replacement for, a low energy diet and increased physical activity. Using network analysis, we found that liraglutide was the most effective and metformin the least effective intervention to lower BMI and weight. In view of the fact that the obesity that affects women with PCOS is predominantly central and this visceral fat is associated with anovulation, diabetes and cardiovascular morbidity, we also assessed the effects of these drugs on waist circumference. For this endpoint, liraglutide was again more effective than metformin, but we did not find a statistically significant effect for orlistat.

In clinical practice, effectiveness has to be weighed against cost. We have not performed an economic evaluation, but on the basis that the cost of liraglutide is approximately 100-fold more expensive than metformin and 10-fold more expensive than orlistat, it seems unrealistic to suggest widespread use of this drug for this indication. The relative cost effectiveness of orlistat and metformin is less obvious, with orlistat having the benefit of greater weight loss but the possible disadvantage of a lesser effect on visceral fat. In the absence of a healthy economic evaluation, the results of our analysis support the use of either metformin or orlistat to induce weight loss in women with PCOS and overweight/obesity. However, the conclusion may seem limited due to the insufficient evidences to date to guide policy recommendations.

Conflict of interest statement

No conflict of interest was declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article. https://doi.org/10.1111/obr.12720

Figure S1. Assessment of publication bias for the standard meta-analysis. (A-C) Funnel plot for the efficacy of metformin with placebo on the change in body mass index (BMI) (A), weight (B), waist circumference (C) after 24 weeks' therapy. (D and E) Funnel plot for the efficacy of metformin with placebo on the change in or waist-to-hip ratio (WHR) based on all included studies (D) or only 24-week studies (E).

Figure S2. Inconsistency detection of network meta-analysis. (A–C) Inconsistencydetecting heat plot for the efficacy of various treatment options on the change in body mass index (BMI) (A), weight loss (B) or waist circumference (C). The area of each grey square is proportional to the contribution of the direct estimate obtained from one design in the column to that in the row. The colours for the diagonal cells show the contribution of inconsistency for the corresponding design. The colours for the offdiagonal cells represent the change in inconsistency between direct and indirect comparison in the row estimate after relaxing the consistency assumption for the design in the column. The warm colours indicate an increase in consistency, whereas the blue colours represent a decrease. The two treatments in comparison examined by studies with more than two arms are marked by '_'. It should be noted that designs where only one intervention was involved in other designs of the network or where the removal of relevant studies would result in a splitting of the network (such that inconsistency contribution cannot be assessed) were not included in the heat plot. LIRA: liraglutide, MET: metformin, ORL: orlistat, PBO: placebo.

Figure S3. Sensitivity analysis (removing studies that contribute significant heterogeneity). Results from network meta-analysis of efficacy of intervention options on change in waist circumference compared with placebo by omitting the trial which contributed significant heterogeneity. PBO: placebo, MD: mean difference, CI: confidence interval, LIRA: liraglutide, MET: metformin, ORL: orlistat, N: sample size.

Figure S4. Sensitivity analysis with respect to sample size. (A-C) Results from network meta-analysis to assess efficacy

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of interventions on change in body mass index (BMI) (A), weight (B), waist circumference (C) compared with placebo by excluding trials with a sample size smaller than 10 per arm. PBO: placebo, MD: mean difference, CI: confidence interval, LIRA: liraglutide, MET: metformin, ORL: orlistat, N: sample size.

Figure S5. Sensitivity analysis with respect to age. (A and B) Results from network meta-analysis to assess efficacy of interventions on change in body mass index (BMI) (A), waist circumference (B) compared with placebo by excluding trials which included adolescents. PBO: placebo, MD: mean difference, CI: confidence interval, LIRA: liraglutide, MET: metformin, ORL: orlistat, N: sample size.

Table S1. Sensitivity analysis (removing studies that contribute significant heterogeneity). Results from network meta-analysis of efficacy of intervention options on change in waist circumference by omitting the trial which contributed significant heterogeneity and using data from all other included studies. A mean difference below zero favours the column-defining treatment. Bold and underlined results are statistically significant. LIRA: liraglutide, MET: metformin, ORL: orlistat, PBO: placebo.

Table S2. Sensitivity analysis with respect to sample size. (A-C) Results from network meta-analysis of efficacy of intervention options on change in body mass index (BMI) (A), weight (B), and waist circumference (C) by omitting the trials with a sample size smaller than 10 per arm and using data from all other included studies. A mean difference below zero favours the column-defining treatment. Bold and underlined results are statistically significant. LIRA: liraglutide, MET: metformin, ORL: orlistat, PBO: placebo.

Table S3. Sensitivity analysis with respect to age. (A and B) Results from network meta-analysis of efficacy of intervention options on change in body mass index (BMI) (A) and waist circumference (B) compared with placebo by excluding trials which included adolescents and using data from all other included studies. A mean difference below zero favours the column-defining treatment. Bold and underlined results are statistically significant. LIRA: liraglutide, MET: metformin, ORL: orlistat, PBO: placebo.

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