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Comparative efficacy of exercise, diet and/or pharmacological interventions on BMI, ovulation, and hormonal profile in reproductive-aged women with overweight or obesity: a systematic review and network meta-analysis

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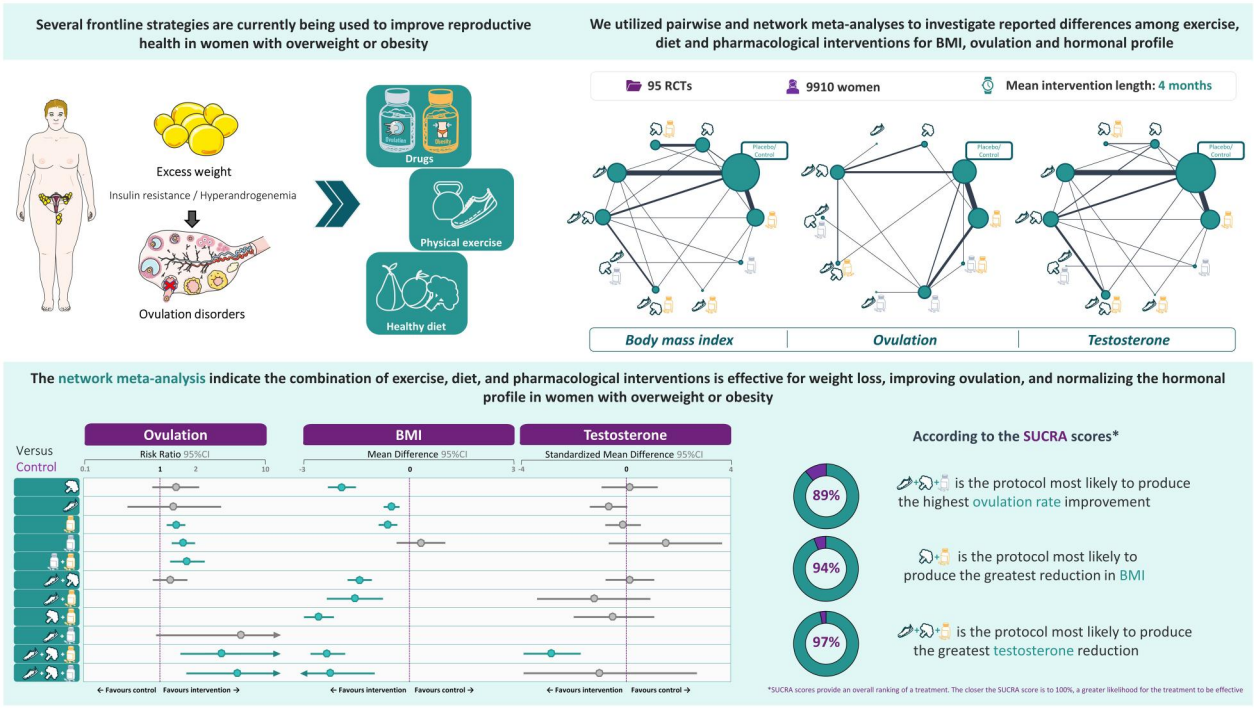
GRAPHICAL ABSTRACT



The combination of exercise, diet, and pharmacological interventions is effective for weight loss, improving ovulation, and normalizing the androgen levels of women with overweight or obesity. RCT, randomized controlled trials; SUCRA, surface under the cumulative ranking curve.

ABSTRACT

BACKGROUND: The increasing prevalence of obesity worldwide poses a significant threat to reproductive function owing, in part, to hormonal disturbances caused by negative feedback between excess adiposity and the hypothalamic–pituitary–ovarian axis. Consequently, finding the most appropriate strategies to lose weight and improve ovulation in women with overweight or obesity is a clinically relevant matter that needs to be investigated. A comprehensive comparison of the independent and combined efficacy of lifestyle and/or pharmacological interventions on BMI, ovulation, and hormonal profile in women with overweight or obesity at risk of anovulatory infertility would facilitate improving fertility strategies in this population.

OBJECTIVE AND RATIONALE: This study aimed to evaluate the comparative efficacy of exercise, diet, and pharmacological interventions on BMI, ovulation, and hormonal profile in reproductive-aged women with overweight or obesity.

SEARCH METHODS: A systematic review was performed by searching PubMed, Scopus, Web of Science, PsycINFO, and Cochrane Library up to 14 December 2023, for randomized controlled trials assessing the effects of exercise, diet and/or pharmacological interventions (i.e. weight-lowering drugs or ovulation inducers) on BMI, ovulation, and/or hormonal profile in reproductive-aged women with overweight or obesity. We performed frequentist random-effect network meta-analyses and rated the certainty of the evidence. The primary outcomes were BMI and ovulation rate, and the secondary outcomes were serum reproductive hormone levels (gonadotrophins, androgens, or oestrogens). We performed sensitivity analyses, including the studies that only involved women with PCOS.

OUTCOMES: Among 1190 records screened, 148 full texts were assessed for eligibility resulting in 95 trials (9910 women), of which 53% presented a high or unclear risk of bias. The network meta-analyses revealed that, compared to control: diet combined with weight-lowering drugs (mean difference (MD) −2.61 kg/m^2; 95% CI −3.04 to −2.19; $\tau^2 = 0.22$) and adding exercise (MD −2.35 kg/m^2; 95% CI −2.81 to −1.89; $\tau^2 = 0.22$) led to the greatest decrease in BMI; exercise combined with diet and ovulation inducers (risk ratio (RR) 7.15; 95% CI 1.94–26.40; $\tau^2 = 0.07$) and exercise combined with diet and weight-lowering drugs (RR 4.80; 95% CI 1.67–13.84; $\tau^2 = 0.07$) produced the highest increase in ovulation rate; and exercise combined with diet and weight-lowering drugs was the most effective strategy in reducing testosterone levels (standardized mean difference (SMD) −2.91; 95% CI −4.07 to −1.74; $\tau^2 = 2.25$), the third most effective strategy in increasing sex hormone-binding globulin levels (SMD 2.37; 95% CI 0.99–3.76; $\tau^2 = 2.48$), and it was coupled with being ranked first in terms of free androgen index reduction (SMD −1.59; 95% CI −3.18 to 0.01; $\tau^2 = 1.91$). The surface under the cumulative ranking curve scores suggested that: diet combined with weight-lowering drugs is the strategy most likely (94%) to produce the highest BMI reduction; and exercise combined with diet and ovulation inducers is the strategy most likely (89%) to produce the highest ovulation rate improvement. The sensitivity analyses, which exclusively included studies involving women diagnosed with PCOS, were consistent with the results presented above.

WIDER IMPLICATIONS: Overall, the findings of this network meta-analysis indicate that the combination of exercise, diet, and pharmacological interventions is effective for weight loss, improving ovulation, and normalizing the androgen levels of women with overweight or obesity. Although higher quality studies are needed, these results support that the optimal treatment strategy for women with overweight or obesity wishing to conceive must consider exercise, diet, and pharmacological interventions during the shared decision-making process.

Keywords: anovulation / dietary intervention / endocrine profile / exercise therapy / infertility / obese / pharmacotherapy / weight loss

Introduction

Obesity is a growing global public health concern in the 21st century (Boutari and Mantzoros, 2022), with 50% of North Americans expected to have obesity by 2030 (Ward et al., 2019). In Europe, 60% of the population has overweight or obesity (Ward et al., 2019; Boutari and Mantzoros, 2022; World Health Organization, 2022). In the Asia-Pacific regions, there has been an exponential increase in the prevalence of overweight/obesity among adults, which is estimated to be over 40% (Helble and Francisco, 2017). Women with overweight and obesity frequently experience ovulatory disorders that may, ultimately, result in unfavourable reproductive outcomes (Silvestris et al., 2018; Penzias et al., 2021). The impact of overweight and obesity on ovulatory disorders, a leading cause of infertility (NICE, 2013), is mainly attributed to endocrine mechanisms and functional disruption of the hypothalamic–pituitary–ovarian axis (Mikhael et al., 2019). In obese women, GnRH pulsatility and gonadotrophin secretion are altered because of increased peripheral aromatization of androgens to oestrogens, decreased levels of sex hormone-binding globulin (SHBG), and elevated production of leptin by adipocytes. At the same time, obesity-associated insulin resistance can lead to hyperandrogenemia (Parihar, 2003; Shukla et al., 2014; Broughton and Moley, 2017). Moreover, weight gain and obesity increase the risk of developing PCOS in women who are genetically predisposed (Azziz, 2018), worsening PCOS symptoms and increasing its phenotype severity (Barber et al., 2019).

Among the different strategies to lose weight and improve the hormonal profile to restore ovulation in women with anovulatory infertility, pharmacological and lifestyle interventions have been investigated (Balen et al., 2016; Belan et al., 2018; Abdalla et al., 2020). For adults dealing with overweight or obesity, weight-lowering drugs provide an alternative for weight loss when lifestyle interventions are ineffective (Shi et al., 2022). However, given the role of hyperinsulinaemia in impairing folliculogenesis in obesity and PCOS, first-line pharmacological interventions are often used for promoting spontaneous ovulation and restoring fertility (Costello et al., 2019). Pharmacological interventions involving oral anti-oestrogen clomiphene citrate, the aromatase inhibitor letrozole, and the insulin sensitizer metformin have demonstrated effectiveness in enhancing hormonal parameters and fertility (Wang et al., 2019; Taghavi et al., 2021). Recently, other drugs like glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) have revealed a prominent role in reproductive research (Jensterle et al., 2019). Lifestyle interventions (i.e. exercise and diet) are effective for weight loss, and have been suggested as treatments for managing anovulatory infertility in women with PCOS (Teede et al., 2018). In fact, for women with overweight or obesity and PCOS, a 5% decrease in body weight is considered a first-line treatment in the management of PCOS (Kiddy et al., 1992; Tarlatzis, 2008). The use of lifestyle and pharmacological interventions for weight loss among women with overweight or obesity and PCOS have been suggested as effective interventions to restore ovarian functions and combat comorbidities associated with excess weight and adipose tissue (American College of Obstetricians and Gynecologists, 2018; Belan et al., 2018; Bazzi and Schon, 2022). However, selecting the most effective strategy requires a comprehensive analysis of the efficacy of each intervention alone and in combination with others, which is difficult to evaluate with a single randomized controlled trial (RCT).

Although the independent and combined effects of exercise, diet and pharmacological interventions are promising, the most effective therapeutic strategy to maximize weight loss and improve the hormonal profile and ovulation in women with overweight or obesity is currently unknown. A meta-analysis of RCTs (Hunter et al., 2021) revealed that women randomized to diet combined with exercise presented significantly better fertility outcomes, including ovulation rates, compared to no or minimal intervention. However, this study overlooked the potential effects of pharmacological interventions alone and in combination with lifestyle modifications in improving weight management and fertility in this group of women. A network meta-analysis, combining both direct and indirect evidence from RCTs, would be a significant step forward to determine the most appropriate strategies for optimizing weight loss and ovulation in women with overweight or obesity, addressing a clinically relevant question. Therefore, the aim of this systematic review and network meta-analysis (NMA) was to systematically review all the available evidence and to evaluate the comparative efficacy of exercise, diet and/or pharmacological interventions on BMI, ovulation, and the hormonal profile in reproductive-aged women with overweight or obesity.

Methods

This systematic review and NMA were registered at PROSPERO (Registration no. CRD42022311023) and were conducted following the Preferred Reporting Items for Systematic Reviews incorporating Network Meta-analysis (PRISMA-NMA) guidelines and the Cochrane Collaboration Handbook (Hutton et al., 2015; Page et al., 2021).

Search strategy and selection criteria

Two researchers (D.R.-G. and A.H.-M.) independently searched PubMed, Scopus, Web of Science, PsycINFO, and Cochrane databases from their inception to 14 December 2023, focusing on RCTs investigating the effects of exercise, diet, or pharmacological interventions (independently or combined) on BMI, ovulation, and hormonal profile in reproductive-aged women with overweight or obesity. The complete search strategy is presented in the Supplementary Data S1. Duplicate records were removed with EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA). Articles eligible for full-text screening were assessed independently by the same two researchers. Any disagreements were resolved by consensus or by a third researcher (I.C.-R.). Reference lists of key reviews and meta-analyses, ClinicalTrials.gov, and grey literature (TESEO and OpenGrey) were also scanned for unpublished or ongoing trials.

Criteria for selecting studies

Type of study and participants

We included RCTs involving reproductive-aged women with overweight or obesity regardless of the follow-up duration. Reproductive-aged women were considered between 15 and 49 years of age. A BMI ≥25 kg/m^2 defined overweight and a BMI ≥ 30 kg/m^2 defined obesity (World Health Organization, 2016).

Type of intervention

We included all randomized trials that evaluated exercise, diet, and pharmacological interventions. The pharmacological interventions were categorized as drugs aimed to reduce weight (weight-lowering drugs) and drugs aimed to facilitate spontaneous ovulation (ovulation inducers). The administration of placebo, standard care, or no intervention was defined as control group. We included studies in which lifestyle strategies (exercise or diet) and pharmacological interventions were directly compared with each other or with control groups. Studies that included a combination of two interventions (e.g. exercise combined with a pharmacological intervention) compared either with

a control group, with a lifestyle intervention, or with a pharmacological intervention, were included. Studies were excluded if they only compared variations of the same intervention (e.g. exercise vs exercise; diet vs diet; weight-lowering drugs vs weight-lowering drugs).

Type of outcome measure

The included studies had to report absolute or relative change from baseline in BMI, ovulation (defined as mid–luteal phase serum progesterone level >3 ng/ml or positive urinary pregnanediol 3-glucuronide test, the onset of the LH surge either in serum or urine, and/or ultrasonographic signs of ovulation resulting in either disappearance or sudden decrease in size of the follicle; increased echogenicity; irregularity of follicular walls; and appearance of free fluid in the pelvis; Su *et al.*, 2017; Erden *et al.*, 2022) and/or serum reproductive hormone levels (total testosterone, androstenedione, SHBG, FSH, LH, oestradiol, progesterone, free androgen index (FAI), and dehydroepiandrosterone-sulphate) or absolute values before and after interventions. The primary outcomes were BMI and ovulation rate, and the secondary outcomes were serum reproductive hormone levels.

Data extraction

Data were extracted by one researcher (D.R.-G.) and checked by a second researcher (A.H.-M.). Discrepancies were resolved by consensus with a third researcher (I.C.-R.) if necessary. Each study provided the following information: study design, participants' characteristics (demographics, infertility diagnosis, BMI, eligibility criteria), sample size, intervention, comparison group, duration of the intervention, follow-up period, number of participants included in the analysis, outcomes measures including BMI, ovulation, and hormonal profile (Supplementary Tables S1 and S2).

Risk of bias assessment

RCTs were assessed for their methodological quality using the Cochrane risk of bias tool (version 1.0), classifying trials for each domain as presenting a low, unclear, or high risk of bias (Higgins *et al.*, 2011) (Supplementary Table S3). This tool included assessment of the following domains: randomization and sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective outcome reporting, and other sources of bias. The risk of bias assessment was independently conducted by two researchers (D.R.-G. and A.H.-M.). Disagreements were resolved by consensus with a third researcher (I.C.-R.).

Data analysis

A NMA was conducted with the frequentist approach by R package *netmeta* (Balduzzi *et al.*, 2023), using a random-effects model (Supplementary Data S2). The estimator was based on Moore–Penrose pseudoinverse method (Rücker, 2012). To estimate the heterogeneity variance between studies, the DerSimonian–Laird random effects model was used (Jackson *et al.*, 2018). We chose the following measures of effect: mean differences (MD) for changes in percentage and absolute BMI; risk ratios (RR) for individual-based binary outcomes, such as ovulation rates; and standardized mean differences (SMD) using Cohen's method for changes in serum reproductive hormone levels (Supplementary Data S3). When reported, we used mean change and SDs. When the authors reported data as measures before and after the intervention, we used methods outlined in the Cochrane Handbook to calculate the mean change and SDs of change (Higgins and Green, 2011). The pharmacological interventions were categorized into two groups: weight-lowering drugs, which encompass drugs designed for weight reduction, such as metformin, orlistat, sibutramine, or GLP-1 RAs (Shi *et al.*, 2022); and ovulation inducers (i.e. clomiphene), aimed at improving ovulation patterns. Network plots were constructed to illustrate the geometry of eligible direct comparisons and we used random effects models to obtain the direct pooled estimates (Supplementary Figs S1, S2, S3, S4, S5, S6, S7, S8, S9, S10, and S11). The transitivity assumption was assessed by comparing the distribution of the key study characteristics across studies grouped by comparison (Supplementary Figs S12, S13, S14, S15, S16, and S17). In addition, 2D graphs were created illustrating treatment efficacy in relation to participants' baseline values for age, BMI, and testosterone levels (Supplementary Figs S18, S19, S20, S21, S22, S23, and S24). We assessed the presence of statistical heterogeneity using the magnitude of the heterogeneity variance parameter (τ^2) and with generalized Cochran's Q (Jackson *et al.*, 2012) (Supplementary Table S4). Statistical heterogeneity in each direct comparison was estimated with the I^2 statistic (Higgins and Thompson, 2002) (Supplementary Table S5). The agreement of direct and indirect evidence was assessed by the node-splitting approach (van Valkenhoef *et al.*, 2016) (Supplementary Table S6) and we created net heat plots (Supplementary Figs S25, S26, S27, S28, S29, S30, S31, S32, S33, and S34) as a method for identifying and locating inconsistency within a network of RCTs (Krahn *et al.*, 2013). League tables (Supplementary Tables S7, S8, S9, S10, S11, S12, S13, S14, S15, S16, and S17), forest plots (Supplementary Figs S35, S36, S37, S38, S39, S40, S41, S42, S43, S44, and S45), and polar plots (Supplementary Figs S46, S47, S48, S49, S50, S51, S52, S53, S54, S55, and S56) of relative treatment effects were used to visualize the comparisons of the network estimations. Strategies were ranked according to the surface under the cumulative ranking curve (SUCRA). SUCRA score ranges between 0% and 100%, where a higher percentage indicates a greater likelihood for the strategy to be effective (Veroniki *et al.*, 2016). We used rankograms to graphically present the probability that each type of strategy was the most effective (Supplementary Figs S57, S58, S59, S60, S61, S62, S63, S64, S65, S66, and S67). Comparison-adjusted funnel plots were used to explore publication bias for all direct comparisons (Supplementary Figs S68, S69, S70, S71, S72, S73, S74, S75, S76, S77, and S78).

We ran sensitivity analyses to evaluate the effects of exercise, diet and/or pharmacological interventions on the ovulation rate and hormonal profile including exclusively studies that involved reproductive-aged women with overweight or obesity diagnosed with PCOS and excluding those without PCOS (Supplementary Figs S79, S80, S81, S82, S83, S84, S85, S86, S87, and S88). In addition, sensitivity network meta-analyses were conducted to assess the effects of each individual drug (i.e. metformin, orlistat, sibutramine, GLP-1 RAs, clomiphene citrate) alone and combined with diet and/or exercise on the study outcomes (Supplementary Figs S89, S90, S91, S92, S93, S94, S95, S96, S97, S98, and S99).

We rated the certainty of the evidence using the Confidence in Network Meta-Analysis framework (CINeMA) (Nikolakopoulou *et al.*, 2020), which allows rating the confidence in the results as high, moderate, low, and very low (Supplementary Table S18). In addition, the percentage contribution of each direct estimate to the estimates of the NMA was represented using percentage contribution matrices (Supplementary Figs S100, S101, S102, S103, S104, S105, S106, S107, S108, S109, and S110).

Results

Details of the study selection process are summarized in the PRISMA flow diagram (Fig. 1). The search retrieved 1190 results. After removing the duplicates and screening of title and abstract

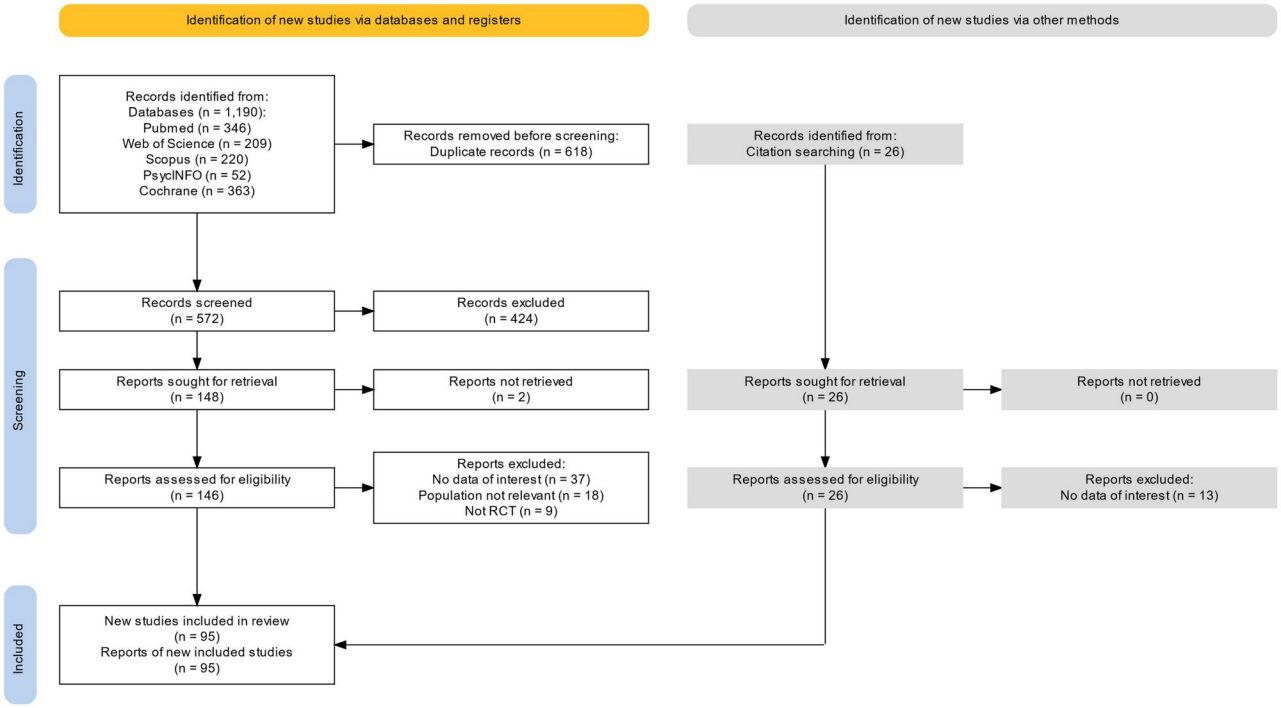


Figure 1. PRISMA flowchart for the selection of studies in a systematic review and network meta-analysis on the comparative efficacy of exercise, diet and/or pharmacological interventions in reproductive-aged women with overweight or obesity.

of the remaining results, the full text of 148 reports was evaluated further. Ninety-five RCTs (96 publications), involving 9910 participants, met the inclusion criteria and were finally included (Supplementary Data S4). The detailed characteristics of the studies and interventions are provided in Supplementary Table S1 (pp. 26–47).

Characteristic of included studies

The 95 included RCTs were conducted between 1994 and 2022. The sample size varied from 11 (Stener-Victorin *et al.*, 2009) to 877 (Wang *et al.*, 2021) participants. The mean age of the participants in the study groups varied from 15.5 (±1.5) (Hoeger *et al.*, 2008) to 45.0 (±8.3) (Kiortsis *et al.*, 2008) years, the mean baseline BMI was 32.8 (±6.3) kg/m^2, and the median length of intervention was 16 (range: 1–48) weeks (Supplementary Table S2). The lowest mean BMI was 25.1 kg/m^2 (Smith *et al.*, 2011), and the highest was 42.4 kg/m^2 (Elkind-Hirsch *et al.*, 2022). In 70 (74%) studies, the participants had a diagnosis of PCOS, and in 47 studies the syndrome was defined by the Rotterdam 2004 consensus criteria (Rotterdam ESHRE and ASRM-Sponsored PCOS Consensus Workshop Group, 2004). The remaining 23 studies involving participants with a diagnosis of PCOS used a criterion of a reduced number of annual menses together with clinical or biochemical evidence of hyperandrogenism, oligomenorrhoea or amenorrhea, anovulation and, to a lesser degree, ultrasound appearance of the ovaries.

Description of interventions

Supplementary Table S1 provides brief details of the types of interventions reviewed. Among the reported interventions to optimize key fertility factors in women with overweight or obesity and risk of anovulatory infertility, two main types of interventions were described: lifestyle and pharmacological interventions. The majority of the lifestyle interventions were aimed to promote weight loss, focusing on exercise and diet modifications. Where described, diets were aimed to reduce daily caloric intake to ranges of 500–800 kcal, setting a daily caloric intake between 1200 and 1600 kcal. Moreover, most of the diet interventions followed healthy eating advice, reducing fat and carbohydrate, and increasing the protein ratio intake. Four studies involved a very low-calorie diet (Guzick *et al.*, 1994; Palomba *et al.*, 2010; Rothberg *et al.*, 2016; Einarsson *et al.*, 2017) with two using liquid substitutes for classic diets (Moran *et al.*, 2011; Einarsson *et al.*, 2017). In two studies (Moran *et al.*, 2011; Orio *et al.*, 2016), the hypocaloric diet was characterized by a high protein composition, constituting 35% of total energy intake. Exercise interventions were based mainly on moderate aerobic exercise, with participants aiming to achieve a minimum of 150 min of weekly exercise. Interventions based on resistance exercise (Almenning *et al.*, 2015; Vizza *et al.*, 2016) and its combination with aerobic exercise (Bruner *et al.*, 2006; Lim *et al.*, 2011; Curi *et al.*, 2012; Nybacka *et al.*, 2013; Share *et al.*, 2015; Geiker *et al.*, 2016) were also included. Moreover, high intensity interval training was prescribed in two studies (Almenning *et al.*, 2015; Kiel *et al.*, 2018). The duration of the lifestyle interventions ranged from 4 weeks to 12 months, with 3 months being the most common intervention length.

Since studies included participants at risk of anovulatory infertility, and most of them with a diagnosis of PCOS and obesity, the pharmacological interventions aimed either to reduce weight and/or to induce ovulation. Two different categories of pharmacological interventions were included in the NMA. On the one hand, the weight-lowering drugs category included all pharmacological interventions that have weight loss as one of their main goals (i.e. metformin, orlistat, GLP-1 RAs, sibutramine) and included: metformin, a recognized insulin sensitizer and administered at doses between 1 and 2 g/daily, was the most studied weight loss drug (n = 49 studies, 52%) and the regimen of 850 mg two times per day was used in 17 RCTs; the lipase inhibitor Orlistat, typically prescribed at 120 mg three times per day (10/15 studies); GLP-1 RAs, with studies examining the effects of liraglutide (n = 7 studies) administered at doses of 1–3 mg and exenatide (n = 4 studies) at doses of 20 μg daily; and Sibutramine, a blocker

of serotonin and norepinephrine transporters, was also used in three studies. On the other hand, the ovulation inducers category included studies analyzing the effects of orally administered clomiphene at daily doses ranging between 50 and 200 mg daily (n = 10 studies), initiated between the second and third day of the onset of the menstrual cycle. Pharmacological interventions ranged from 6 weeks to 12 months.

Assessment of risk of bias, heterogeneity, and inconsistency

The risk of bias varied across the RCTs contributing to the NMA, with 53% of the studies (n = 50 of 95 trials) presenting a high or unclear risk of bias (Supplementary Table S3). Randomization was appropriately implemented in over half of the trials (n = 53; 56%). Allocation concealment often could not be assessed owing to insufficient information (n = 49; 52% trials) and blinding of staff and participants presented a low risk of bias in 31 (33%) trials. Incomplete outcome data were deemed at low risk in 61 (64%) trials, and selective reporting of outcomes resulted in low risk in 75 (79%) trials. An overview of the risk of bias of the trials informing the results is presented in Supplementary Fig. S111. The overall I^2 values were 98% for BMI and 55% for ovulation, with corresponding global τ^2 values of 0.22 for BMI and 0.07 for ovulation (Supplementary Figs S35, S36, S37, S38, S39, S40, S41, S42, S43, S44, and S45). The I^2 values for each direct comparison are presented in Supplementary Table S5. In general, the NMA did not demonstrate local inconsistencies (Supplementary Table S6) in the direct, indirect, and network analyses. However, the test of incoherence from the node-splitting model showed significant differences between some (i.e. 5 out of 18) comparisons for BMI (Supplementary Table S6).

Primary outcomes

BMI

The NMA for BMI included 60 RCTs with 5955 women. Figure 2A shows the network of eligible comparisons for changes in BMI after different interventions. The results of both the pairwise and the NMA are presented in Table 1. Compared to control, all the treatment options, except for ovulation inducers, were found to be effective at reducing BMI (Fig. 3). Diet combined with weight-lowering drugs (MD −2.61 kg/m^2, [95% CI −3.04 to −2.19], n = 299) and adding exercise interventions (MD −2.35 kg/m^2, [95% CI −2.81 to −1.89], n = 463) led to the greatest decrease in BMI compared to control.

In terms of changes in BMI, strategies that combined diet with weight-lowering drugs presented the highest SUCRA score and, therefore, was the most likely to result in the highest BMI reduction (94.3%), followed by exercise combined with diet and weight-lowering drugs (84.8%), and exercise combined with diet and ovulation inducers (80.2%) (Fig. 4A; Supplementary Fig. S57).

The sensitivity analyses (n = 72, 6785 women) analyzing each drug independently revealed that the combination of exercise and diet with drugs, such as GLP-1 RAs (MD −3.34 kg/m^2, [95% CI −4.06 to −2.62], n = 99) and orlistat (MD −3.16 kg/m^2, [95% CI −3.91 to −2.42], n = 261), resulted in more pronounced reductions in BMI. Furthermore, the impact of metformin on BMI reduction was enhanced when it was combined with exercise and diet interventions (MD −2.42 kg/m^2, [95% CI −3.02 to −1.82], n = 155) (Supplementary Fig. S89).

Ovulation

The NMA for ovulation included 25 RCTs with 2195 women. Figure 2B shows the network of eligible comparisons for ovulation. The results of both the pairwise and the NMA are presented in Table 1. Exercise combined with diet and ovulation inducers (RR 7.15, [95% CI 1.94 to 26.40], n = 32) and exercise combined with diet and weight-lowering drugs (RR 4.80, [95% CI 1.67 to 13.84], n = 65) resulted in significantly higher ovulation rates compared to control (Fig. 3). Strategies that combined exercise with diet and ovulation inducers had the highest SUCRA score (89.3%), followed by exercise combined with ovulation inducers (85.2%) and interventions that combined exercise with diet and weight-lowering drugs (82.7%), while placebo or no treatment (5.5%) had the lowest SUCRA score (Supplementary Fig. S58).

The results including only women with PCOS (n = 23, 2149 women), were consistent with those obtained in the main analysis (Supplementary Fig. S79), indicating that strategies combining exercise with diet and ovulation inducers (RR 7.12, [95% CI 1.91 to 26.56], n = 32) resulted in significantly higher ovulation rates compared to control. The sensitivity analyses (n = 28, 2340 women) analyzing each drug independently revealed that the addition of exercise and diet strategies to drugs, such as orlistat (RR 13.54, [95% CI 1.66 to 110.24], n = 30), clomiphene (RR 7.17, [95% CI 1.95 to 26.31], n = 42), or metformin (RR 3.44, [95% CI 1.03 to 11.48], n = 30), were associated with a greater ovulation improvement, although the power of these analyses was limited owing to the small number of studies (Supplementary Fig. S90).

Secondary outcomes

Androgen profile

The NMA for circulating concentrations of testosterone (nmol/l) included 53 RCTs with 3941 women (Supplementary Table S1). Figure 2C shows the network of eligible comparisons for changes in levels of total testosterone. Compared to control, the NMA revealed that exercise combined with diet and weight-lowering drugs (SMD −2.91, [95% CI −4.07 to −1.74], n = 521) produced the greatest decrease in testosterone levels. SUCRA scores showed that exercise combined with diet and weight-lowering drugs were most likely to result in the highest testosterone reduction (97.2%), followed by the exercise combined with weight-lowering drugs (70.9%) and exercise interventions alone (65.0%) (Supplementary Fig. S59). The results, including only women with PCOS (n = 46, 2676 women), were consistent with those obtained in the main analysis (Supplementary Fig. S80), indicating that strategies combining exercise with diet and weight-lowering drugs (SMD −2.89, [95% CI −4.44 to −1.33], n = 333) resulted in a significantly greater decrease in testosterone levels compared to control. However, interventions combining diet with weight-lowering drugs (SMD) −2.03, [95% CI −3.99 to −0.07], n = 82) showed a greater testosterone-reducing effect in women with PCOS. Sensitivity analyses (n = 62, 4451 women) evaluating the effect of individual drugs alone or combined with exercise and/or diet interventions revealed that the addition of exercise and diet strategies to drugs, such as orlistat, GLP-1 RAs, and metformin, were associated with greater testosterone reduction in overweight or obese women (Supplementary Fig. S91).

The NMA for SHBG (nmol/l) included 42 RCTs with 4135 women (Supplementary Table S1). Figure 2D shows the network of eligible comparisons for changes in SHBG levels. Compared to control, the NMA revealed that exercise combined with diet and ovulation inducers (SMD 7.72, [95% CI 3.31 to 12.13], n = 32) and exercise combined with diet (SMD 3.11, [95% CI 2.15 to 4.06], n = 762) produced the greatest increase in SHBG levels. The NMA results are shown in Fig. 3. SUCRA scores showed that exercise combined with diet and ovulation inducers were most likely to result in the highest SHBG increase (99.7%), followed by exercise combined with diet (86.8%) and exercise combined with diet and

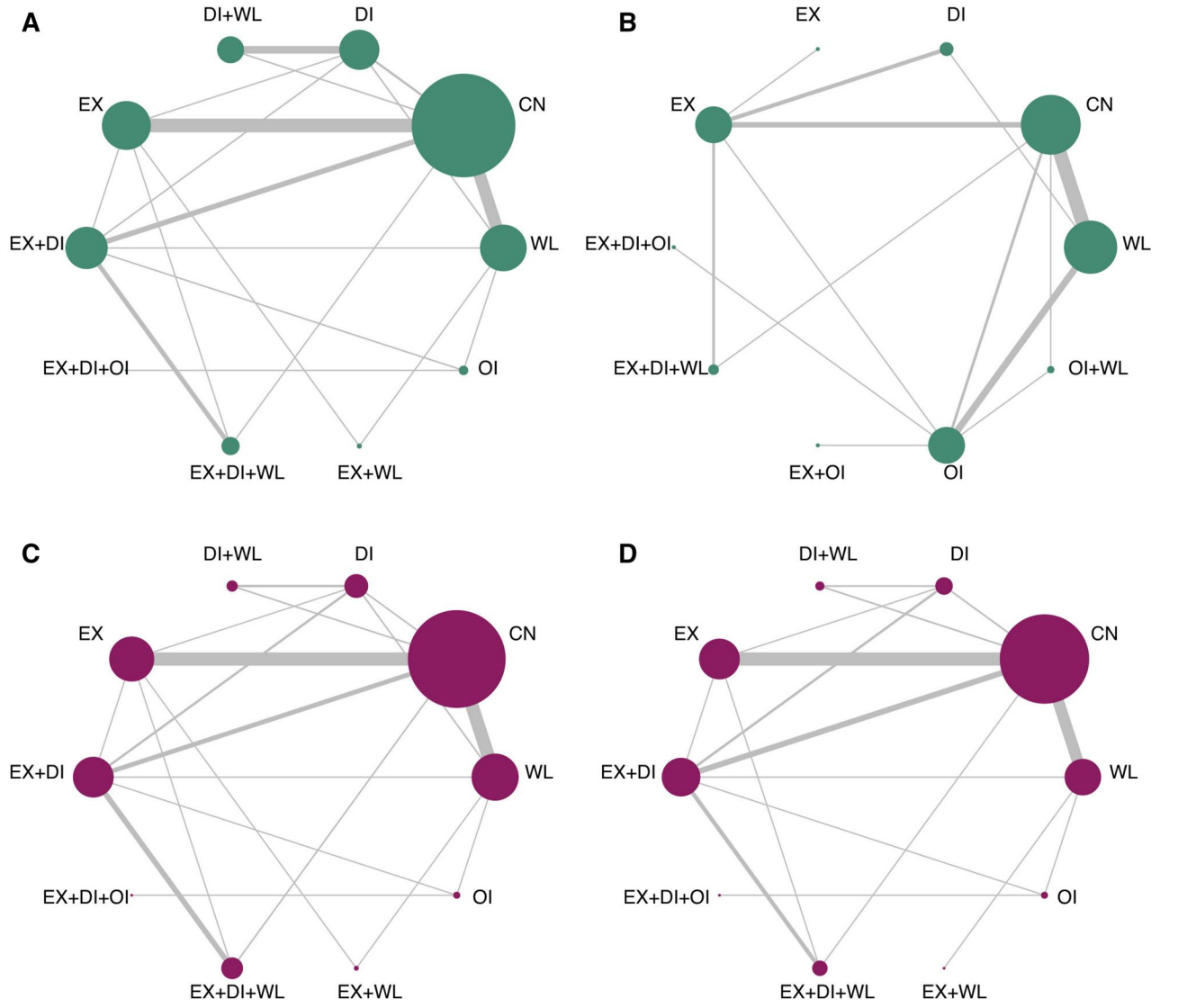


Figure 2. Network plots of available direct comparisons of outcomes when using different interventions. BMI change from baseline (**A**), ovulation (**B**), testosterone change from baseline (**C**), and SHBG change from baseline (**D**). The size of the nodes is proportional to the number of participants (i.e. sample size) involving the specific treatment intervention. The solid lines link treatments with direct comparison with the thickness proportional to the number of trials. CN, control; DI, diet; EX, exercise; OI, ovulation inducers; WL, weight-lowering drugs. SHBG: sex hormone-binding globulin.

weight-lowering drugs (77.7%) (Supplementary Fig. S60). The results, including only women with PCOS (n = 35, 2146 women), showed a similar trend to the main analysis (Supplementary Fig. S81), although with a smaller effect size for strategies combining exercise with diet (SMD 1.30, [95% CI 0.15 to 2.45], n = 354) and exercise combined with diet and weight-lowering drugs (SMD 1.08, [95% CI −0.51 to 2.66], n = 231). The sensitivity analyses (n = 50, 4565 women) evaluating the effect of individual drugs alone or combined with exercise and/or diet interventions revealed that the addition of exercise and diet to drugs, such as sibutramine (SMD 4.09, [95% CI 0.89 to 7.29], n = 57), metformin (SMD 2.27, [95% CI 0.56 to 3.97], n = 144), and orlistat (SMD 2.14, [95% CI −0.10 to 4.37], n = 218), were associated with a larger SHBG increase in overweight or obese women (Supplementary Fig. S92).

The NMA for androstenedione (nmol/l) included 19 RCTs with 1452 women. Compared to control, the NMA revealed that exercise combined with diet and ovulation inducers (SMD −4.54, [95% CI −8.90 to −0.19], n = 32) and the combination of diet with weight-lowering drugs (SMD −2.81, [95% CI −5.43 to −0.19], n = 62) produced the greatest reduction of androstenedione levels. The results of the NMA are presented in Supplementary Fig. S42. SUCRA scores showed that interventions combining exercise with diet and ovulation inducers were most likely to result in the highest androstenedione reduction (95.7%), followed by diet combined with weight-lowering drugs (88.5%) and weight-lowering drugs alone (58.4%). The results including only women with PCOS (n = 18, 1151 women) were consistent with those obtained in the main analysis (Supplementary Fig. S85), although with a smaller effect size for strategies combining exercise with diet and ovulation inducers (SMD −3.75, [95% CI −9.06 to 1.55], n = 32) and diet combined with weight-lowering drugs (SMD −2.68, [95% CI −5.86 to 0.50], n = 62).

The NMA for FAI included 26 RCTs with 1830 women (i.e. all diagnosed with PCOS). Compared to control, the NMA identified that interventions based on the combination of exercise with diet and ovulation inducers (SMD −1.60, [95% CI −5.10 to 1.91], n = 32) and the combination of exercise with diet and weight-lowering drugs (SMD −1.59, [95% CI −3.18 to 0.01], n = 275) showed a non-significant trend towards a further reduction of FAI.

Table 1. Results from pairwise meta-analysis (where possible) and network meta-analysis assessing the effects of the interventions under study on BMI, ovulation rates, total testosterone, and sex hormone-binding globulin in women of reproductive age with overweight or obesity.

	Pairwise meta-analysis		Network meta-analysis	
Treatment versus control	**No of studies**	**Effect size (95% CI)**	**Effect size (95% CI)**	**95% PrI**
BMI (MD)				
Diet	3	−2.68 [−3.29; −2.06]	−1.94 [−2.30; −1.57]	−2.95 to −0.92
Diet+weight-lowering drugs	2	−2.01 [−2.75; −1.28]	−2.61 [−3.04; −2.19]	−3.65 to −1.57
Exercise	14	−0.51 [−0.74; −0.29]	−0.50 [−0.72; −0.29]	−1.47 to 0.46
Exercise+diet	7	−1.03 [−1.52; −0.54]	−1.42 [−1.76; −1.09]	−2.42 to −0.42
Exercise+diet+ovulation inducers	NA	NA	−2.24 [−3.50; −0.99]	−3.83 to −0.65
Exercise+diet+weight-lowering drugs	1	0.57 [−0.70; 1.84]	−2.35 [−2.81; −1.89]	−3.40 to −1.29
Exercise+weight-lowering drugs	NA	NA	−1.56 [−2.37; −0.76]	−2.81 to −0.31
Ovulation inducers	NA	NA	0.34 [−0.36; 1.03]	−0.84 to 1.51
Weight-lowering drugs	13	−0.82 [−1.11; −0.53]	−0.61 [−0.88; −0.35]	−1.59 to 0.36
Ovulation rates ([a]RR)				
Diet	NA	NA	1.51 [0.84; 2.73]	0.67 to 3.44
Exercise	NA	NA	1.39 [0.41; 4.73]	0.34 to 5.62
Exercise+diet	4	1.30 [0.86; 1.96]	1.31 [0.86; 2.01]	0.65 to 2.65
Exercise+diet+ovulation inducers	NA	NA	7.15 [1.93; 26.40]	1.63 to 31.31
Exercise+diet+weight-lowering drugs	1	2.10 [0.53; 8.28]	4.80 [1.67; 13.84]	1.39 to 16.56
Exercise+ovulation inducers	NA	NA	7.86 [0.96; 64.28]	0.81 to 76.64
Ovulation inducers	2	1.68 [1.10; 2.54]	1.79 [1.33; 2.39]	0.96 to 3.32
Ovulation inducers+weight-lowering drugs	1	1.96 [1.23; 3.10]	1.97 [1.25; 3.11]	0.96 to 4.05
Weight-lowering drugs	9	1.57 [1.01; 2.42]	1.52 [1.20; 1.92]	0.84 to 2.74
Total testosterone (SMD)				
Diet	2	−0.08 [−2.21; 2.06]	0.12 [−0.95; 1.20]	−3.07 to 3.32
Diet+weight-lowering drugs	1	−0.15 [−2.33; 2.03]	−0.52 [−2.07; 1.03]	−3.91 to 2.87
Exercise	13	−0.93 [−1.68; −0.18]	−0.66 [−1.35; 0.03]	−3.74 to 2.42
Exercise+diet	6	−0.63 [−1.89; 0.62]	0.13 [−0.78; 1.03]	−3.01 to 3.27
Exercise+diet+ovulation inducers	NA	NA	−1.05 [−4.78; 2.68]	−5.89 to 3.80
Exercise+diet+weight-lowering drugs	2	−0.89 [−3.09; 1.30]	−2.91 [−4.07; −1.74]	−6.13 to 0.32
Exercise+weight-lowering drugs	NA	NA	−1.25 [−3.44; 0.94]	−4.99 to 2.49
Ovulation inducers	NA	NA	1.52 [−0.67; 3.71]	−2.22 to 5.26
Weight-lowering drugs	14	0.15 [−0.59; 0.90]	−0.13 [−0.83; 0.56]	−3.21 to 2.95
Sex hormone-binding globulin (SMD)				
Diet	2	1.45 [−0.81; 3.71]	0.20 [−1.09; 1.49]	−3.22 to 3.62
Diet+weight-lowering drugs	1	−1.63 [−3.94; 0.68]	0.91 [−0.84; 2.67]	−2.72 to 4.54
Exercise	12	0.59 [−0.21; 1.39]	0.79 [0.04; 1.54]	−2.46 to 4.04
Exercise+diet	7	4.66 [3.36; 5.96]	3.11 [2.15; 4.06]	−0.19 to 6.41
Exercise+diet+ovulation inducers	NA	NA	7.72 [3.31; 12.13]	2.20 to 13.23
Exercise+diet+weight-lowering drugs	1	0.04 [−3.25; 3.33]	2.37 [0.99; 3.76]	−1.09 to 5.83
Exercise+weight-lowering drugs	NA	NA	−0.47 [−3.75; 2.80]	−5.08 to 4.13
Ovulation inducers	NA	NA	−3.12 [−5.57; −0.68]	−7.15 to 0.91
Weight-lowering drugs	11	−0.92 [−1.80; −0.04]	−0.80 [−1.64; 0.03]	−4.08 to 2.47

MD, mean difference; NA, not available; PrI, predictive interval; RR, risk ratio; SMD, standardized mean difference.
[a] Risk ratios (RR) refer to the risk of ovulation happening in each strategy compared to the risk of ovulation happening in control groups. RR greater than 1 favour the intervention.

SUCRA scores showed that exercise combined with diet and weight-lowering drugs was most likely to result in the highest FAI reduction (79.4%), followed by interventions combining exercise with diet and ovulation inducers (69.8%) and diet combined with weight-lowering drugs (62.3%) (Supplementary Fig. S63).

Gonadotrophin profile

Serum levels of gonadotrophins (FSH and/or LH) were obtained from 26 studies. Supplementary Figs S5 and S6 shows the network of eligible comparisons for changes in the gonadotrophin levels. The NMA for FSH included 24 RCTs with 1309 women. Compared to control, the NMA revealed that exercise combined with weight-lowering drugs (SMD 2.19, [95% CI 0.84 to 3.55], n = 15) increased the levels of FSH. Conversely, the combination of exercise with diet and ovulation inducers (SMD −1.78, [95% CI −3.28 to −0.28], n = 32) and interventions combining diet with weight-lowering drugs (SMD −1.32, [95% CI −2.07 to −0.57], n = 100) produced a significant reduction in FSH levels compared to control. SUCRA scores showed that exercise combined with weight-lowering drugs was most likely to rank first (99.9%), followed by weight-lowering drugs alone (76.4%) and exercise combined with diet (75.6%) for increasing FSH levels (Supplementary Fig. S61).

The NMA for LH included 26 RCTs with 1351 women. Compared to control, the NMA revealed (Supplementary Fig. S40 (p. 143)) that exercise combined with diet and weight-lowering drugs, produced a significant increase in LH levels (SMD 2.52, [95% CI 0.62 to 4.42], n = 125). SUCRA scores showed that exercise combined with diet and weight-lowering drugs was most likely to be ranked first (93.6%), followed by exercise combined with diet (85.8%) and exercise interventions alone (55.6%) for increasing LH levels (Supplementary Fig. S62).

The inclusion of studies only with women diagnosed with PCOS showed that for FSH (n = 22, 1185 women) and LH (n = 23, 1215 women) levels, the results were in line with the main analysis (Supplementary Figs S82 and S83), indicating that exercise combined with weight-lowering drugs (SMD 2.20, [95% CI 0.78 to 3.63], n = 15) increased the levels of FSH and strategies combining exercise with diet and weight-lowering drugs produced a significant increase in LH levels (SMD 2.89, [95% CI 0.81 to 4.96], n = 125).

Figure 3. Polar plots for outcomes. BMI change from baseline, ovulation, testosterone change from baseline and SHBG change from baseline. The polar plots show the relative effects of each strategy and control groups. Colour indicates the relative performance of the intervention of interest and the precision of the estimate in comparison with placebo, from green (the intervention is better than placebo), to red (the intervention is worse than placebo). Coloured intervention boxes indicates the certainty of the evidence using the CINeMA framework. The relative effects are measured as a mean difference (95% CI) for BMI change, risk ratios (95% CI) for ovulation outcome and standardized mean differences for changes in serum reproductive hormone levels. CN, control; DI, diet; EX, exercise; OI, ovulation inducers; RR, risk ratio; WL, weight-lowering drugs. CINeMA: Confidence in Network Meta Analysis; SHBG: sex hormone-binding globulin.

Oestrogen profile

The NMA for oestradiol included 22 RCTs with 1906 women (Supplementary Table S1). Compared to control, the NMA revealed a significant reduction in oestradiol levels among women in the weight-lowering drugs groups (SMD −1.71, [95% CI −2.98 to −0.44], n = 258). The NMA results are shown in Supplementary Fig. S44 (p. 147). SUCRA scores (Supplementary Fig. S66) showed that weight-lowering drugs were most likely to be ranked first (78.3%), followed by interventions that combined exercise with diet (67.0%) and exercise interventions alone (65.7%) for reducing the increased oestradiol levels in overweight and obese women (Fig. 5). The results including only women with PCOS (n = 19, 1110 women) showed some variation, indicating a better trend for exercise interventions alone (SMD −1.18, [95% CI −2.41 to 0.04], n = 152) to reduce oestradiol levels (Supplementary Fig. S87).

Progesterone profile

The NMA for progesterone included seven RCTs with 423 women diagnosed with PCOS. The results of the pairwise and NMA are presented in Supplementary Table S15. Compared to control, the NMA revealed no significant effects of any combination of interventions on the progesterone levels. Weight-lowering drugs (SMD −0.28, [95% CI −1.21 to 0.65], n = 11) and exercise (SMD −0.23, [95% CI −0.75 to 0.29], n = 57) showed a non-significant trend towards greater decrease in progesterone compared to control. Although not statistically significant, SUCRA scores showed that exercise was the strategy most likely to rank first (70.4%), followed by weight-lowering drugs (68.4%) for reducing progesterone levels (Supplementary Fig. S65).

Discussion

This NMA involving 95 studies that enrolled 9910 women with overweight or obesity indicate that, compared to control: either exercise, diet, and weight-lowering drugs are effective in reducing BMI, with a larger effect size observed for strategies that included dietary interventions; exercise combined with diet and ovulation inducers and exercise combined with diet and weight-

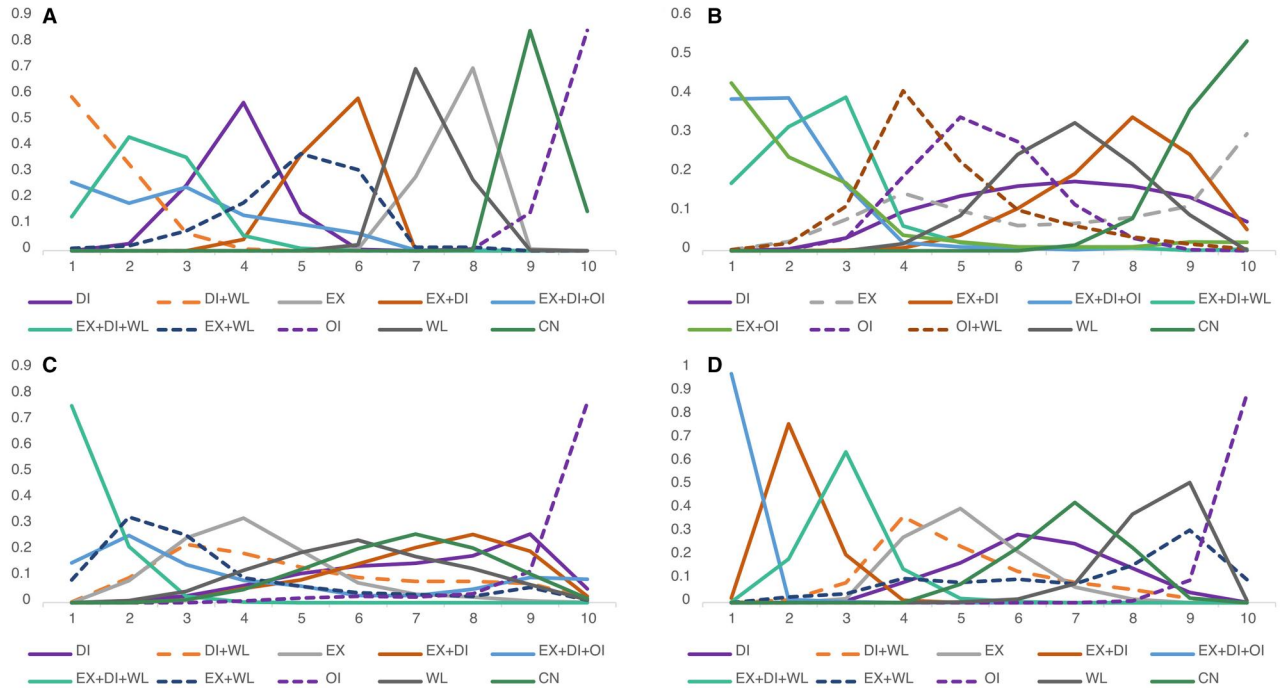


Figure 4. Cumulative rank probability analysis on intervention outcomes. BMI change from baseline (**A**), ovulation (**B**), testosterone change from baseline (**C**), and SHBG change from baseline (**D**). The number on the *X*-axis represents the rank. As the number goes up, the rating goes down. The number on the *Y*-axis represents the probability of a treatment to achieve each rank. Higher SUCRA score (*Y*-axis) indicates a greater likelihood for the strategy to be effective. CN, control; DI, diet; EX, exercise; OI, ovulation inducers; WL, weight-lowering drugs; SHBG, sex hormone-binding globulin; SUCRA, surface under the cumulative ranking curve.

lowering drugs are more effective than other strategies in improving the ovulation rate; the combination of exercise, diet, and weight-lowering drugs was associated with the best improvement in the androgen profile, producing a reduction of total testosterone and FAI levels in conjunction with an increase in SHBG levels; and strategies combining exercise with diet and weight-lowering drugs might also be effective for increasing LH levels. These results were consistent when the analyses were restricted exclusively to studies involving women with PCOS, which strengthens our conclusions. These findings highlight the importance of a holistic approach that includes both lifestyle and pharmacological interventions in the management of women with overweight or obesity at risk of anovulatory infertility.

Effects on BMI

Evidence-based guidelines recommend adopting a healthy lifestyle to lose weight for women with obesity and/or PCOS (Balen *et al.*, 2007; Tarlatzis *et al.*, 2008; American Dietetic Association *et al.*, 2009; Moran *et al.*, 2009; Dondorp *et al.*, 2010), but its efficacy and potential role in combination with pharmacological interventions are currently unclear. Several previous trials have shown that weight loss in overweight and obese women is an effective method for improving fertility outcomes (Kort *et al.*, 2014; Dağ and Dilbaz, 2015; Silvestris *et al.*, 2018). Therefore, the role of lifestyle combined with pharmacological interventions on weight management is still of high research and clinical interest. A previous systematic review reported a mean weight loss of 4.7 kg using lifestyle (diet and exercise) interventions compared with no intervention (Hunter *et al.*, 2021), but their combination with pharmacological interventions was not studied. Another systematic review of lifestyle interventions alone compared with standard of care in women at childbearing age wishing to conceive (Lan *et al.*, 2017) showed a mean reduction in BMI of 1.4 kg/m^2, but only two studies were included in the analysis. Our results regarding the effects of the interventions on weight loss align with and expand the findings of these previous reviews. Importantly, the present study includes pharmacological interventions aimed at weight loss, such as orlistat, or weight loss candidates, such as metformin (Bessesen and Van Gaal, 2018), which could explain the larger effect size observed on BMI reduction compared to previous reviews when the diet was combined with weight-lowering drugs (MD −2.61 kg/m^2) and when these are also combined with exercise (MD −2.35 kg/m^2). In the present analysis, the weight-lowering effects of these drugs proved less effective than interventions based on lifestyle (particularly diet) modifications.

GLP-1 RAs and GLP-1 RAs plus metformin exhibited superior efficacy in reducing BMI than other investigated drugs, consistent with previous literature on obese women and women diagnosed with PCOS (Cena *et al.*, 2020; Singh and Singh, 2020). The effects of GLP-1 RAs on BMI are likely attributed to the administration of liraglutide at doses of 1–3 mg and exenatide at doses of 20 μg daily, driven by their glucose-lowering impact and increased sense of satiety (Bessesen and Van Gaal, 2018; Nauck and Meier, 2018). However, these effects of drugs were higher when combined with lifestyle interventions. Our sensitivity analysis further supports the utilization of GLP-1 RAs in conjunction with lifestyle interventions to enhance the BMI reduction. In line with prior research (Panidis *et al.*, 2014; Naderpoor *et al.*, 2015), Orlistat exhibited remarkable efficacy in our study. Doses of 120 mg taken two to three times a day resulted in a BMI reduction of 3.16 kg/m^2 when used in combination with exercise and diet. Moreover, our findings indicate that metformin at a standard dose of 1–2 g daily might be more effective when coupled with exercise and diet, resulting in a 2.42 kg/m^2 reduction in BMI after an average 5-month intervention compared to controls. Nevertheless, healthcare providers should comprehensively inform patients

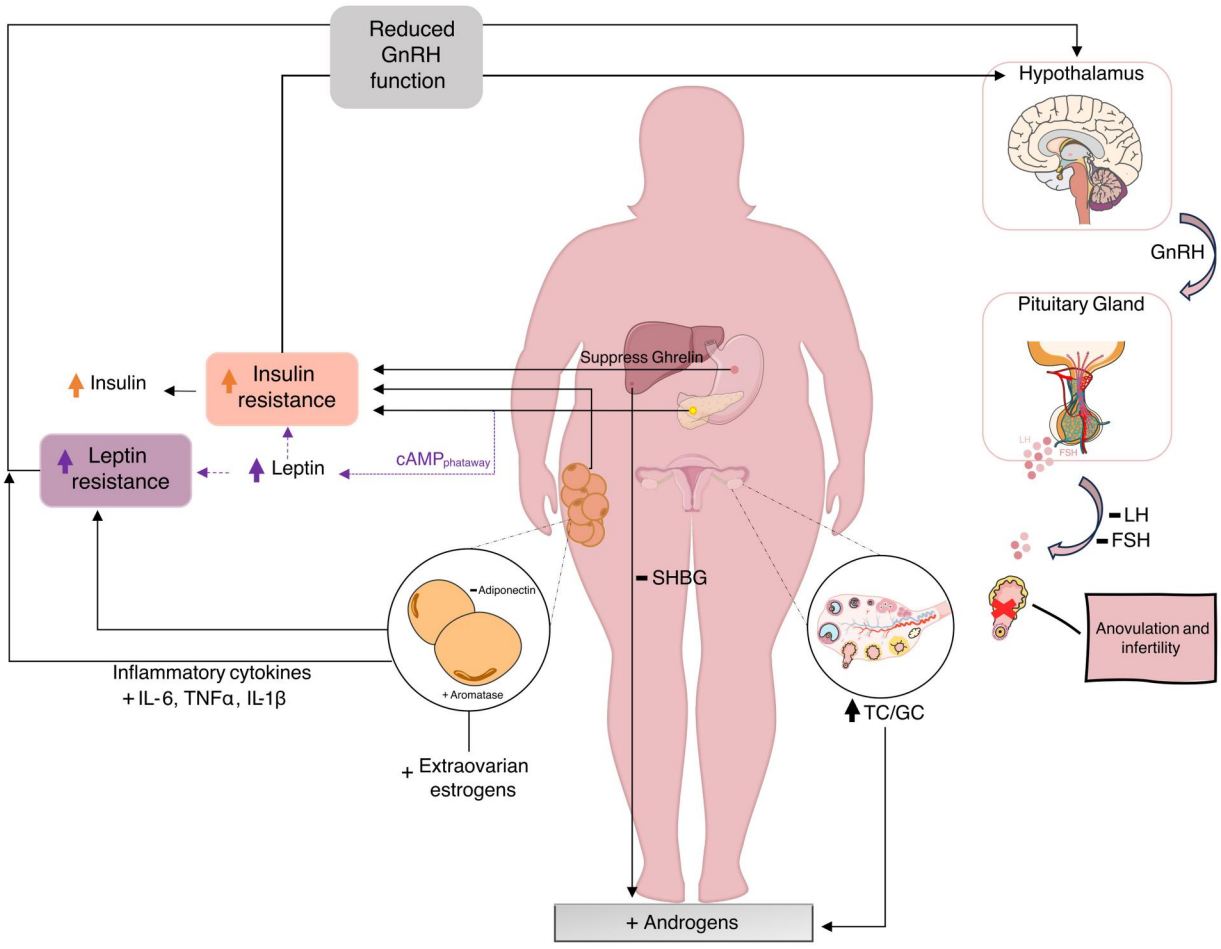


Figure 5. Mechanisms linking obesity with functional disruption of the hypothalamic–pituitary–ovarian axis. GC, granulosa cells; SHBG, sex hormone-binding globulin; TC, Theca cells; TNF-α, tumor necrosis factor alpha.

about the benefits and potential risk associated with weight-loss drugs (Bessesen and Van Gaal, 2018).

Effects on ovulation

Most common fertility treatments involve the use of ovulation inducers (e.g. clomiphene, which produce an oestrogenic negative feedback inhibition, increasing gonadotrophins) or aromatase inhibitors, such as letrozole (Balen *et al.*, 2016). Research in women with PCOS has demonstrated that exercise has the capacity to restore the GnRH cycle, resulting in spontaneous ovulation (Froment and Touraine, 2006). In addition, a systematic review showed that exercise can restore function of the hypothalamic–pituitary–gonadal axis (Hakimi and Cameron, 2017), which might reinstitute ovulation in overweight/obese women with PCOS (Harrison *et al.*, 2011; Best *et al.*, 2017; Hakimi and Cameron, 2017). However, previous meta-analyses have not consistently shown that lifestyle interventions improve ovulation rates. One meta-analysis (Mena *et al.*, 2019) involving young women who were overweight or obese showed no significant improvement in the ovulation rate with exercise interventions (RR 1.42, [95% CI 0.90 to 2.24]). Conversely, another meta-analysis (Hunter *et al.*, 2021) reported that exercise combined with diet produced a significant improvement in the ovulation rate (RR 4.24) but included only two studies and the potential influence of pharmacological interventions was overlooked.

Our analyses provided support for using metformin (RR = 1.52) at a standard dose of 1–2 g daily, clomiphene (RR = 1.79) at oral doses of 50–200 mg daily and a combination of metformin and clomiphene (RR = 1.98) as treatments to enhance ovulation rates. This aligns with previous literature demonstrating the impact of metformin on ovulation in infertile women with PCOS (Tang *et al.*, 2012; Misso *et al.*, 2013). Notably, our results revealed that the improvements in ovulation rates were amplified when combined with exercise and diet. Furthermore, GLP-1 RAs, which are receiving significant attention as a therapeutic approach in the field of reproduction (Jensterle *et al.*, 2019), showed a non-significant trend towards greater improvement in the ovulation rates compared to other weight loss drugs. The limited number of studies currently available on this topic partially explains the non-significant results and the relatively wide CIs, which suggests that further research with larger sample sizes is needed to confirm or refute these findings.

Effects on the reproductive hormonal profile

Androgen profile

From an endocrine perspective, insulin resistance and hyperandrogenism are key factors for anovulation (Fig. 5), representing a clinically relevant problem in women with obesity (Zain and Norman, 2008). Androgen dysregulation is a key component in the pathophysiology of PCOS. Nevertheless, elevated androgen levels are not confined to women with PCOS and are also observed in women with obesity without a diagnosis of PCOS. Several studies have revealed a positive connection between free testosterone levels and adipose tissue (Pasquali and Gambineri,

2006; Janssen *et al.*, 2010). Furthermore, subcutaneous fat enhances testosterone production through enzymes that exhibit a positive correlation with BMI (Seidell *et al.*, 1990). Additionally, obesity causes a reduction in SHBG in women, leading to increased circulation of free sex steroids, including testosterone. Consequently, this prompts an elevation in the metabolic clearance of these hormones (Brewer and Balen, 2010).

Several reviews indicate that interventions combining exercise and diet modifications may improve the androgen profile (Kim and Lee, 2022). However, although exercise alone has been shown to influence androgen levels the most (Haqq *et al.*, 2014), some studies failed to demonstrate any significant effect of exercise interventions on androgen levels (Ennour-Idrissi *et al.*, 2015). Previous studies highlight the potential of pharmacological interventions to improve reproductive outcomes (Morley *et al.*, 2017; Wang *et al.*, 2017). Insulin sensitizing drugs (such as metformin) can positively affect serum testosterone levels, and oral contraceptives alone or in combination with metformin may reverse the hyperandrogenic situation in women with PCOS by reducing testosterone levels and the FAI (Morley *et al.*, 2017; Guan *et al.*, 2020; Zhao *et al.*, 2021). However, the effect of pharmacological interventions alone, and particularly combined with lifestyle interventions, on the hormonal parameters of women who are overweight or obese remain poorly understood.

Our study revealed that GLP-1RAs exhibited a greater beneficial impact on testosterone levels in women of reproductive age with overweight or obesity compared to other weight-lowering drugs studied. This concurs with previous research indicating that liraglutide, specifically, led to a substantial androgen suppression (Jensterle *et al.*, 2015; Nylander *et al.*, 2017). However, in the study by Kahal *et al.* (2015) liraglutide did not produce significant effects on SHBG or FAI in women with PCOS. Our sensitivity analyses revealed that the effectiveness of these pharmacological interventions was outranked when combined with exercise and dietary modifications (Supplementary Figs S91 and S92). Hence, drugs such as metformin, orlistat, GLP-1 RAs, and clomiphene exhibited a notable influence on crucial reproductive hormones, including testosterone and SHBG. These findings align with previous research underscoring the potential benefits of integrating exercise and diet interventions as adjuncts to drugs such as metformin (Naderpoor *et al.*, 2015).

Gonadotrophin profile

For women with obesity and/or PCOS who wish to improve their reproductive health, the gonadotrophin profile has a great clinical relevance. PCOS is linked to heightened frequency and amplitude of GnRH and LH pulsatile secretion (Rojas *et al.*, 2014). Nevertheless, LH levels seem to exhibit an inverse correlation with BMI in studies involving women with and without PCOS (Bohlke *et al.*, 1998; Pagán *et al.*, 2006; Jain *et al.*, 2007). This inverse relation may be associated with obesity-related hypogonadism, potentially influenced by factors such as inflammatory cytokines, insulin and leptin resistance, and reduced adiponectin, all of which could diminish GnRH neuronal activity (Wojciechowska *et al.*, 2019; Eng *et al.*, 2024). These obesity-related alterations lead to anovulation, producing a subsequent disturbance in female fertility (Giviziez *et al.*, 2016; Silvestris *et al.*, 2018). Current evidence is less consistent regarding the changes that lifestyle or pharmacological interventions could produce on the gonadotrophin profile, with particular emphasis on LH levels. A previous systematic review summarizing the efficacy of combining lifestyle interventions with metformin in women with PCOS found no significant effects on LH levels compared to interventions based on lifestyle changes alone (Naderpoor *et al.*, 2015). Another review also found no effect of exercise compared to control on LH levels (dos Santos *et al.*, 2020). Our results revealed that exercise combined with diet and weight-lowering drugs might significantly increase LH levels, which may be clinically important in women with overweight or obesity. Moreover, the current NMA suggested that use of weight-lowering drugs was the strategy most likely to result in the highest oestradiol reduction, with metformin producing the greatest effect.

Strengths and limitations

This study has limitations that must be underlined. First, many comparisons provided only low-certainty evidence, not only because of heterogeneity and imprecision but also the high or unclear risk of bias among a relatively high proportion of the studies. According to CINeMA, we rated many comparisons as low or very low quality, and many trials did not adequately report randomization and allocation concealment, suggesting that higher quality trials are needed. We present full details on the risk of bias for all included studies and CINeMA in Supplementary Table S18. Second, we did not consider the characteristics of each intervention because the protocols for the proposed interventions also presented marked variations in dosages and duration of interventions. Studies encompassing lifestyle interventions generally exhibited low to moderate quality. This was primarily because the authors did not provide sufficient details on the interventions and did not implement available reporting checklists, which hinders a comprehensive categorization of these lifestyle-based interventions. In addition, since the included pharmacological interventions act differently on the endocrine system, sensitivity analyses were performed to identify the effect of individual drugs independently and in combination with lifestyle interventions, although the number of available studies was limited. Third, many studies did not report the menstrual cycle phase in which the serum samples were collected and hormonal variables, such as testosterone, FSH, and LH, change throughout the menstrual cycle. Since the studies included a relatively high percentage of women with PCOS (98% for ovulation analyses and ranging from 52% to 100% for hormones), it was challenging to assess the cycle phase. However, all the included studies were RCTs, and the cycle phase distribution across study groups is expected to be balanced.

Despite these limitations this study has several strengths, including the innovative comparison of lifestyle combined with pharmacological interventions (grouped as weight-lowering drugs and ovulation inducers) in comparison to control groups, the comprehensive systematic review methodology and the introduction of indirect comparisons through a NMA. Moreover, our analysis used robust methods, including frequentist NMA and quality assessment by CINeMA. Previous meta-analyses on this topic mainly performed a pairwise design focused on individual interventions and provided inconsistent results (Haqq *et al.*, 2014; Lan *et al.*, 2017). Our study incorporated direct and indirect comparisons of interventions into a single analysis and provided a ranking of the available interventions on modulating BMI, ovulation rates, and reproductive hormone profile by non-surgical treatments for reproductive-aged women with overweight or obesity. Importantly, different sensitivity analyses were carried out that provided relevant results. First, the results were consistent when the studies included were exclusively on women diagnosed with PCOS, indicating the robustness of our conclusions; second, the analyses assessing the independent effects of individual drugs alone and combined with lifestyle interventions represent another strength of the study that might provide valuable information for clinicians to make decisions.

Conclusion

For reproductive-aged women with overweight or obesity, the combination of exercise, diet, and pharmacological interventions is more effective than individual intervention strategies for losing weight, enhancing ovulation, and restoring the androgen profile. Interventions that combine exercise with diet and weight-lowering drugs were found to be among the most effective strategies in achieving ovulation and were associated with the best improvement in the hormonal profile, with a reduction of testosterone and FAI levels in conjunction with increased SHBG and LH levels. Dietary interventions alone or combined with weight-lowering drugs offered an additional advantage for reducing BMI. Importantly, these findings were consistent when the analyses were restricted to studies including only women with PCOS. These results provide strong evidence on the efficacy of lifestyle combined with pharmacological interventions to improve ovulation and reduce BMI and androgen excess as key fertility factors in women with overweight or obesity who wish to improve their reproductive health. These results are clinically important as they will serve clinicians during a shared decision-making process in women with overweight or obesity wishing to conceive.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Authors' roles

D.R.-G., I.C.-R., S.A., A.M.F.-A., and A.S.-M. conceived and designed the study. D.R.-G., I.C.-R., and A.H.-M. screened, selected the articles, and extracted the data. D.R.-G. and I.C.-R. conducted the statistical analyses. D.R.-G. interpreted the data with input from A.M.F.-A., S.A., and A.S.-M. D.R.-G. wrote the initial draft with significant input from A.S.-M. All the authors critically reviewed the article for important intellectual content and approved the final submitted version.

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Conflict of interest

None declared.

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