Metformin and lifestyle modification in polycystic ovary syndrome: systematic review and meta-analysis

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BACKGROUND: Polycystic ovary syndrome (PCOS) is a common endocrine disorder with diverse reproductive and metabolic features. It is underpinned by insulin resistance that is exacerbated by obesity. Lifestyle modification is the first line treatment in PCOS, but it is associated with low adherence and sustainability. In small studies, metformin improves outcomes such as hyperinsulinaemia, ovulation and menstrual cyclicity. We conducted a systematic review and meta-analysis to compare the effect of lifestyle modification + metformin with lifestyle modification ± placebo, and of metformin alone with lifestyle modification ± placebo in PCOS on anthropometric, metabolic, reproductive and psychological outcomes.

METHODS: Databases including MEDLINE, EMBASE, Pubmed, Scopus, Cochrane, PsycINFO, CINAHL, Clinical Trials registry and ANZCTR were searched for RCTs conducted on humans and published in English up to August 2014. Inclusion criteria were diagnosis of PCOS based on Rotterdam criteria (inclusive of National Institutes of Health criteria) at any age and with any BMI. Interventions of interest included lifestyle + metformin (with any dose and any duration) or metformin alone compared with lifestyle ± placebo.

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Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting up to 6–21% of women of reproductive age, depending on the population studied (March et al., 2010; Boyle et al., 2012; Yildiz et al., 2012). Diagnosis is based on reproductive features using the internationally accepted Rotterdam criteria, ratified by the Australian PCOS Alliance and the US National Institutes of Health (NIH) (REA-SPCW group, 2004; Teede et al., 2011; NEbw panel, 2012), which require two of three features of androgen excess, ovulatory dysfunction and polycystic ovarian morphology (REA-SPCW group, 2004). PCOS however has broader features across reproductive (infertility, miscarriage and pregnancy complications), metabolic (obesity, insulin resistance, prediabetes, type 2 diabetes (DM2), cardiometabolic), and psychological (anxiety, depression) health (Teede et al., 2010). A large retrospective study that compared 2566 women with PCOS with 25 660 age matched controls in Australia and used several linked health datasets showed that having PCOS was associated with an increased risk of obesity (16 versus 3.7%), adult-onset diabetes (12.5 versus 3.8%), hypertensive disorder (3.8 versus 0.7%), ischaemic heart disease (0.8 versus 0.2%), asthma (10.6 versus 4.5%), endometrial cancer (0.4 versus 0.02%), stress/anxiety (14 versus 5.9%), depression (9.8 versus 4.3%) and mortality (0.7 versus 0.4%). Women with PCOS had twice as many hospital admissions as women without the condition over the 15-year follow-up (Hart and Doherty, 2015). Based on the wealth of existing literature it is now clear that PCOS has profound short- and long-term health consequences.

Although there is evidence supporting the involvement of genetic and environmental/lifestyle factors in development of PCOS, the exact aetiology remains unknown. Insulin resistance and hyperandrogenism play a key role in the pathophysiology of PCOS and insulin resistance affects ~85% (75% of lean and 95% of overweight) of cases (Stepto et al., 2013). Despite the vast majority of women with PCOS being insulin resistant, routine measurement of insulin resistance is discouraged in evidence-based PCOS guidelines. This is primarily because it can only be accurately measured using invasive clamp studies, unsuitable in clinical practice (Teede et al., 2011). The resulting hyperinsulinaemia increases androgen production and reduces sex hormone-binding globulin (SHBG) leading to hyperandrogenism (Teede et al., 2007).

Insulin resistance is further exacerbated by overweight and obesity, a common finding in PCOS (risk ratio (95% confidence interval (CI)): 1.95 (1.52, 2.50) and 2.77 (1.88, 4.10), respectively, for women with PCOS compared with controls from a systematic review) (Ng et al., 2014). Emerging data suggest obesity has a bidirectional relationship with PCOS, with obesity increasing PCOS prevalence and PCOS increasing weight gain and obesity (Teede et al., 2013). Obesity further exacerbates hormonal and clinical reproductive, metabolic and psychological features of PCOS (Lim et al., 2013). Consistently, weight loss through lifestyle modification (comprising dietary modification, physical activity and/or behavioural change), medications (metformin, orlistat, incretin mimetics) or bariatric surgery improves insulin resistance, reduces hyperandrogenism and alleviates PCOS clinical severity (Moran et al., 2011; Vosnakis et al., 2013; Jensterle et al., 2015). Lifestyle management is first line therapy in PCOS for prevention of weight gain and for weight loss (Teede et al., 2011). However, as in the general population, the efficacy of lifestyle management for established obesity has been limited in PCOS (Moran et al., 2011), with new approaches needed.

Pharmacotherapy is also used in PCOS, including the oral contraceptive pill (OCP), insulin-sensitizing agents including metformin, cyclic progestins, anti-androgens and fertility treatments such as clomiphene citrate. Metformin increases insulin sensitivity by decreasing glucoseogenesis, lipogenesis and enhancing glucose uptake in the liver, skeletal muscle, adipose tissue and ovaries. It is known in other populations to prevent weight gain and appears to assist with weight loss, to prevent and manage DM2, gestational diabetes, fatty liver, and reduce cardiovascular disease in DM2 (Lord et al., 2003; Desilets et al., 2008; Nestler, 2008; Batra et al., 2009; Nieuwenhuis-Ruifrok et al., 2009; Oppelt et al., 2010; Diabetes Prevention Program Research Group, 2012; Viollet et al., 2012) (Fig. 1). In PCOS, metformin reduces insulin resistance and inhibits ovarian androgen production via effects on steroidogenic acute regulatory protein and 17alpha-hydroxylase (Diamanti-Kandarakis et al., 2010; Viollet et al., 2012). Based on current guidelines, metformin is indicated in PCOS in some scenarios to improve fertility (Teede et al., 2011; Legro et al., 2013), for management of menstrual irregularity if women are unable to take OCPs, and in co-existent prediabetes or DM2, where lifestyle modification fails (Legro et al., 2013). However key knowledge gaps remain on the efficacy of metformin and its specific role in PCOS, including in weight management.

RESULTS: Of 2372 identified studies, 12 RCTs were included for analysis comprising 608 women with PCOS. Lifestyle + metformin were associated with lower BMI (mean difference (MD) = −0.73 kg/m², 95% confidence intervals (CI) −1.14, −0.32, P = 0.0005) and subcutaneous adipose tissue (MD −92.49 cm², 95% CI −164.14, −20.84, P = 0.01) and increased number of menstrual cycles (MD 1.06, 95% CI 0.30, 1.82, P = 0.006) after 6 months compared with lifestyle + placebo. There were no differences in other anthropometric, metabolic (surrogate markers of insulin resistance, fasting and area under the curve glucose, lipids and blood pressure), reproductive (clinical and biochemical hyperandrogenism), and psychological (quality of life) outcomes after 6 months between lifestyle + metformin compared with lifestyle + placebo. With metformin alone compared with lifestyle + placebo, weight and BMI were similar after 6 months, but testosterone was lower with metformin.

CONCLUSIONS: Lifestyle + metformin is associated with lower BMI and subcutaneous adipose tissue and improved menstruation in women with PCOS compared with lifestyle ≥ placebo over 6 months. Metformin alone compared with lifestyle showed similar BMI at 6 months. These results suggest the combination of lifestyle with metformin has a role to play in weight management: a key concern for women with PCOS. Existing study limitations include small sample sizes, short durations and risk of bias. With international guidelines now acknowledging that lifestyle and pharmacotherapy are required for weight loss and maintenance in obesity, future studies of appropriate size and duration are vital to clarify the role of metformin in PCOS management.

Key words: polycystic ovary syndrome / lifestyle / metformin / weight loss
A number of systematic reviews have been conducted on the efficacy of metformin or lifestyle modification, or on the effect of metformin with lifestyle, clomiphene citrate, contraceptive pills and other insulin sensitizing agents, on outcomes in PCOS including weight loss, ovulation, menstruation, hyperandrogenism, insulin resistance, and risk of DM2 and cardiovascular disease (Costello and Eden, 2003; Costello et al., 2007; Moll et al., 2007; Jing et al., 2008; Palomba et al., 2009; Du et al., 2012; Siebert et al., 2012; Tang et al., 2012; Xiao et al., 2012; Domecq et al., 2013; Misso et al., 2013). However, there is currently no systematic review comparing the effect of lifestyle + metformin with that of lifestyle + placebo in PCOS. The primary aim of this study was to undertake a comprehensive systematic review and meta-analysis comparing the effect of lifestyle + metformin with lifestyle + placebo in PCOS on a range of end-points including weight outcomes. We also studied the effect of metformin alone compared with lifestyle modification.

Methods
This systematic review addressed the efficacy of (i) lifestyle + metformin compared with lifestyle + placebo and (ii) metformin alone compared with lifestyle + placebo in women with PCOS for improving anthropometric, reproductive, metabolic, cardiovascular and psychological outcomes. It was completed by an experienced multidisciplinary clinical research team including an evidence synthesis expert (M.L.M.).

Selection criteria
The PICO (population, intervention, comparison, outcome) framework was used to establish a priori selection criteria and included all RCTs comparing (i) lifestyle + metformin versus lifestyle + placebo, (ii) metformin alone versus lifestyle + placebo for women of any age with PCOS.

The inclusion criteria for the population studied were diagnosis of PCOS based on Rotterdam criteria (inclusive of NIH criteria) at any age including adolescents, pre and post-menopausal women and with any BMI. The exclusion criteria were presence of other aetiologies for hyperandrogenism or infertility, such as hypothyroidism, congenital adrenal hyperplasia and Cushing's syndrome, or concurrent medication use (e.g. OCPs, orlistat, clomiphene citrate, etc.) even if the same between groups. The multivitamins and folic acid prescribed in pregnancy were accepted. Interventions of interest included: lifestyle + metformin (with any dose and any duration) or metformin alone.

Lifestyle modification was defined as any duration of diet, behavioural change (by education, counselling, and cognitive therapy or stress management), exercise or combinations of these. The comparison of interest was lifestyle + placebo. Primary outcomes included anthropometric [BMI] and metabolic [surrogate markers of insulin resistance (fasting insulin, oral glucose tolerance test (OGTT) insulin, insulin area under the curve (AUC), the homeostatic model assessment (HOMA) index, insulinogenic index, insulin sensitivity index, quantitative insulin sensitivity check index (QUICKI)) and glucose intolerance (impaired fasting glucose (IFG), IGT or DM2)] parameters. Secondary outcomes included anthropometric [waist circumference, waist to hip ratio (WHR), subcutaneous and visceral fat], reproductive [menstruation, pregnancy rate, total testosterone, SHBG, free androgen index (FAI), dehydroepiandrosterone sulphate, hirsutism, acne], metabolic [fasting glucose, AUC glucose, highly sensitive C reactive protein (hsCRP), blood pressure, lipids], and psychological [quality of life] parameters.

Search method
The literature was searched up to August 2014 and was limited to English language articles. There were no limits on year of publication.

Data sources
Ovid MEDLINE (from 1946), EMBASE (from 1980), Pubmed, Scopus, Cochrane, PsycINFO, CINAHL, NHMRC (clinical practice guidelines clearinghouse), Clinical Trials registry and ANZCTR databases were employed to
identify relevant literature. Bibliographies of relevant studies identified by the search strategy and relevant reviews were also searched for identification of additional studies.

**Study selection**

One trained clinical reviewer (N.N.), under the supervision of a senior author with extensive experience in conducting systematic reviews and meta-analysis (LM) and with assistance where required of an evidence synthesis expert (MM), screened the titles and abstracts of every record retrieved by the search strategy according to the selection criteria. Full articles were retrieved for further assessment if the information given suggested that the study met the inclusion criteria. Where there was any doubt about inclusion, the study was reviewed and discussed with other reviewers (L.J.M. and H.J.T).

**Risk of bias appraisal**

To assess the methodological quality of the included studies, a risk of bias (RoB) assessment tool developed *a priori* was employed. Individual quality items were investigated using a descriptive component approach that included items such as conflict of interest of authors, prespecified selection criteria, methods of randomization and allocation of patients to study groups, blinding of patients, carers, investigators or outcome assessors, methods of outcome assessment and reporting, and statistical issues such as powering and methods of data analysis. Any disagreement or uncertainty was resolved by discussion among reviewers to reach a consensus. Using this approach, each study was allocated a RoB rating of low, medium, high.

**Data extraction**

Data were extracted from included studies by two independent reviewers (N.N., S.S.) using a specially developed data extraction form according to the selection criteria. Information extracted included description of study (authors, country, year of publication, setting, diagnostic criteria for PCOS, inclusion and exclusion criteria, primary and secondary outcomes, sample size, dropout rate), participants (mean age, BMI, ethnicity, age at PCOS diagnosis, comorbidities), intervention (type and duration of lifestyle modification, dose and duration of metformin use) and study results according to the outcomes outlined above. When the data of interest (methodology or results) were not available in the published paper, authors were contacted by email.

**Data synthesis and meta-analysis**

Continuous outcomes underwent meta-analysis using weighted mean difference and 95% CI in RevMan5.2 (the Nordic Cochrane Centre, The Cochrane Collaboration (2012) Copenhagen). I² > 30% was considered as moderate to high heterogeneity. The fixed-effect model was used for variables with low heterogeneity and the random-effect model was used for variables with moderate or high heterogeneity. Meta-analyses were conducted for outcomes at 6 and 12 months. Where a study presented data at an alternative end-point (e.g. 4 months (Otta et al., 2010)) these data were not combined in the meta-analyses and were instead presented narratively. Where it was not appropriate to conduct meta-analysis, for instance due to a small number of studies measuring the same outcome, the end-point data are presented narratively.

**Results**

**Study selection**

From 2372 search results, 31 studies were selected for full text review (Fig. 2). Nineteen studies were excluded (Supplementary Table SI). Twelve RCTs met the inclusion criteria (Pasquali et al., 2000; Hoeger et al., 2004, 2008; Vanky et al., 2004; Gambineri et al., 2006; Tang et al., 2006; Karimzadeh and Javedani, 2010; Otta et al., 2011a, b; Curi et al., 2012; Esfahanian et al., 2013; Ladson et al., 2011a, b). Nine RCTs compared lifestyle + metformin with lifestyle ± placebo. Four studies compared metformin alone with lifestyle (± placebo) (Hoeger et al., 2004, 2008; Curi et al., 2012; Esfahanian et al., 2013). Hoeger et al. (2004) was included in both groups as it included metformin alone, metformin + lifestyle, and lifestyle + placebo in three arms. Study characteristics are presented in Table I.

Studies were conducted at obstetrics and gynaecology, endocrine or infertility outpatient clinics of academic hospitals or research centres in the USA (Hoeger et al., 2004, 2008; Ladson et al., 2011a, b), Iran (Karimzadeh and Javedani, 2010; Esfahanian et al., 2013), Italy (Pasquali et al., 2000; Gambineri et al., 2006), Norway (Vanky et al., 2004), UK (Tang et al., 2006), Argentina (Otta et al., 2010) and Brazil (Curi et al., 2012).

Interventions ranged from 3 to 12 months with a total of 608 participants aged 12–39 years in lifestyle + metformin or lifestyle ± placebo or metformin alone arms of RCTs. Participants receiving other medications, such as the OCP or clomiphene citrate, were excluded. Most studies were for 6 months and 6-month data were also available for the two longer 48- and 52-week studies. Six-month data were therefore selected for meta-analysis. Results from one study that involved pregnant women with PCOS were not included in the meta-analysis to reduce heterogeneity. Participants were obese with a mean BMI > 30 kg/m² in all but one study (Karimzadeh and Javedani, 2010). Mean BMI was > 35 kg/m² in 7 of 12 RCTs (Pasquali et al., 2000; Hoeger et al., 2004, 2008; Gambineri et al., 2006; Tang et al., 2006; Ladson et al., 2011a, b).

For lifestyle modification, three studies used dietary advice only (Pasquali et al., 2000; Vanky et al., 2004; Gambineri et al., 2006) while the remaining nine used combined diet and exercise. Behavioural education and support were provided in two (Hoeger et al., 2004, 2008) and access to a fitness facility in two other studies (Ladson et al., 2011a, b). Apart from two studies based on 1500 kcal/day (Otta et al., 2010) and 1200–1400 kcal/day (Pasquali et al., 2000), diets were individualized by a dietician. Daily calorie intake reduction of 500 kcal was used in eight of 12 RCTs (Hoeger et al., 2004, 2008; Gambineri et al., 2006; Tang et al., 2006; Karimzadeh and Javedani, 2010; Ladson et al., 2011a, b; Curi et al., 2012).
Table I Characteristic of selected studies of metformin and lifestyle modification in polycystic ovary syndrome.

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Sample size</th>
<th>PCOS diagnostic criteria</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Primary outcomes</th>
<th>Mean age (years)</th>
<th>Mean BMI (baseline)</th>
<th>Lifestyle modification</th>
<th>Metformin dose</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Pasquali, 2000</td>
<td>Outpatient clinic (endocrine and gastroenterology)</td>
<td>LS + MF: 10, LS + P: 8</td>
<td>Rotterdam criteria</td>
<td>BMI &gt; 28 kg/m² and waist to hip ratio &gt;0.8</td>
<td>DM2, cardiovascular, renal or liver dysfunction, diet or medication 3 months prior to study</td>
<td>Body composition, fat distribution, androgens, insulin, glucose</td>
<td>LS + MF: 30.8 (7.4), LS + P: 32.3 (5.0)</td>
<td>LS + MF: 39.8 (7.9), LS + P: 39.6 (6.9)</td>
<td>1200–1400 kcal/day, 50% CHO, 20% protein, 30% fat.</td>
<td>850 mg bd</td>
<td>6 months</td>
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<tr>
<td>Vanky, 2004</td>
<td>Outpatient clinic (gynaecology and infertility)</td>
<td>LS + MF: 17, LS + P: 21</td>
<td>Rotterdam criteria</td>
<td>Diagnosis of PCOS before pregnancy, age 18–40, gestation 5–12 weeks, singleton fetus by US</td>
<td>Known liver disease, cr &gt; 130 mmol/l, known alcohol abuse, DM, FBGL &gt; 5.6, on oral glucocorticoids or any drug known to interfere with MF</td>
<td>Androgens</td>
<td>LS + MF: 28.9 (4.8), LS + P: 28.3 (3.7)</td>
<td>LS + MF: 32.0 (6.3), LS + P: 29.4 (8.2)</td>
<td>Verbal and written diet and lifestyle counselling at inclusion and after GDM diagnosis</td>
<td>850 mg/day</td>
<td>from week 5–12 of pregnancy till post-partum</td>
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<td>Gambineri, 2006</td>
<td>University medical centre, endocrine division</td>
<td>LS + MF: 20, LS + P: 19</td>
<td>Rotterdam criteria</td>
<td>Reproductive age (18–45), BMI ≥ 28 kg/m², waist circumference ≥ 88 cm</td>
<td>Use of any medications, significant modification in weight within previous 3 m, dieting</td>
<td>Androgens</td>
<td>LS + MF: 28 (4), LS + P: 26 (5)</td>
<td>LS + MF: 35 (5)</td>
<td>500 kcal deficit, final composition ranged 1200–1400 kcal/day</td>
<td>850 mg bd</td>
<td>12 months</td>
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<tr>
<td>Tang, 2006</td>
<td>Infertility clinic</td>
<td>LS + MF: 56, LS + P: 66</td>
<td>Rotterdam criteria</td>
<td>BMI &gt; 30 kg/m², 18–39 years old and a desire to conceive. Presence of at least one patent Fallopian tube, normal semen analysis, normal PRL, thyroid, renal and liver function, haematological indices including B12, negative B12</td>
<td>Concurrent hormone therapy within the previous 6 weeks, any chronic disease that could interfere with absorption, distribution, metabolism or excretion of metformin, renal or liver disease. Sig systemic dis or DM2, irregular menses due to pathology of genital tract</td>
<td>Menstrual cycle, anthropometric measurements, endocrine parameters, insulin sensitivity, lipids</td>
<td>LS + MF: 29.7 (3.7), LS + P: 29.8 (3.8)</td>
<td>LS + MF: 38.1 (5.08), LS + P: 37.9 (6.5)</td>
<td>Verbal and written advice, 500 kcal/day deficit, 50% CHO, 10% fat, encouraged to adhere to regime at monthly visits. Encouraged to increase daily exercise by 15 min but not formally assessed.</td>
<td>850 mg bd</td>
<td>6 months</td>
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<tr>
<td>Study</td>
<td>Referral Source</td>
<td>NIH Criteria</td>
<td>Age</td>
<td>BMI</td>
<td>Ethnicity</td>
<td>Any Hormonal Therapy or Insulin Sensitizers in Previous 2 Months</td>
<td>Androgens, Lipids</td>
<td>Mennopause Status</td>
<td>Mammography Status</td>
<td>Referral from</td>
<td>Recruitment Type</td>
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<td>Hoeger, 2008 (Hoeger et al., 2008)</td>
<td>Community or local physician referral</td>
<td>MF: 6</td>
<td>12–18, BMI &gt; 95th percentile, post-menarchal</td>
<td>Any hormonal therapy or insulin sensitizers in previous 2 months</td>
<td>Androgens, lipids</td>
<td>MF: 16 (1.7), LS: 15.4 (1.2)</td>
<td>MF: 35.0 (8.2), LS: 36.0 (6.2)</td>
<td>500 kcal/day deficit, 30 min/day of mod to intense activity. Closed group format with 5–6 subjects per group (16-session core curriculum) hands-on kitchen training, behavioural support including peer support, electronic communications + structured group exercise weekly</td>
<td>850 mg bd 6 months (started with 425 mg and was increased gradually)</td>
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<td>Hoeger, 2004 (Hoeger et al., 2004)</td>
<td>Direct advertisement, referral from physicians, reproductive endocrinology clinic</td>
<td>LS + MF: 9</td>
<td>BMI &gt; 25 kg/m², normal TSH, PRL, FSH and metabolic profile, DHEAS, 17 OH progesterone and 24 h UFC, negative Bhcg</td>
<td>Any hormonal medication within the last 2 months before entry, not dieting at the time of entry</td>
<td>Ovulation, recruitment, dropout and compliance with a long-term lifestyle intervention in PCOS</td>
<td>LS + MF: 30.4 (5.4), LS: 27.1 (4.3), MF: 29.5 (6.4)</td>
<td>LS + MF: 41.7 (6.2), LS: 40 (7.4), MF: 37.1 (4.9)</td>
<td>Modified from Diabetes Prevention Trial, aim for 7–10% weight loss, 500–1000 kcal/day deficit, 50% CHO, 25% protein, 25% fat, weekly interactive group education and monitoring (2 groups of 10 individuals) and 24 weeks maintenance (biweekly progress monitoring and group support meetings)</td>
<td>850 mg bd 48 weeks</td>
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<td>Karimzadeh, 2010 (Karimzadeh and Javedani, 2010)</td>
<td>Infertility clinic Rotterdam criteria</td>
<td>LS + MF: 90</td>
<td>Age 19–35, BMI 25–29.9 kg/m² with primary infertility, normal thyroid, liver and kidney function, PRL, negative hCG, spouse with sperm concentration &gt; 20 million/ml, motility &gt;50%, morphology &gt;30%</td>
<td>menstrual cycle, waist circumference, lipids, endocrine parameters</td>
<td>taking MF in previous 8 weeks</td>
<td>LS + MF: 27.33 (2.34), LS: 27.84 (2.69)</td>
<td>LS + MF: 27.17 (1.73), LS: 27.92 (1.05)</td>
<td>500 kcal/day deficit, 50–60% CHO, 15–20% protein, 25–30% fat and 3–5 times a week exercise of 20–60 min both aerobic and strength training</td>
<td>500 mg/day gradually increased to 1.5 g/day 6 months</td>
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<td>Ladson, 2011 (adolescents) (Ladson et al., 2011a)</td>
<td>Mennopause criteria</td>
<td>LS + MF: 111</td>
<td>Age 13–18, BMI &gt; 27 kg/m², otherwise healthy</td>
<td>Use of any confounding medications (hormonal contraceptives, diabetic medications)</td>
<td>Androgens</td>
<td>LS + MF: 16.1 (1.5), LS + P: 15.4 (1.2)</td>
<td>LS + MF: 37.1 (5.8), LS + P: 35.9 (6.6)</td>
<td>3d food log, 500 kcal/day deficit, 55% CHO, 15% protein, 30% fat, goal of ≥7% weight loss, monthly review by a dietitian and a personal trainer, 150 min/week aerobic exercise including an opportunity to attend ≥2 sessions per week at a fitness facility</td>
<td>500 mg/day 6 months gradually increased to 2 g/day every 5 days</td>
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<tr>
<th>Study</th>
<th>Setting</th>
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<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Primary outcomes</th>
<th>Mean age (years)</th>
<th>Mean BMI (baseline)</th>
<th>Lifestyle modification</th>
<th>Metformin dose</th>
<th>Duration</th>
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<tr>
<td>Ladson, 2011 (adults)</td>
<td>Two academic medical centres</td>
<td>LS + MF: 22</td>
<td>NIH criteria</td>
<td>Age 21–39, otherwise healthy, any BMI</td>
<td>Use of any confounding meds (hormonal contraceptives, diabetic medications)</td>
<td>Ovulation, androgens</td>
<td>LS + MF: 29 (4.5), LS + P: 28.8 (4.6)</td>
<td>LS + MF: 38.0 (7.8), LS + P: 38.3 (8.0)</td>
<td>500 kcal/day deficit, goal of ≥7% weight loss, 150 min/week aerobic exercise with an opportunity to attend ≥2 sessions per week a fitness facility, a daily physical activity log once per month and monthly test of aerobic capacity</td>
<td>500 mg/day</td>
<td>6 months</td>
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<td>Ladson et al., 2011b</td>
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<td>LS + P: 16</td>
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<tr>
<td>Esfahanian, 2012</td>
<td>Endocrine clinic</td>
<td>MF: 17</td>
<td>Rotterdam criteria</td>
<td>Age 20–30, BMI ≥ 27 kg/m²</td>
<td>DM2, smoking, alcohol use, taking sex steroids or drugs known to affect lipids and weight during the preceding 3m</td>
<td>CRP, insulin resistance</td>
<td>MF: 21.9 (9.3), LS (diet): 20 (4.6)</td>
<td>MF: 31.1 (3.3), LS: 34.1 (5.4)</td>
<td>Dietitian review for 5–10% weight loss, frequent contacts (phone, email and visit) weekly to support diet programme</td>
<td>500 mg bd</td>
<td>12 weeks</td>
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<td>(Esfahanian et al., 2013)</td>
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<td>LS: 13</td>
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<tr>
<td>Otta, 2010</td>
<td>Endocrine clinic</td>
<td>LS + MF: 14</td>
<td>NIH criteria</td>
<td>Age 20–34, negative Bhcg, any BMI kg/m²²</td>
<td>Cushing, thyroid, late CAH, DM, high PRL, androgen-secreting tumours, Hepatic or renal dysfunction, severe infections, CVD, no meds for at least 3 m prior to study</td>
<td>Endocrine and metabolic parameters</td>
<td>LS + MF: 25.47 (4.92), LS + P: 24.7 (3.46)</td>
<td>LS + MF: 32.4 (6.7) , LS + P: 35.6 (4.98)</td>
<td>1500 kcal/day diet, 50% CHO, 20% protein, 30% fat, minimum of 40 min daily brisk walk, 4 times/week, monthly visits</td>
<td>500 mg/day</td>
<td>4 months</td>
</tr>
<tr>
<td>(Otta et al., 2010)</td>
<td></td>
<td>LS + P: 15</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Curi, 2012</td>
<td>Obstetrics and gynaecology clinic</td>
<td>MF: 15</td>
<td>Rotterdam criteria</td>
<td>Age 18–34, BMI ≥ 25 kg/m²², sedentary lifestyle</td>
<td>Cushing, thyroid, late CAH, DM, high PRL, androgen-secreting tumours, HTN, Gl, hepatic or renal dysfunction, hormonal or other medications interfering with weight in the preceding 6 months before study</td>
<td>Menstrual pattern</td>
<td>MF: 24.6 (1.3), LS: 26.3 (1.4)</td>
<td>MF: 31.4 (1.4), LS: 31.8 (1.6)</td>
<td>500 kcal deficit, 50% CHO, 20% protein, 30% fat, 30 min walk and 3 self-weight resistance exercise (total 40 min), record of food intake and physical activity on a daily card, monthly review by dietitian</td>
<td>850 mg bd</td>
<td>6 months</td>
</tr>
<tr>
<td>(Curi et al., 2012)</td>
<td>(presentation for hirsutism or menstrual disturbances)</td>
<td>LS: 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

CVD, cardiovascular disease; CAH, congenital adrenal hyperplasia; CHO, carbohydrate; Cr, créatinine; DHEAS, Dehydroepiandrosterone; DM, diabetes mellitus; DM2, Type 2 diabetes mellitus; FBGL, fasting blood glucose level; GI, gastrointestinal; GDM, gestational diabetes mellitus; 17 OH progesterone, 17 hydroxy progesterone; HTN, hypertension; LS, lifestyle; MF, metformin; P, placebo; PRL, prolactin; PCOS, polycystic ovary syndrome; TSH, thyroid stimulating hormone; UFC, urine free cortisol.
All studies used immediate release metformin hydrochloride. Metformin dose ranged from 1.5 to 2 g/daily. The regimen of 850 mg bd was used in 7 of 12 RCTs (Pasquali et al., 2000; Hoeger et al., 2004, 2008; Vanky et al., 2004; Gambineri et al., 2006; Tang et al., 2006; Curi et al., 2012). Gradual dose escalation was applied in seven RCTs (Vanky et al., 2004; Hoeger et al., 2008; Karimzadeh and Javedani, 2010; Otta et al., 2010; Ladson et al., 2011a, b; Esfahanian et al., 2013) to reduce gastrointestinal side effects of metformin. The dropout rate was 25% (71/279) for lifestyle + metformin or metformin alone treatment and 29% (79/271) for lifestyle ± placebo treatment. The dropout rate was not reported for one study (Karimzadeh and Javedani, 2010).

Participants with DM2 but not glucose intolerance were excluded before randomization in all studies except for one (Hoeger et al., 2008).

Author contact
Six authors were contacted by e-mail to request further data regarding eight publications, with responses received for five publications. The data were not available for one RCT due to prolonged time since publication and we did not receive a response from two authors.

Risk of bias
Apart from two studies (Hoeger et al., 2004, 2008) participants were selected from specialized outpatient clinic referrals. All studies adequately described PCOS diagnostic criteria, inclusion and exclusion criteria. Duration of follow-up, except for two studies (Hoeger et al., 2004; Gambineri et al., 2006), was 6 months or shorter.

There was one study with high RoB, seven studies with moderate and three with low RoB. RoB could not be assessed for one study due to insufficient information (Karimzadeh and Javedani, 2010). Main reasons for higher RoB include lack of blinding of outcome assessors (detection bias), not applying intention to treat analysis, and high dropout rates (Table II).

None of the authors had a conflict of interest. There were no significant differences in baseline characteristics between intervention groups within each study for the variables of age, BMI, waist circumference, glucose and insulin levels (fasting and post OGTT), fat distribution, lipid and androgen levels. The specified methods of measurement for these variables were all standard and reliable.

Lifestyle + metformin versus lifestyle ± placebo
Primary outcomes
Anthropometric parameters: BMI was measured in all studies comparing a combination of lifestyle + metformin with lifestyle ± placebo. Lifestyle + metformin was associated with a lower BMI at study completion compared with lifestyle ± placebo (n = 493, MD −0.73 kg/m², 95% CI −1.14, −0.32, P < 0.0005) (Fig. 3). Two studies not included in the meta-analysis (Vanky et al., 2004; Otta et al., 2010) did not report a significant between-group difference in mean BMI at study end.

Metabolic parameters:
Markers of insulin resistance: Insulin resistance was assessed in five of nine studies comparing lifestyle + metformin with lifestyle ± placebo (Pasquali et al., 2000; Hoeger et al., 2004; Gambineri et al., 2006; Ladson et al., 2011a, b). There were no significant differences in post OGTT insulin (insulin AUC) (MD 0.18 µU/ml/min, 95% CI −0.18, 0.55, P = 0.31) (Fig. 4), fasting insulin, insulinogenic index, insulin sensitivity index and QUICKI (Table III) at study completion between lifestyle + metformin groups compared with lifestyle ± placebo. A meta-analysis was not performed on HOMA due to small study numbers (n = 2). In the study not included in the meta-analysis due to shorter duration (Otta et al., 2010), lifestyle + metformin was associated with lower fasting insulin and HOMA compared with baseline, but these differences were not statistically significant compared with lifestyle + placebo.

Glucose intolerance: IFG or IGT was assessed in five of nine studies comparing lifestyle + metformin with lifestyle ± placebo (Hoeger et al., 2004, 2008; Vanky et al., 2004; Gambineri et al., 2006; Otta et al., 2010). Meta-analysis was not possible with the data provided. In Hoeger et al., abnormal fasting or 2 h post OGTT glucose levels were reported in two subjects on metformin, three on lifestyle and none on lifestyle + metformin at baseline. At study end (48 weeks), no subjects had IFG or IGT (Hoeger et al., 2004). In another study by Hoeger et al. (2008), IFG or IGT was seen in 25% of subjects at baseline (four IFG and six IGT) and one subject had DM2, although assignment groups were not noted. At study end, new onset IGT was noted in one subject on metformin and none on lifestyle (Hoeger et al., 2008). In Gambineri et al. (2006), IFG was seen in three (15%) subjects on lifestyle + metformin and two (11%) on lifestyle + placebo that were unchanged at study end (12 months). In addition, IGT was seen in three (15%) subjects on lifestyle + metformin and two (11%) on lifestyle + placebo at baseline which decreased to two (10%) and 0 respectively at 12 months. There were two (10%) subjects with both IFG and IGT on lifestyle + metformin and one (5%) on lifestyle + placebo at baseline, which were all normal at 12 months (Gambineri et al., 2006). In Otta et al., one subject on lifestyle + metformin and five on lifestyle + placebo were prediabetic (no definition provided) at baseline and all normalized by study end (4 months) (Otta et al., 2010). Vanky et al. (2004) reported gestational diabetes in eight (47%) pregnant women on lifestyle + metformin and nine (43%) pregnant women on lifestyle + placebo. None of the women on lifestyle + metformin and two on lifestyle + placebo required additional insulin treatment (Vanky et al., 2004).

Secondary outcomes
Anthropometric parameters: Body composition as assessed by computed tomography (CT) at L4-5 was provided in two (Pasquali et al., 2000; Gambineri et al., 2006) of nine studies comparing lifestyle + metformin with lifestyle ± placebo. Lifestyle + metformin was associated with decreased subcutaneous adipose tissue compared with lifestyle ± placebo (MD −92.49 cm², 95% CI −164.14, −20.84, P = 0.01) (Fig. 5). There were no differences in visceral and total adipose tissue, waist circumference and WHR (Table III) at study end for lifestyle + metformin compared with lifestyle ± placebo. Two studies that used dual-energy X-ray absorptiometry (DEXA) for body composition could not be included for meta-analysis as one reported mean change and the other reported only the end result. They found no differences in total and percentage of body fat between the groups (Ladson et al., 2011a, b).

Reproductive parameters: There were no differences in biochemical hyperandrogenism, acne or Ferriman–Gallwey score for hirsutism (Table III) at study end for lifestyle + metformin compared with lifestyle ± placebo studies. Similarly Vanky et al. noted no difference in maternal androgen levels in pregnant women with PCOS for lifestyle + metformin compared with lifestyle + placebo (Vanky et al., 2004).

Menstruation was assessed in seven of nine studies comparing lifestyle + metformin with lifestyle ± placebo. However, only three studies (Pasquali et al., 2004; Hoeger et al., 2008; Vanky et al., 2004),
### Table II Summary of risk of bias assessment.

<table>
<thead>
<tr>
<th>Study</th>
<th>Adequate randomization</th>
<th>Concealed allocation</th>
<th>Blinding patients</th>
<th>Blinding care providers</th>
<th>Blinding outcome assessors</th>
<th>Dropout rate at study completion (%)</th>
<th>Intention to treat</th>
<th>Reporting bias</th>
<th>Sufficient power</th>
<th>Total risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pasquali, 2000 (Pasquali et al., 2000)</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>(2/12) 16.7% LS + MF, (0/8) 0% LS + P</td>
<td>No</td>
<td>No</td>
<td>NR</td>
<td>Moderate</td>
</tr>
<tr>
<td>Vanky, 2004 (Vanky et al., 2004)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>(1/18) 5.55% LS + MF, (1/22) 4.54% LS + P</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>Gambineri, 2006 (Gambineri et al., 2006)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>(0/20) 0% LS + MF, (1/10) 5% LS</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Tang, 2006 (Tang et al., 2006)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>(13/69) 18.84% LS + MF, (8/74) 10.8% LS + P</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Hoeger, 2008 (Hoeger et al., 2008)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>(4/10) 40% MF, (3/11) 27.3% LS</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>Moderate</td>
</tr>
<tr>
<td>Hoeger, 2004 (Hoeger et al., 2004)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>(4/9) 44.44% MF, (4/9) 44.44% LS + MF, (5/11) 45.45% LS + P</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>Moderate</td>
</tr>
<tr>
<td>Karimzadeh, 2010 (Karimzadeh and Javedani 2010)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>Not sufficient data</td>
</tr>
<tr>
<td>Ladson, 2011 (adolescents) (Ladson et al., 2011a)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>(1/11) 9% LS + MF, (3/11) 27% LS + P</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Ladson, 2011 (adults) (Ladson et al., 2011b)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>(33/55) 60% MF + LS (43/59) 72% LS + P</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>Esfahanian, 2012 (Esfahanian et al., 2013)</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>(3/20) 15% MF, (7/20) 35% LS</td>
<td>No</td>
<td>Yes</td>
<td>NR</td>
<td>High</td>
</tr>
<tr>
<td>Otta, 2010 (Otta et al., 2010)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>(1/15) 6.66% of MF + LS, (0/15) 0% of LS</td>
<td>No</td>
<td>No</td>
<td>NR</td>
<td>Moderate</td>
</tr>
<tr>
<td>Curi, 2012 (Curi et al., 2012)</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>(5/20) 25% MF, (8/20) 40% LS</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

NR, not reported.
et al., 2000; Hoeger et al., 2004; Gamberini et al., 2006) could be included in the meta-analysis due to differences in the reporting of data, i.e. mean number of cycles (Pasquali et al., 2000; Hoeger et al., 2004; Gamberini et al., 2006), percentage of participants who had a menstrual cycle (Karimzadeh and Javedani, 2010), days of vaginal bleeding (Ladson et al., 2011b), median (Tang et al., 2006) and ratio (Ladson et al., 2011a). The lifestyle + metformin group had a greater number of menstrual cycles over 6 months compared with lifestyle + placebo (MD 1.06, 95% CI, \( P = 0.006 \)) (Fig. 6). The remaining four studies did not report significant differences in menstruation between groups (Tang et al., 2006; Karimzadeh and Javedani, 2010, Ladson et al., 2011a, b).

Pregnancy rate was not a primary outcome in any studies comparing lifestyle + metformin with lifestyle + placebo. It was a secondary outcome in one study (Karimzadeh and Javedani, 2010) with a pregnancy rate of 14% (13/90) on lifestyle + metformin and 20% (15/75) on lifestyle alone, with no significant difference. In another study with participants who all desired pregnancy, pregnancy rates were 8.7% (6/69) on lifestyle + metformin and 2.7% (2/74) on lifestyle + placebo, with no significant difference (Tang et al., 2006). In two studies (Gamberini et al., 2006; Ladson et al., 2011b), participants were advised to use a non-hormonal contraception to avoid pregnancy during the study. One study involved adolescents (Ladson et al., 2011a) and one included only pregnant women (Vanky et al., 2004). Two participants on lifestyle + metformin (16% [2/12]) in one study (Pasquali et al., 2000) who became pregnant were excluded and two pregnancies (18% [2/11]) occurred on lifestyle + placebo in another study (Hoeger et al., 2004).

**Figure 3** Meta-analysis of lifestyle + metformin versus lifestyle ± placebo for BMI (Kg/m²). CI, confidence interval.

**Figure 4** Meta-analysis of lifestyle + metformin versus lifestyle ± placebo for insulin area under the curve (\( \mu U/ml/min \)).

Metabolic parameters: There were no differences in fasting glucose (Fig. 7), glucose AUC, lipids or blood pressure (Table III) at study end for lifestyle + metformin versus lifestyle ± placebo. hsCRP was not measured in any study comparing lifestyle + metformin with lifestyle ± placebo.

Psychological parameters: There were no differences in quality of life (Table III) at study end for lifestyle + metformin compared with lifestyle ± placebo (Ladson et al., 2011a, b).

**Twelve-month outcomes**

Data on BMI, testosterone, SHBG, FAI, menstruation, fasting glucose, glucose AUC and insulin AUC were also available from two studies with durations of 12 months and 48 weeks (Hoeger et al., 2004; Gamberini et al., 2006). The number of menstrual cycles from 6 to 12 months was greater in the lifestyle + metformin compared with lifestyle ± placebo groups (MD 1.38, 95% CI, \( P = 0.003 \)). There were no significant differences in other outcomes (Supplementary Table SII).

**Metformin alone versus lifestyle ± placebo**

There were four RCTs comparing metformin alone with lifestyle (± placebo) (Hoeger et al., 2004, 2008; Curi et al., 2012; Esfahanian et al., 2012). Key findings after 6 months included no difference in BMI, lower waist circumference and higher SHBG with lifestyle compared with metformin alone group, and lower total testosterone in the metformin group. No significant difference was observed in fasting glucose, insulin AUC and glucose AUC between groups (Supplementary Table SIII).
We report for the first time in a systematic review and meta-analysis in PCOS, that in nine studies with 608 participants analysed, 6 months of combined lifestyle + metformin is associated with a lower BMI and subcutaneous fat and improved menstrual cyclicity compared with lifestyle + placebo. Studies on metformin alone compared with lifestyle + placebo, suggest similar effects on BMI. Other end-points were inconsistently measured and other metabolic, reproductive or psychological outcomes did not differ significantly across comparator groups. Heterogeneity across the studies was limited, however most studies had small sample sizes and moderate to high RoB.

Women with PCOS report significant concern regarding weight gain, have higher rates of weight gain and are more likely to be obese (Lim et al.,...
While evidence-based guidelines recommend lifestyle modification as first line treatment in PCOS (Teede et al., 2011), engagement, compliance and sustainability remain challenging. The role of metformin in augmenting lifestyle induced weight management is therefore highly relevant. Prior systematic reviews of metformin in PCOS have notable limitations. One review reported a trend for improved weight loss with lifestyle + metformin compared with metformin alone (Nieuwenhuis-Ruifrok et al., 2009), although not all studies were in PCOS or included lifestyle modification. Two other systematic reviews on metformin alone compared with placebo or no intervention in PCOS, showed no effect on BMI (Lord et al., 2003; Tang et al., 2012). Here we advance the field by demonstrating that adding metformin at a standard dose of 1.5–2 g daily to lifestyle intervention, resulted in a 0.73 kg/m² lower BMI after 6 months compared with lifestyle + placebo in women with PCOS. We also show that metformin alone compared with lifestyle + placebo, had similar effects on BMI in PCOS.

Our current results suggest that metformin may be most effective in PCOS when combined with lifestyle intervention. This is consistent with recent international guidelines on the management of adults who are overweight with co-morbidities and in those who are obese. These guidelines recognize that weight loss may induce adaptive responses, which contribute to poor sustainability, rendering lifestyle alone often inadequate in obese adults. Pharmacotherapy is now recommended in addition to lifestyle to overcome adaptive responses and to optimize weight loss and maintenance. Whilst most approved anti-obesity agents are contraindicated in women of reproductive age, metformin has relatively few side effects, has long-term safety data, is low cost and is already used in PCOS (Teede et al., 2011; Legro et al., 2013; Apovian et al., 2015). Metformin use in weight management is supported by data in general populations with DM2 and in those with prediabetes, a similar metabolically affected population to PCOS. In these groups, lifestyle + metformin maintained body weight, while lifestyle (without metformin) was associated with significant weight gain (Ramachandran et al., 2006). In obese euglycemic populations, metformin may also improve weight management (Desilets et al., 2008). Whilst this current systematic review suggests metformin has a role in augmenting lifestyle in weight management in PCOS, it is acknowledged that most studies remain small and short term. We therefore propose that a large scale multicentre study of metformin in addition to lifestyle is now vital to verify the currently observed benefits and clarify the therapeutic role of metformin in addition to lifestyle in PCOS, especially in weight management.

PCOS has been identified by the International Diabetes Federation as an independent risk factor for DM2 (Alberti et al., 2007); hence the role of metformin and lifestyle in preventing DM2 in PCOS is highly relevant. Here we report that lifestyle + metformin versus lifestyle + placebo has better efficacy on BMI, but not on glucose tolerance. We did also find that metformin alone versus lifestyle has similar impacts on BMI and glucose tolerance. However, there are no RCTs or systematic reviews that we were able to identify, evaluating the effect of lifestyle + metformin or metformin alone in those with glucose intolerance on DM2 development in PCOS. The Indian and US Diabetes Prevention studies, conducted in people with prior prediabetes or gestational diabetes mellitus (GDM) and likely to include many women with PCOS, reported that metformin lowered weight and BMI and reduced progression to DM2 (Knowler et al., 2002; Ramachandran et al., 2006), with metformin more effective for women with prior GDM (Ratner et al., 2008). While we had insufficient data to conduct a meta-analysis in this area, individual studies generally reported improvement of...
The key take home messages from this work are that while lifestyle management is the first and most important step in the management of PCOS, addition of metformin to lifestyle modification appears to provide additional advantages in improving BMI and menstrual cyclicity. However current RCTs have limitations including small sample sizes and short duration. The subgroups that may benefit most from adding metformin to lifestyle modification and the benefits from longer term addition of metformin to lifestyle modification beyond 6 months remain to be defined by future studies.

**Conclusion**

PCOS is closely inter-related to obesity and weight management is first line therapy. Achieving and or sustaining a healthy weight is key in the management of PCOS and needs engagement of affected women in lifestyle modification. Pharmacotherapy for weight management can be considered as an adjunct to lifestyle modification to improve outcomes where compliance and sustainability with lifestyle modification are limited.

Here, in the first systematic review and meta-analysis to explore the addition of metformin to lifestyle versus lifestyle + placebo, we report that lifestyle + metformin appears to offer benefits in weight loss and menstrual cyclicity. Metformin alone also had similar effects on BMI compared with lifestyle. In the context of increasing recognition that pharmacotherapy has an important role in the management of excess weight in those with comorbidities, we suggest that metformin may have a key role in PCOS, in addition to lifestyle, to assist in weight management and cycle regulation. However, given the limitations of existing studies, a large scale, long-term multicentre RCT, utilizing gold standard methodology including women across the BMI range and PCOS phenotypes, focusing on metformin in addition to first line lifestyle therapy is warranted to definitively guide metformin use in PCOS.

**Supplementary data**

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Authors’ roles

H.J.T. and L.J.M. conceptualized the systematic review. L.J.M., H.J.T and N.N. developed the PICO. L.J.M., N.N. and M.L.M. defined the search protocol and conducted the literature search. N.N. screened the studies and selected the eligible RCTs with input from H.J.T. and L.J.M. where required. S.S. and N.N. extracted data and conducted the meta-analysis under supervision of M.L.M. N.N. drafted the manuscript and all authors contributed to, reviewed and approved the manuscript.

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Conflict of interest

None declared.

References
