

The impact of metformin with or without lifestyle modification versus placebo on polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Objective: Available evidence has shown that metformin improves insulin sensitivity and weight management in polycystic ovary syndrome (PCOS). Nevertheless, key knowledge gaps remain regarding its efficacy and the specific outcomes in this population. This review evaluates the effectiveness of metformin and lifestyle modification compared with placebo in the management of PCOS and will inform the forthcoming, 2023 evidence-based PCOS guidelines.

Design: Systematic review and meta-analysis of the literature.

Methods: A search was performed in MEDLINE, EMBASE, PsycINFO, All EBM, and CINAHL. The review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and included randomized controlled trials published in English through July 2022.

Results: Moderate certainty of evidence showed a larger reduction of body mass index (BMI) (mean difference [MD] -0.53, 95% confidence interval [CI] -0.95 to -0.12 kg/m²), homeostatic model assessment for insulin resistance (MD -0.50, 95% CI -0.91 to -0.09) (critical outcomes), and fasting glucose (MD -0.13, 95% CI -0.19 to -0.07 mmol/L) with metformin compared to placebo with increased mild gastrointestinal adverse effects (odds ratio [OR] 7.67, 95% CI 2.74-21.46). Low certainty of evidence showed a larger reduction of waist-hip ratio (MD -0.02, 95% CI -0.03 to -0.00), total cholesterol (MD -0.24, 95% CI -0.43 to -0.05 mmol/L), low-density lipoprotein (MD -0.16, 95% CI -0.30 to -0.01 mmol/L), and triglycerides (MD -0.11, 95% CI -0.20 to -0.02 mmol/L) with metformin than placebo.

Conclusions: Metformin should be considered an efficacious adjunct to lifestyle interventions in adults with PCOS, especially for those with a higher BMI, to improve weight loss, insulin resistance, and lipids.

Keywords: polycystic ovary syndrome, metformin, lifestyle, meta-analysis, systematic review, management

⁺ A.M. and H.T. contributed equally as senior author.

Received: March 8, 2023. Revised: April 20, 2023. Editorial Decision: May 2, 2023. Accepted: May 2, 2023

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Significance

Polycystic ovary syndrome (PCOS) affects up to 13% of all women globally. This chronic disorder is characterized by irregular menses, subfertility, excess hair growth, and an increased risk for metabolic conditions (such as weight gain, diabetes, hypertension, and cardiovascular diseases). Based on expert opinion, metformin has been used for decades among those with PCOS. Yet, key knowledge gaps persist regarding its efficacy for specific outcomes in this population. This extensive, up to date review, confirms clear benefits of metformin for improving weight management, insulin resistance, and lipids in women with PCOS. Metformin should, therefore, be considered in adults with PCOS and overweight or obesity and can also be considered in adolescents or adults with normal BMI, acknowledging limited evidence.

Introduction

Polycystic ovary syndrome (PCOS) remains a key public health burden as it is one of the most common endocrine and metabolic disorders affecting 8%-13% of women globally.¹ The 2003 Rotterdam diagnostic criteria for adult women were updated and internationally endorsed in the 2018 International PCOS guideline.² Two of three clinical features are required in adults: (1) ovulatory and menstrual dysfunction, (2) biochemical and/or clinical hyperandrogenism, and (3) polycystic ovary morphology on ultra-sound.^{2,3} However, PCOS is now clearly understood as a complex disorder with endocrine, metabolic, reproductive, and psychological manifestation. The features encompass metabolic (insulin resistance, hyperinsulinemia, weight gain, obesity, diabetes, hypertension, and cardiovascular diseases), endocrine (hyperandrogenism, hirsutism, and acne), and psychosocial features (depression, anxiety, and poor quality of life).^{2,4,5} A recent population-based study⁶ showed that women with PCOS have an overall high morbidity rate and medication use, independent of body mass index (BMI).

It is widely accepted that increased insulin resistance plays a key role in the pathophysiology of PCOS. This is independent of weight, but is exacerbated by excess weight gain.^{7,8} Rates of weight gain are higher from adolescence when waist-hip ratio (WHR) and BMI are increased.^{9,10,11} A strong focus on prevention of weight gain is needed in this condition to limit both excess weight and metabolic consequences.² While lifestyle management is strongly recommended for weight management,^{2,12} for those with higher BMI, sustainable efficacy for weight loss can be limited and additional pharmacological treatment may be needed. In a systematic review,¹³ metformin appeared to lower BMI and decrease insulin resistance compared to placebo. These findings led to the prior International Guideline recommending metformin, in addition to lifestyle, for adults with PCOS in the treatment of weight, hormonal, and metabolic outcomes.² However, for many outcomes such as weight, WHR, and lipids, the certainty of the available evidence was low and recommendations were conditional.

This systematic review and meta-analysis aimed to address the question "What is the effectiveness of metformin and lifestyle compared to placebo in the management of hormonal and clinical features of PCOS?" to inform the update of the 2023 International Guidelines on PCOS on the efficacy and side effects of metformin alone or with lifestyle compared to placebo or lifestyle.

Methods

This systematic review and meta-analysis build on the previous systematic review¹³ and is conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.^{14,15} The study protocol was registered prior to full-text screening in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42022345640) in July 2022. This study complies with the Declaration of Helsinki. As this is a systematic review of the published literature, Institutional Review Board approval was not required for this study.

Data sources

For the 2018 PCOS guideline, a literature search was performed from induction until 2017 using the databases Ovid Medline, Embase, PsycINFO, All EBM, and CINAHL.² For this study, we updated the search from 2017 until seventh July 2022 using the same search string and databases. The original search strategy addressed a broader set of questions. For this review, the specific question related to metformin was extracted. Our search strategy was limited to English language articles. All included and excluded full texts identified by the previous systematic review were re-evaluated for comprehensiveness. The same search string as in the previous systematic review was used (Table SA).

Selection criteria

The PICO (Population, Intervention, Comparison, and Outcome) frameworks for this systematic review were established *a priori* and were used for study selection (Table SB). Two authors (J.M., M.F., or S.A.) independently screened each potential study on title and abstract with the use of COVIDENCE. Disagreements were solved by discussion. The same authors performed the full-text screening in duplication to determine the final included studies.

Data extraction and quality appraisal of the evidence

Data extraction was performed by J.M. and cross-checked by M.F., using a standardized extraction form (Table SC). Disagreements were resolved by discussion and inspection of the original data. If data were presented in a form not usable for meta-analysis (eg, median or interquartile range), we presented the data narratively.

The quality appraisal of the included studies, in terms of risk of bias (ROB), was performed by J.M. using an adapted version of RoB2¹⁶ and independently cross-checked by M.F. or S.A. Disagreements were resolved by discussion and re-inspection of the full-text article. Each study was allocated as having a low, moderate, or high ROB. Using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) prescribed method and scale,¹⁷ each outcome was allocated as having a high, moderate, low, or very low certainty of

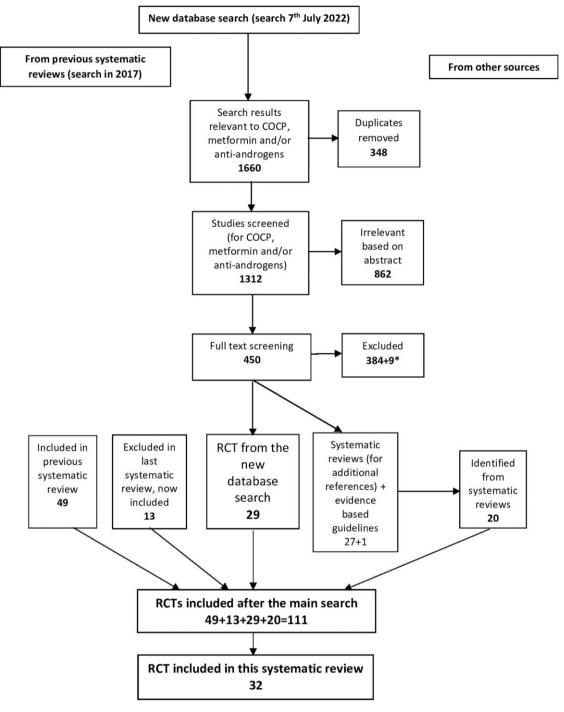


Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart of study selection. Abbreviations: COCP, combined oral contraceptive pill; RCT, randomized controlled study. * Included in COCP and/or anti-androgen questions, but not for metformin.

evidence. The GRADE assessments were conducted by J.M. and double-checked by M.F. or S.A. The GRADE tables for this systematic review are included in Table SD.

Statistical analysis

Meta-analyses were performed by J.M. using Review Manager 5.4. Due to study heterogeneity from differences in metformin doses and durations of treatment, a random effects model was used for the meta-analyses. For meta-analyses of

continuous outcomes, we report weighted mean differences (MDs) and for dichotomous outcomes odds ratios (ORs), both with corresponding 95% confidence intervals (CIs). Meta-analyses are also presented in forest plots and publication bias was assessed using funnel plots.

We performed subgroup analyses by BMI, categorized as those with BMI < 25 kg/m² and those with BMI \ge 25 kg/m². Studies using other BMI cutoffs were categorized as BMI < or >25 kg/m². When meta-analyses could not be performed, study data are presented narratively.

Author,	Population	Duration		Intervention	Mean BMI (kg/m ²)	Mean age (years)	Outcomes	Type of	ROB
year, country		(months)	group	details				analysis and subgroup	
Amiri et al.	Adult women	6	(1) LS + metformin = 25	LS + metformin	>19 and <35 kg/m ²	18–40	WHR, BMI,	Meta	ROB
2014	with PCOS		(2) Placebo + LS = 26	850 mg × 2/day	Ŭ		SHBG, T,		moderate
Iran							hirsutism	BMI < or >25 Adults	
Baillargeon	Non-obese,	6	(1) Metformin = 28	Metformin	(1) 24.6 ± 0.2	(1) 27.7 ± 0.9	Weight, whr,	Meta	ROB
et al. 2004	adult women		(2) Placebo = 30	850 mg × 1/day	(2) 24.6 ± 0.2	(2) 27.2 ± 0.9	BMI, SHBG, T,	DMI-25	moderate
Venezuela	with PCOS						DHEAS	BMI<25 Adults	
Bodur et al.	Non-obese,	6	(1) Metformin = 29	(1) Metformin	$(1) 25.06 \pm 3.08$	$(1) 26.24 \pm 3.96$	f-gluc, crp,	Meta	ROB
2018 Turkey	adult women with PCOS		(2) Placebo = 17	1700 mg/day	(2) 23.82 ± 2.80	(2) 29.18 ± 5.20	PAI, HOMA-IR	BMI < or >25	high
runcy	with t 000							Adults	
Bridger et	Adolescents	3	(1) Metformin = 11	Metformin	(1) 33.6 ± 5.6	(1) 16.07 ± 0.97	BMI, T, f-gluc,	Individual	ROB low
al. 2006 Canada	with PCOS		(2) Placebo = 10	750 mg × 2/day	(2) 30.81 ± 3.0	(2) 16.08 ± 1.39	HOMA-IR, lipids, restored	BMI < or >25	
Gallaua							menses	Adolescents	
Chou et al.	Adult, obese	3	(1) Metformin = 14	Metformin	(1) 35.6 ± 4.9	(1) 24 ± 5	WHR, BMI,	Meta	ROB
2003 Brozil	women with		(2) Placebo = 16	500 mg × 3/day	(2) 37.4 ± 6	(2) 24.5 ± 6.1	SHBG, T,	DMI>25	moderate
Brazil	PCOS						f-insulin, f-gluc, lipids	Adults	
Eisenhardt	Adult, obese	3	(1) Metformin = 19	Metformin	(1) 28.9 (23.3–34.1) ^a	(1) 27.0 (24.9 – 30.7) ^a	BMI, SHBG, T,	Meta	ROB
et al. 2006	women with		(2) Placebo 19	500 mg × 3/day	(2) 32.4 (27.9 –37.5) ^a	(2) 29.7 (26.8 – 32.4) ^a	f-insulin, f-gluc,	DMIN OF	moderate
Germany	PCOS						HOMA, DHEAS	BMI≥25 Adults	
Esfahanian	Adult, obese	3	(1) Metformin = 17	Metformin	(1) 31.1 ± 3.3	(1) 21.9 ± 9.3	BMI, WHR, T,	Meta	ROB
et al. 2013	women with		(2) LS = 13	1000-	(2) 34.1 ± 5.4	(2) 20 ± 4.6	DHEAS,		high
Iran	PCOS			2000 mg/day			f-insulin, f-gluc, lipids, HOMA,	BMI≥25 Adults	
							CRP, adverse	Aduits	
							effects		
Fleming et	Adult, obese	4	(1) Metformin = 26	Metformin	(1) 34.2 (31.7–36.7) ^a	(1) 28.6 (26.9–30.3) ^a	BMI, SHBG, T,	Meta	ROB
al. 2002 UK	women with PCOS		(2) Placebo = 39	850 mg × 2/day	(2) 35.0 (32.6–37.3) ^a	(2) 29.2 (27.5–30.7) ^a	f-insulin, f-gluc, lipids	BMI≥25	high
on	1000						•	Adults	
Fux Otta et	Adult women	4	(1) LS + metformin = 14	LS + metformin	$(1) 32.4 \pm 6.7$	$(1) 25.5 \pm 4.8$	BMI	Meta	ROB
al. 2010 Argentina	with PCOS		(2) LS + placebo = 15	750 mg × 2/day	(2) 35.6 ± 5.0	(2) 24.7 ± 3.5		BMI < or >25	moderate
rugonana								Adults	
Gambineri	Adult, obese	6	(1) LS + metformin = 20	LS + metformin	$(1) 35 \pm 4$	$(1) 28 \pm 8$	Weight, BMI,	Meta	ROB low
et al. 2006 Italy	women with PCOS		(2) LS + placebo = 20	500 mg × 3/day	(2) 37 ± 5	(2) 26 ± 5	SHBG, T, hirsutism	BMI≥25	
itory	1000						moutom	Adults	
Heidari et	Adult, obese	3	(1) Metformin = 33	Metformin	$(1) 36.2 \pm 10.3$	(1) 32.4 ± 7.5	Weight, WHR,	Meta and	ROB
al. 2019 USA	women with PCOS		(2) Placebo = 15	1500 mg/day	(2) 37.7 ± 8.1	(2) 33.1 ± 5.9	BMI, T, f-insulin, f-gluc,	individual	moderate
004	1000						lipids, CRP,	BMI≥25	
		-					HOMA-IR	Adults	
Hoeger et al. 2004	Adult, obese women with	6	(1) Metformin = 6 (2) LS + placebo = 8	(1) Metformin 850 mg × 2/day	(1) 37.1 ± 4.9 (2) 40 ± 7.4	(1) 29.5 ± 6.4 (2) 27.1 ± 4.3	BMI, SHBG, FAI, T,	Meta	ROB moderate
USA ^a	PCOS		(3) LS + metformin = 5	000 mg × 2/0ay	$(3) 41.7 \pm 6.2$	$(2) 27.1 \pm 4.3$ (3) 30.4 ± 5.4	f-insulin, f-gluc	BMI≥25	mouerate
			(4) Placebo = 7		(4) 37.1 ± 4.6	(4) 27.1 ± 4.5		Adults	
Hoeger et al. 2008	Adolescents, obese with	6	(1) Metformin = 6(2) Placebo = 10	(1) Metformin 850 mg × 2/day	(1) 35.0 ± 8.2 (2) 34.9 ± 6.7	(1) 16 ± 1.7 (2) 15.4 ± 1.7	BMI, hirsutism, SHBG, FAI, T,	Meta	ROB moderate
USA	PCOS		(2) Placebo = 10 (3) LS = 8	000 mg × 2/uay	$(2) 34.9 \pm 0.7$ (3) 36.0 ± 6.2	(2) 15.4 ± 1.7 (3) 15.4 ± 1.2	f-insulin, f-gluc,	BMI≥25	moderate
							lipids, CRP,	Adolescents	
			(4) 14 (5 - 1 - 400		(1) 00 0 + 0 0	(4) 07 0 + 0 0	PAI		DOD
Karimzadeh et al. 2007	Adult, obese women with	3	(1) Metformin = 100 (2) Placebo = 100	(1) Metformin 500 mg/day for	(1) 28.8 ± 3.2 (2) 29.5 ± 4.7	(1) 27.2 ± 6.8 (2) 28.6 ± 7.4	Lipids	Meta	ROB high
Iran	PCOS		(2) 1 100000 100	1 week and then		(2) 20.0 ± 1.4		BMI≥25	mgn
				500 mg × 3/day			1.12 - 22	Adults	DCD
Kelly et al. 2002	Adult women with PCOS	6	10 in total	(1) Metformin 500 mg/day to	NR	NR	Hirsutism, SHBG, FAI, T,	Meta	ROB high
2002 UK	wiut r 000			500 mg/day to 500 mg × 3/day.			DHEAS	BMI < or >25	(iig))
(Crossover)				over 3 weeks.				Adults	
Ladson et	Adult women	6	(1) LS + metformin = 22	LS + metformin	$(1) 38.0 \pm 7.8$	$(1) 29 \pm 4.5$	BMI	Meta	ROB
al. 2011 USA	with PCOS		(2) LS + placebo = 16	500 mg × 4/day	(2) 38.3 ± 8.0	$(2) 28.8 \pm 4.6$		BMI < or >25	high
- -	1	Î	1		1	1		Adults	1

Table 1. Characteristics of included studies.

Table 1. Continued

Ladson et al. 2011 USA	Adolescents with PCOS	6	(1) LS + metformin = 11 (2) LS + placebo = 11	LS + metformin 500 mg × 4/day	(1) 37.1 ± 5.8 (2) 35.9 ± 6.6	(1) 16.1 ± 1.5 (2) 15.4 ± 1.2	BMI	Meta BMI < or >25 Adolescents	ROB low
Lingaiah et al. 2019 Finland	Adult women with PCOS	3	(1a) Metformin = 40 (BMI < 25) (1b) Metformin = 17 (BMI ≥ 25) (2a) Placebo = 34 (BMI < 25) (2b) Placebo = 27 (BMI ≥ 25)	(1a) Metformin 500 + 1000 mg/ day (1b) Metformin 1000 mg + 1000 mg/day	(1a) 22.5 (2.2) (1b) 33.4 (4.3) (2a) 22.7 (2.6) (2b) 33.3 (4.4)	(1a) 27.1 (3.1) (1b) 28.8 (3.8) (2a) 27.9 (4.2) (2b) 27.3 (5.0)	Weight, WHR, BMI, SHBG, T, f-insulin, f-gluc, HOMA-IR, DHEAS, A	Meta	ROB moderate
Lord et al. 2006 UK	Adult women with PCOS	3	(1) Metformin = 16 (2) Placebo = 16	Metformin 500 mg × 3/day	(1) 33.74 ± 6.74 (2) 36.37 ± 7.46	(1) 27.76 ± 4.89 (2) 30.63 ± 4.84	Weight, WHR, BMI, SHBG, T, f-insulin, f-gluc, lipids, HOMA- IR, DHEAS	BMI≥25 Adults	ROB low
Maciel et al. 2004 Brazil	Adult, obese and non-obese women with PCOS	6	(1a) Metformin = 7 (BMI < 30) (1b) Metformin = 8 (BMI > 30) (2a) Placebo = 8 (BMI < 30) (2b) Placebo = 6 (BMI > 30)	(1) Metformin 500 mg × 3/day	(1a) 25.3 ± 2.1 (1b) 37.2 ± 1.7 (2a) 25.1 ± 1.6 (2b) 35.8 ± 1.5	(1a) 22.5 ± 1.9 (1b) 19.9 ± 0.4 (2a) 20.5 ± 1.9 (2b) 21.1 ± 0.7	BMI, hirsutism, SHBG, T, f-insulin, f-gluc, lipids, A	Meta BMI≥25 BMI < or >25 Adults	ROB moderate
Morin- Papunen et al. 2012 Finland	Adult women with PCOS	3	(1) Metformin = 106 (2) Placebo = 111	Metformin 1000 mg × 2/day (obese) Metformin 500 mg + 1000 mg/day (non- obese)	(1) 27.1 ± 6.3 (2) 27.4 ± 6.2	(1) 28.4 ± 3.9 (2) 27.9 ± 4.1	Weight, WHR, BMI	Meta BMI < or >25 Adults	ROB low
Naka et al. 2011 Greece	Adult women with PCOS	6	(1) Metformin = 15 (2) Placebo = 14	Metformin 850 mg × 2/day	(1) 29.4 ± 6.5 (2) 28.3 ± 4.9	(1) 22.2 ± 3.6 (2) 24.3 ± 6.0	Weight, WHR, BMI, hirsutism, SHBG, T, f-insulin, f-gluc, lipids	Meta BMI < or >25 Adults	ROB moderate
Ng et al. 2001 Hong Kong	Adult, non- obese women with PCOS	3	(1) Metformin = 8 (2) Placebo = 7	(1) Metformin 500 mg × 3/day	(1) 24.1 (19.6–34.2) (2) 23.8 (17.9–30.8)	(1) 30.5 (27–33) (2) 32.0 (26–34)	BMI, SHBG, T, f-gluc, lipids	Meta Adults BMI<25	ROB moderate
Onalan et al. 2005 Turkey	Adult women with PCOS, subgrouped according to BMI	6	(1a) Metformin = 15 (BMI < 25) (1b) Metformin = 7 (BMI 25–30) (1c) Metformin = 6 (BMI > 30) (2a) Placebo = 16 (BMI < 25) (2b) Placebo = 9 (BMI 25–30) (2c) Placebo = 6 (BMI > 30)	Metformin 500 mg × 1/day for 5 days, then 850 mg × 2/day	(1a) 21.16 ± 2.25 (1b) 28.1 ± 1 (1c) 31.6 ± 1.1 (2a) 21.96 ± 1.52 (2b) 28.2 ± 0.7 (2c) 32.2 ± 3.2	(1a) 26.4 ± 4.1 (1b) 24.6 ± 4.8 (1c) 31.8 ± 4.0 (2a) 27.1 ± 4.8 (2b) 27.3 ± 4.4 (2c) 621.1 ± 5.5	WHR, BMI, hirsutism, f-insulin, f-gluc, lipids, DHEAS	Meta BMI<25 BMI>25 Adults	ROB high
Palomba et al. 2007 Italy	Adult, non- obese women with PCOS	6	(1) Metformin = 14 (2) Placebo = 13	(1) Metformin 850 mg × 2/day	(1) 24.3 ± 3.1 (2) 24.8 ± 2.7	(1) 22.4 ± 2.7 (2) 22.7 ± 1.9	BMI, hirsutism, SHBG, T, DHEAS, A	Meta BMI<25 Adults	ROB moderate
Pasquali et al. 2000 Italy	Adult, obese women with PCOS	7	(1) LS + metformin = 10 (2) LS + placebo = 8	LS + metformin 850 mg × 2/day	(1) 39.8 ± 7.9 (2) 39.6 ± 6.9	(1) 30.8 ± 7.4 (2) 32.3 ± 5.0	Weight,WHR, BMI, SHBG, T	Meta BMI≥25 Adults	ROB moderate
Romualdi et al. 2010 Italy	Adult, non- obese women with PCOS	6	(1) Metformin = 13 (2) Placebo = 10	Metformin 500 mg × 2/day	(1) 22.2 ± 2.2 (2) 22.3 ± 3.9	(1) 24.7 ± 4.4 (2) 27.2 ± 2.6	WHR, BMI, hirsutism, SHBG, T, lipids, DHEAS	Meta BMI<25 Adults	ROB moderate
Tang et al. 2006 UK	Adult, obese women with PCOS	6	(1) LS + metformin = 69 (2) LS + placebo = 74	LS + metformin 850 mg × 2/day	(1) 37.6 ± 5.0 (2) 38.9 ± 9.5	(1) 29.7 ± 3.7 (2) 29.8 ± 3.8	Weight, WHR, BMI	Meta BMI≥25 Adults	ROB low
Tiwari et al. 2018 India	Adult women with PCOS	6	(1) LS + metformin = 33 (2) LS + placebo = 33	LS + metformin 1700 mg/day	(1) 25.2 ± 4.6 (2) 26.3 ± 3.7	(1) 24.3 ± 3.9 (2) 24.5 ± 4.8	Weight, WHR, BMI, hirsutism	Meta BMI < or >25 Adults	ROB low

Table 1. Continued

Trolle et al. 2010	Adult women with PCOS	6	(1) Met = 29–41 (2) Placebo = 29–41	Metformin 850 mg × 2/day	71% had BMI > 30	18–45	Weight, WHR, SHBG, T,	Meta	ROB moderate
Denmark							f-insulin, f-gluc, lipids, HOMA-IR	BMI < or >25 Adults	
Trolle et al. 2007 Denmark	Adult women with PCOS	6	(1) Met = 23 (2) Placebo = 27	Metformin 850 mg × 2/day	33.8 (22.2–46.0) ^b	32 (21–42) ^b	- 3 - 4	Meta BMI < or >25 Adults	ROB low
Zahra et al. 2017 Pakistan	Adult women with PCOS	3	(1) Metformin = 20 (2) Placebo = 20	Metformin 500 mg × 3/day	(1) 26.7 ± 6.5 (2) 29.6 ± 9.9	(1) 25.8 ± 6.1 (2) 27.0 ± 6.3	f-insulin, f-gluc,	Meta BMI < or >25 Adults	ROB high

Rows highlighted gray indicate studies with participants described as obese, rows shaded green indicate that participants had BMI in the normal weight category, and rows shaded white indicates a BMI in the normal and/or overweight category. Abbreviations: A; androstenedione; BMI, body mass index; CRP, C-reactive protein; DHEAS, dehydroepiandrosterone sulfate; DM2, diabetes mellitus type

Abbreviations: A; androstenedione; BMI, body mass index; CRP, C-reactive protein; DHEAS, dehydroepiandrosterone sulfate; DM2, diabetes mellitus type 2; FAI; free androgen index; f-gluc, fasting glucose; f-insulin, fasting insulin; HOMA-IR, Homeostatic model assessment for insulin resistance; LS; lifestyle; OGTT, oral glucose tolerance test; PAI-1, Plasminogen activator inhibitor-1; PCOS, polycystic ovary syndrome; QoL, quality of life; RCT, randomized controlled trial; ROB, risk of bias; SHBG; sex hormone binding globulin; T, testosterone; WHR, waist–hip ratio.

^aMedian and range (1–3 quartile). ^bMean (5%–95% percentiles), values are for all participants, not reported for individual groups.

Outcomes

Outcomes selected as being of critical importance in our systematic review included BMI, homeostatic model assessment for insulin resistance (HOMA-IR), hirsutism, number of participants with regular menstrual cycles, and menstrual cycle duration. Non-critical outcomes of this study include weight, WHR, free androgen index (FAI), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), total testosterone, androstenedione, fasting insulin, fasting glucose, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, C-reactive protein (CRP), plasminogen activator inhibitor-1 (PAI-1), oligomenorrhea, amenorrhea, quality of life (QoL), and adverse gastrointestinal effects.

Results

Search results and study characteristics

The updated search returned 1660 full-text studies for review (Ovid Medline, Medline Epub, Medline IP = 688, EMBASE = 370, PsycINFO = 3, All EBM = 185, and CINAHL = 414). In addition, we screened 120 excluded and 56 included studies from the previous search in 2017.¹³ Following full-text screening, 111 randomized controlled trials (RCTs) and 28 systematic reviews and guidelines (used for double checking the included studies) were identified. Of these 111 RCTs, 23 compared metformin to placebo, 8 compared metformin and lifestyle to placebo and lifestyle, and 3 compared metformin to lifestyle. Notable is that some RCTs included multiple comparisons. Altogether 32 RCTs were included in this systematic review, whereas the other RCTs (n = 79) were on comparisons not included in this systematic review. The PRISMA flowchart is shown in Figure 1.

Study characteristics of included studies are presented in Table 1. Follow-up duration ranged from three to seven months across the included studies. Of the 32 RCTs, 14 were performed in Europe,^{18–31} six in North America,^{32–37} four in south America,^{38–41} and eight in the Middle East.^{42–49} The metformin dose ranged from 850 to 2000 mg per day. The included studies did not report use of extended-release preparations.

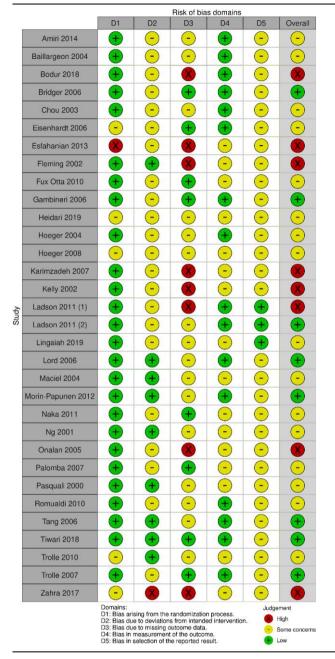
The majority of studies were on adult populations (n = 29 in adults, n = 3 in adolescents). The ROB in the included studies varied from low to high ROB (n = 8 high ROB, n = 16 moderate ROB, and n = 8 low ROB studies) and are reported in Table 2. Overall, evidence was mostly of moderate or low certainty, except for total testosterone, fasting insulin, HDL cholesterol, CRP, PAI, and oligomenorrhea where the evidence was of very low certainty. Of the 32 included studies, two^{33,35} could not be included in the meta-analyses due to measuring MD and were instead presented narratively. For most outcomes in the meta-analyses, results showed little statistical heterogeneity indicating a true effect.

Metformin vs placebo

We identified 23 RCTs comparing metformin with placebo, of which all but one³³ were included in the meta-analyses. Two RCTs were on adolescents^{33,34} and 21 on adults. Regarding the critically important outcomes, the reduction of BMI (MD -0.53, 95% CI -0.95 to -0.12 kg/m²), HOMA-IR (MD -0.50, 95% CI -0.91 to -0.09) (moderate certainty), and menstrual cycle (MD -38.25, 95% CI -52.77 to -23.74 days) (very low certainty) was larger with metformin compared to placebo. No significant differences in hirsutism (low certainty) or in the number of women with regular menstrual cycles (low certainty) were found (Figure 2).

For the remaining outcomes, we found that the reduction of WHR (MD -0.02, 95% CI -0.03 to -0.00) (low certainty), total testosterone (MD -0.47, 95% CI -0.86 to -0.07 nmol/L) (very low certainty), fasting glucose (MD -0.13, 95% CI -0.19 to -0.07 mmol/L) (moderate certainty), total cholesterol (MD -0.24, 95% CI -0.43 to -0.05 mmol/L) (low certainty), LDL (MD -0.16, 95% CI -0.30 to -0.01 mmol/L) (low certainty), triglycerides (MD -0.11, 95% CI -0.20 to -0.02 mmol/L) (low certainty), CRP (MD -3.51, 95% CI -5.48 to -1.53 nmol/L) (very low certainty), and PAI-1 (MD -4.99, 95% CI -6.78 to -3.21 ng/mL) (very low certainty) was larger with metformin compared to placebo. Women using metformin had more mild adverse gastrointestinal effects compared with placebo (OR 7.67, 95% CI 2.74-21.46) (moderate certainty). Four RCTs reported adverse gastrointestinal effects among all women and two only reported adverse effects in women that discontinued treatment.

Table 2. Risk of bias assessment of included studies.



Regarding subgroup analyses according to BMI, for women with PCOS and normal weight (BMI < 25 kg/m²), the reduction of WHR (MD -0.01, 95% CI -0.02 to -0.01), FAI (MD -1.01, 95% CI -1.72 to -0.29) (moderate certainty), and androstenedione (MD -5.40, 95% CI -8.65 to -2.15 nmol/L) (low certainty) was larger with metformin than placebo. For women with PCOS and BMI \geq 25 kg/m², the reduction of BMI (MD -0.89, 95% CI -1.43 to -0.35 kg/m²) (moderate certainty), fasting glucose (MD -0.13, 95% CI -0.23 to -0.02 mmol/L) (moderate certainty), total cholesterol (MD -0.41, 95% CI -0.68 to -0.14 mmol/L) (moderate certainty), and LDL (MD -0.35, 95% CI -0.62 to -0.08) (low certainty) was larger with metformin than placebo. For st plots for all outcomes are presented in Figure 2.

Bridger et al.³³ measured the MD and 95% CI for MD between adolescents receiving metformin versus placebo and found that metformin was superior in lowering testosterone (-1.33, 95% CI infinity to -0.01 nmol/L) and improving HDL (0.18, 95% CI 0.02–0.47 mmol/L) in adolescents. The number of adolescents with restored menses was also greater after metformin compared with placebo (2.50, 95% CI 1.12–5.58). No statistically significant differences were found for BMI, fasting glucose, total cholesterol, LDL, triglycerides, or HOMA-IR (Table SC).

Metformin and lifestyle vs placebo and lifestyle

Eight RCTs, including one RCT in adolescents,³⁶ comparing metformin and lifestyle with placebo and lifestyle were included in the meta-analyses. Regarding critical important outcomes, women using metformin and lifestyle had a lower BMI (MD –1.09, 95% CI –2.12 to –0.06 kg/m²) (moderate certainty) compared to those using placebo and lifestyle. For hirsutism, no differences were observed (low certainty). Women using metformin and lifestyle had more menstrual cycles over 6 months (OR 1.05, 95% CI 0.30–1.80) (very low certainty) and more mild gastrointestinal adverse effects (OR 3.28, 95% CI 1.64–6.57) (moderate certainty) compared to women using placebo and lifestyle (Figure 3).

One RCT,⁴¹ not included in the meta-analyses, found that HOMA-IR was lower in participants treated with metformin and lifestyle (P = .006). Tiwari et al.⁴⁹ found that participants treated with metformin and lifestyle had less oligomenorrhea compared with placebo and lifestyle (P = .02). Ladson et al.³⁵ studied quality of life (subgrouped into physical, emotional, and general wellbeing) and found no significant differences between the comparison groups. Another RCT by Ladson et al.³⁶ on 22 adolescents, comparing BMI changes among participants with metformin and lifestyle to those with placebo and lifestyle found no significant differences in BMI (Table SC).

Metformin vs lifestyle

Only three RCTs comparing metformin with lifestyle were identified. All studies were on women with PCOS and $BMI \ge 25 \text{ kg/m}^2$, one study³⁴ focused on adolescents.

Regarding critical outcomes, no significant difference in BMI was observed (MD -0.53, 95% CI -3.42 to 2.35 kg/m²). Metformin was superior in lowering testosterone (MD -0.17, 95% CI -0.31 to -0.03 nmol/L) and participants with lifestyle only had an improved SHBG (MD -10.73, 95% CI -20.65 to -0.82 nmol/L). However, certainty in the evidence was very low for all outcomes (Figure 4).

One RCT,⁴⁵ not included in the meta-analyses, found that DHEAS was lower in participants using metformin compared to those with lifestyle only (P = .003) and WHR was lower among participants with lifestyle only (P = .001) (Table SC).

Discussion

This systematic review and meta-analysis of 32 RCTs was performed to directly inform recommendations in the updated, forthcoming 2023 International PCOS Evidence-based Guideline. Our findings provide moderate certainty evidence that metformin reduces BMI in adults with a BMI of ≥ 25 kg/m² compared with placebo, with or without lifestyle change.

1 Metformin versus placebo

1.1 Weight [kg]

	Met	formin		Pla	acebo			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [kg]	SD [kg]	Total	Mean [kg]	SD [kg]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
1.1.1 BMIÓ25kg/m2										
Heidari 2019	102.3	31.6	29	100.9	19.7	13	0.3%	1.40 [-14.31, 17.11]		
Lingaiah 2019 - O	88.4	11.8	17	90.1	14	27	1.0%	-1.70 [-9.40, 6.00]		
Lord 2006	94.7	27.1	16	94.9	15.5	16	0.3%	-0.20 [-15.50, 15.10]		
Subtotal (95% CI)			62			56	1.6%	-0.95 [-7.25, 5.36]	-	
Heterogeneity: Tau ² =	0.00; Chi ² = 0	.13, df = :	2 (P = (0.94); l ² = 0%	,					
Test for overall effect:	Z = 0.29 (P =	0.77)								
1.1.2 BMI<25kg/m2									82.57	
Baillargeon 2004	61.4	1.59	28	61.4	1.64	30	89.5%	0.00 [-0.83, 0.83]		
Lingaiah 2019 - NO	60.4	7.5	40	62.3	8.7	34	4.4%	-1.90 [-5.64, 1.84]		
Subtotal (95% CI)			68			64	94.0%	-0.09 [-0.90, 0.72]	•	
Heterogeneity: Tau ² = Test for overall effect:			1 (P = (0.33); l² = 0%)					
resciol overall effect.	z = 0.22 (F =	0.03)								
1.1.4 BMI <and>25kg/</and>	m2									
Morin-Papunen 2012	73.5	18	106	76	18	111	2.7%	-2.50 [-7.29, 2.29]		
Naka 2011	78.5	16.1	15	74.8	15.5	27	0.6%	3.70 [-6.33, 13.73]	<u> </u>	
Trolle 2010	94.1	21.2	41	97.3	21.5	41	0.7%	-3.20 [-12.44, 6.04]		
Zahra 2017	63.35	12.8	20	74.2	23.9	20	0.4%	-10.85 [-22.73, 1.03]		
Subtotal (95% CI)			182			199	4.5%	-2.61 [-6.78, 1.56]	-	
Heterogeneity: Tau ² =	2.39; Chi ² = 3	.39, df = :	3 (P = 0	0.34); l ² = 11 ⁴	%					
Test for overall effect:	Z = 1.23 (P =	0.22)		E 2414						
Total (95% CI)			312			319	100.0%	-0.21 [-1.00, 0.57]	•	
Heterogeneity: Tau ² =	0.00; Chi ² = 6	6.16, df = 8	3 (P = (0.63); I ² = 0%)					<u> </u>
Test for overall effect:	Z = 0.53 (P =	0.59)	2012	885					-20 -10 0 10 2 Metformin Placebo	0
Test for subgroup diffe		,	= 2 (P	$= 0.49$) $l^2 = 0.49$	2%				Metormin Placebo	

Risk of bias legend

1.2 WHR

	Me	tformi	n	PI	acebo	,		Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
1.2.1 BMIÓ25kg/m2							010			
Chou 2003	0.95	0.03	14	0.92	0.02	16	10.2%	0.03 [0.01, 0.05]		
Fleming 2002	0.88	0.07	26	0.88	0.07	39	7.2%	0.00 [-0.03, 0.03]		
Heidari 2019	0.9	0.1	29	0.9	0.1	13	3.6%	0.00 [-0.07, 0.07]		
Lingaiah 2019 - O	0.83	0.05	17	0.84	0.05	27	8.0%	-0.01 [-0.04, 0.02]		
Lord 2006	0.83	0.06	16	0.88	0.07	16	5.7%	-0.05 [-0.10, -0.00]		
Onalan 2005 - O1	0.86	0.02	7	0.92	0.02	9	10.0%	-0.06 [-0.08, -0.04]		
Onalan 2005 - O2	0.89	0.05	6	0.95	0.03	6	5.5%	-0.06 [-0.11, -0.01]		
Subtotal (95% CI)			115			126	50.0%	-0.02 [-0.05, 0.01]		
Heterogeneity: Tau ² =	0.00; Ch	i² = 49).52, df	= 6 (P <	< 0.000	001); l²	= 88%			
Test for overall effect: 2	Z = 1.21	(P = 0	.23)							
1.2.2 BMI<25kg/m2										
Baillargeon 2004	0.8	0.01	28	0.81	0.01	30	12.0%	-0.01 [-0.02, -0.00]	-	
Lingaiah 2019 - NO	0.76	0.06	40	0.78	0.07	34	8.1%	-0.02 [-0.05, 0.01]		
Onalan 2005 - NO	0.83	0.07	15	0.86	0.03	16	6.6%	-0.03 [-0.07, 0.01]		
Romualdi 2010	0.75	0.1	13	0.76	0.1	10	2.5%	-0.01 [-0.09, 0.07]		
Subtotal (95% CI)			96			90	29.2%	-0.01 [-0.02, -0.01]	◆	
Heterogeneity: Tau ² =	0.00; Ch	i² = 1.4	41, df =	3 (P =	0.70);	$l^2 = 0\%$, ,			
Test for overall effect: 2	Z = 4.15	(P < 0	.0001)							
1.2.4 BMI <and>25kg/r</and>	n2									
Morin-Papunen 2012	0.8	0.1	106	0.81	0.1	111	8.7%	-0.01 [-0.04, 0.02]		
Naka 2011	0.81	0.06	15	0.8	0.06	14	5.9%	0.01 [-0.03, 0.05]		
Trolle 2010	0.86	0.09	37	0.86	0.09	37	6.2%	0.00 [-0.04, 0.04]		
Subtotal (95% CI)			158			162	20.8%	-0.00 [-0.02, 0.02]	-	
Heterogeneity: Tau ² =	0.00; Ch	j ² = 0.0	62, df =	2 (P =	0.73);	$I^2 = 0\%$)			
Test for overall effect: 2	Z = 0.35	(P = 0	.73)							
Total (95% CI)			369			378	100.0%	-0.02 [-0.03, -0.00]	•	
Heterogeneity: Tau ² =	0.00; Ch	i² = 52	2.66, df	= 13 (P	< 0.00	0001); I	² = 75%	97 5) 883) 473)		
Test for overall effect: 2									-0.1 -0.05 0 0.05 Metformin Placebo	0.1
Test for subgroup diffe		·		f = 2 (P	= 0.66), $ ^2 = 0$	1%		Medornih Placebo	
Risk of bias legend										

Figure 2. Forest plots presenting meta-analyses on different outcomes when comparing metformin to placebo. Abbreviations: CI: confidence interval; SD, standard deviation.

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1.3 BMI [kg/m2]

	Met	tformin		Pla	acebo			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [kg/m2]	SD [kg/m2]	Total	Mean [kg/m2]	SD [kg/m2]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
1.3.1 BMIÓ25kg/m2										
Chou 2003	34.9	5	14	37.2	6.4	16	1.0%	-2.30 [-6.39, 1.79]		
Eisenhardt 2006	29.82	2.82	19	32.15	2.6	19	5.1%	-2.33 [-4.05, -0.61]		
Fleming 2002	35.2	8.9	26	35.3	8.6	39	0.9%	-0.10 [-4.46, 4.26]		
Heidari 2019	36.2	10.3	29	37.7	8.1	13	0.5%	-1.50 [-7.28, 4.28]	8.2 * *	
Hoeger 2004	34.7	4.7	5	37.2	4.6	7	0.6%	-2.50 [-7.85, 2.85]		
Hoeger 2008	35.7	8.6	6	35.5	6.8	10	0.3%	0.20 [-7.87, 8.27]		
Karimzadeh 2007	28.45	2.8	100	29.29	4.8	100	10.8%	-0.84 [-1.93, 0.25]		
Lingaiah 2019 - O	32.9	4.4	17	33.3	4.5	27	2.2%	-0.40 [-3.09, 2.29]		
Lord 2006	34.6	9.13	16	35.26	6.53	16	0.6%	-0.66 [-6.16, 4.84]		
Maciel 2004 - O	36.5	6.77	8	36.2	2.92	6	0.6%	0.30 [-4.94, 5.54]		
Ng 2001	24.4	4.3	8	22.7	3.5	7	1.1%	1.70 [-2.25, 5.65]		
Onalan 2005 - O1	27.83	0.68	7	28.37	0.88	9	17.5%	-0.54 [-1.30, 0.22]		
Onalan 2005 - O2	30.53	1.82	6	34.66	3.46	6	1.7%	-4.13 [-7.26, -1.00]		
Subtotal (95% CI)			261			275	42.7%	-0.89 [-1.43, -0.35]	•	
Heterogeneity: Tau ² =	0.00; Chi ² = 10.64	4, df = 12 (P =	0.56);	l ² = 0%					~~	
Test for overall effect:	Z = 3.23 (P = 0.0	01)								
1.3.2 BMI<25kg/m2										
Baillargeon 2004	24.3	0.53	28	24.3	0.54	30	36.6%	0.00 [-0.28, 0.28]		
Onalan 2005 - NO	21.61	3.15	15	22.08	1.8	16	4.6%	-0.47 [-2.29, 1.35]		
Palomba 2007	22.4	2	14	22.6	1.9	13	6.7%	-0.20 [-1.67, 1.27]		
Romualdi 2010	22.1	2.52	13	23.3	4.1	10	2.0%	-1.20 [-4.09, 1.69]		
Subtotal (95% CI)			70			69	49.8%	-0.03 [-0.29, 0.24]	•	
Heterogeneity: Tau ² =	0.00; Chi ² = 0.95,	df = 3 (P = 0.	81); l² =	= 0%						
Test for overall effect:	Z = 0.20 (P = 0.84	4)								
1.3.3 BMI <and>25kg/</and>	m2									
Maciel 2004 - NO	24.9	7.12	7	25.3	5.07	8	0.4%	-0.40 [-6.74, 5.94]		
Morin-Papunen 2012	26.9	6.2	106	27.7	6.2	111	5.5%	-0.80 [-2.45, 0.85]		
Naka 2011	29.3	6.5	15	28.1	5.5	14	0.9%	1.20 [-3.17, 5.57]		
Zahra 2017	25.3	5.7	20	29.7	9.7	20	0.7%	-4.40 [-9.33, 0.53]	← +	
Subtotal (95% CI)			148			153	7.5%	-0.87 [-2.30, 0.57]	-	
Heterogeneity: Tau ² =	0.00; Chi ² = 2.86,	df = 3 (P = 0.4	41); l² =	= 0%						
Test for overall effect:	Z = 1.19 (P = 0.24	4)								
Total (95% CI)			479			497	100.0%	-0.53 [-0.95, -0.12]	•	
Heterogeneity: Tau ² =	0.10; Chi ² = 23.16	6, df = 20 (P =	0.28);	l² = 14%						
Test for overall effect:			1.						-4 -2 0 2 4 Metformin Placebo	
Test for subgroup diffe			0.01).	l ² = 77.0%					Mettormin Placebo	
Risk of bias legend		,								
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Risk of bias legend

1.4 Hirsutism [FG score]

	Met	formin		Pla	icebo			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [FG score]	SD [FG score]	Total	Mean [FG score]	SD [FG score]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
1.4.1 BMIÓ25kg/m2										
Hoeger 2008	8.2	3.4	6	11.6	4.9	10	6.2%	-3.40 [-7.48, 0.68]		
Maciel 2004 - O	7.3	5.36	8	9.1	6.83	6	2.4%	-1.80 [-8.41, 4.81]		
Onalan 2005 - O1	9.81	8.13	7	4.53	7.85	9	1.7%	5.28 [-2.63, 13.19]		
Onalan 2005 - O2 Subtotal (95% CI)	10.22	6.24	6 27	14.13	7.61	6 31	1.7% 11.9%	-3.91 [-11.78, 3.96] -1.66 [-5.22, 1.90]		
Heterogeneity: Tau ² = 3	3.26; Chi² = 3.93, df	= 3 (P = 0.27); l ²	= 24%						52	
Test for overall effect: Z	z = 0.91 (P = 0.36)									
1.4.2 BMI<25kg/m2										
Maciel 2004 - NO	9.4	5.54	7	9.2	4.23	8	4.1%	0.20 [-4.84, 5.24]		
Onalan 2005 - NO	8.93	7.42	15	8.09	5.79	16	4.7%	0.84 [-3.87, 5.55]		
Palomba 2007	11	2	14	10.8	1.8	13	50.4%	0.20 [-1.23, 1.63]	+	
Romualdi 2010	9.3	3.5	13	10.6	7.4	10	4.2%	-1.30 [-6.27, 3.67]		
Subtotal (95% CI)			49			47	63.4%	0.15 [-1.13, 1.43]	•	
Heterogeneity: Tau ² = C		= 3 (P = 0.94); I ²	= 0%							
Test for overall effect: Z	2 = 0.23 (P = 0.82)									
1.4.4 BMI <and>25kg/n</and>	n2								-	
Kelly 2002	15.8	4.42	10	17.5	3.79	10	8.0%	-1.70 [-5.31, 1.91]		
Naka 2011	8.6	2.8	15	9.9	3.9	14	16.8%	-1.30 [-3.79, 1.19]		
Subtotal (95% CI)			25			24	24.7%	-1.43 [-3.48, 0.62]	-	
Heterogeneity: Tau ² = 0 Test for overall effect: 2		= 1 (P = 0.86); I ²	= 0%							
Total (95% CI)			101			102	100.0%	-0.49 [-1.51, 0.53]	•	
Heterogeneity: Tau ² = 0	0.00; Chi² = 7.09, df	= 9 (P = 0.63); l ²	= 0%						-10 -5 0 5 10	
Test for overall effect: Z	z = 0.95 (P = 0.34)								-10 -5 0 5 10 Metformin Placebo	
Test for subgroup differ	ences: Chi ² = 2.16,	df = 2 (P = 0.34)	² = 7.2	2%						
Risk of bias legend										

1.5 FAI

	Me	tformi	n	PI	acebo			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
1.5.1 BMIÓ25kg/m2							10.00			
Hoeger 2004	12.3	11.7	5	10.1	3.37	7	1.1%	2.20 [-8.35, 12.75]		
Hoeger 2008	10.9	7.9	6	16.8	11.2	10	1.3%	-5.90 [-15.29, 3.49]		
Lingaiah 2019 - O	3.6	2.1	17	5	3.4	27	22.4%	-1.40 [-3.03, 0.23]		
Lord 2006	10.36	4.75	16	7.94	2.73	16	12.2%	2.42 [-0.26, 5.10]		
Subtotal (95% CI)			44			60	37.1%	-0.10 [-3.18, 2.99]		
Heterogeneity: Tau ² =	4.70; Cł	ni² = 7.	24, df =	= 3 (P =	0.06);	l ² = 59	%			
Test for overall effect:	Z = 0.06	6 (P = 0	0.95)							
1.5.2 BMI<25kg/m2										
Lingaiah 2019 - NO	2.1	1.3	40	3.1	1.9	34	36.1%	-1.00 [-1.76, -0.24]	-	
Palomba 2007	21.2	5.3	14	22.7	5.1	13	6.7%	-1.50 [-5.42, 2.42]		
Romualdi 2010	4.19	2.1	13	5.05	3.91	10	12.3%	-0.86 [-3.54, 1.82]		
Subtotal (95% CI)			67			57	55.2%	-1.01 [-1.72, -0.29]	•	
Heterogeneity: Tau ² =	0.00; Ch	ni² = 0.	07, df =	= 2 (P =	0.96);	$l^2 = 0\%$	þ			
Test for overall effect:	Z = 2.76	6 (P = (0.006)							
1.5.4 BMI <and>25kg/</and>	/m2									
Kelly 2002	10.6	5.37	10	14.7	6.64	10	4.0%	-4.10 [-9.39, 1.19]		
Naka 2011	9.3	5.4	15	14.6	9	14	3.8%	-5.30 [-10.75, 0.15]		
Subtotal (95% CI)			25			24	7.7%	-4.68 [-8.48, -0.89]	-	
Heterogeneity: Tau ² =	0.00; Cł	ni² = 0.	10. df =	= 1 (P =	0.76):	$ ^2 = 0\%$	þ			
Test for overall effect:	Z = 2.42	2 (P = 0	0.02)							
Total (95% CI)			136			141	100.0%	-1.01 [-2.11, 0.10]	•	
Heterogeneity: Tau ² =	0.73; Cł	ni² = 11	1.65, df	= 8 (P	= 0.17); I ² = 3	1%			
Test for overall effect:									-10 -5 0 5 10	
Test for subgroup diffe				df = 2 (F	P = 0.1	4), $ ^2 =$	48.6%		Metformin Placebo	
0 1		10000000		- (-						
Risk of bias legend				- (.						

1.6SHBG[nmol/l]

Metformin Placebo Mean Difference Mean Difference **Risk of Bias** Study or Subgroup Mean [nmol/I] SD[nmol/I] Total Mean [nmol/I] SD[nmol/I] Total Weight IV, Random, 95% CI IV, Random, 95% CI 1.6.1 BMIÓ25kg/m2 Chou 2003 23.5 4.16 14 21.62 2.73 16 17.1% 1.88 [-0.68, 4.44] Eisenhardt 2006 23.72 0.25 [-3.61, 4.11] 4.22 19 23.47 7.47 14.5% 19 Fleming 2002 16.8 0.60 [-6.48, 7.68] 29.2 12.3 26 28.6 8.9% 39 Hoeger 2004 -0.10 [-11.07, 10.87] 22.9 10 5.0% 5 23 8.9 7 Hoeger 2008 2.00 [-6.89, 10.89] 19.1 10 6.7% 21.1 8.4 6 9.4 Lingaiah 2019 - O Lord 2006 5.30 [-8.49, 19.09] 419 16 1 17 36.6 30.4 27 3 5% 27.41 9.98 16 30.27 9.35 16 9.4% -2.86 [-9.56, 3.84] Maciel 2004 - O 194 1 110.54 236.5 133.46 0.0% -42.40 [-173.82, 89.02] 8 6 140 65.3% 1.05 [-0.81, 2.91] Subtotal (95% CI) 111 Heterogeneity: Tau² = 0.00; Chi² = 2.76, df = 7 (P = 0.91); I² = 0% Test for overall effect: Z = 1.10 (P = 0.27) 1.6.2 BMI<25kg/m2 Lingaiah 2019 - NO Ng 2001 60.9 9.10 [-6.59, 24.79] 70 41.3 40 27 34 2.8% 25.7 11.7 8 31.8 16.2 7 3.2% -6.10 [-20.58, 8.38] Palomba 2007 27.1 5.3 14 26.3 4.1 13 15.1% 0.80 [-2.76, 4.36] Romualdi 2010 45.1 15.5 13 49.6 18.8 10 3.3% 4.50 [-18.88, 9.88] Subtotal (95% CI) 64 24.4% 0.53 [-2.75, 3.82] 75 Heterogeneity: Tau² = 0.00; Chi² = 2.44, df = 3 (P = 0.49); I² = 0% Test for overall effect: Z = 0.32 (P = 0.75) 1.6.4 BMI<and>25kg/m2 Kelly 2002 37 18.33 23.8 5.06 10 4.5% 13.20 [1.41, 24.99] 10 Maciel 2004 - NO 169.5 63.05 7 274.3 26.5 8 0.3% -104.80 [-154.99, -54.61] Naka 2011 33.3 14.8 15 30.5 13.5 14 32 5.5% 2.80 [-7.50, 13.10] Subtotal (95% CI) 32 10.3% -13.93 [-43.89, 16.03] Heterogeneity: Tau² = 547.99; Chi² = 20.42, df = 2 (P < 0.0001); l² = 90% Test for overall effect: Z = 0.91 (P = 0.36) Total (95% CI) 218 236 100.0% 0.89 [-1.95, 3.73] Heterogeneity: Tau² = 10.60; Chi² = 26.58, df = 14 (P = 0.02); l² = 47% -20-10 0 10 20 Test for overall effect: Z = 0.61 (P = 0.54) Metformin Placebo Test for subgroup differences: $Chi^2 = 1.01$, df = 2 (P = 0.60), $I^2 = 0\%$

Test for subgroup differences: $Chi^2 = 1.01$, df = 2 (P = 0.60), I² = 0% <u>Risk of bias legend</u>

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1.7 DHEAS [umol/l]

	Met	formin		Pla	icebo			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [umol/l]	SD[umol/l]	Total	Mean [umol/l]	SD[umol/I]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
1.7.1 BMI≥25										
Eisenhardt 2006	4.31	0.71	19	4.7	0.65	19	20.6%	-0.39 [-0.82, 0.04]	-	
Lingaiah 2019 - O	5.3	2.2	17	5.3	1.9	27	10.4%	0.00 [-1.27, 1.27]		
Lord 2006	7.03	3.91	16	4.83	2.39	16	4.7%	2.20 [-0.05, 4.45]		
Onalan 2005 - O1	6.65	1.33	7	9.74	2.2	9	6.9%	-3.09 [-4.83, -1.35]		
Onalan 2005 - O2	7.33	3.26	6	8.25	2.04	6	2.8%	-0.92 [-4.00, 2.16]		
Subtotal (95% CI)			65			77	45.4%	-0.48 [-1.72, 0.77]	-	
Heterogeneity: Tau ² =	1.28; Chi ² = 14.7	9, df = 4 (P =)	0.005);	l² = 73%						
Test for overall effect:	Z = 0.75 (P = 0.4	5)								
1.7.2 BMI<25										
Baillargeon 2004	8.22	5.59	28	10.64	4.75	30	3.5%	-2.42 [-5.10, 0.26]		
Lingaiah 2019 - NO	5.6	2.5	40	6	2.7	34	11.1%	-0.40 [-1.59, 0.79]		
Onalan 2005 - NO	9.04	0.62	15	9.01	2.04	16	12.6%	0.03 [-1.02, 1.08]		
Palomba 2007	7.11	1.11	14	7	1.19	13	14.8%	0.11 [-0.76, 0.98]		
Romualdi 2010	5.97	1.98	13	6.13	1.95	10	7.7%	-0.16 [-1.78, 1.46]		
Subtotal (95% CI)			110			103	49.7%	-0.15 [-0.68, 0.39]		
Heterogeneity: Tau ² =	0.00; Chi ² = 3.38	df = 4 (P = 0)	.50); l ² =	= 0%						
Test for overall effect:	Z = 0.53 (P = 0.5	9)								
1.7.3 BMI <and>25kg/r</and>	m2									
Kelly 2002	5.81	2.5	10	5.81	2.5	10	4.9%	0.00 [-2.19, 2.19]		
Subtotal (95% CI)	5.61	2.5	10	5.61	2.5	10	4.9%	0.00 [-2.19, 2.19]		
Heterogeneity: Not app	olicable								· · · · · · · · · · · · · · · · · · ·	
Test for overall effect:	Z = 0.00 (P = 1.0	0)								
Total (95% CI)			185			190	100.0%	-0.34 [-0.88, 0.21]	•	
Heterogeneity: Tau ² =	0.33: Chi ² = 18.9	0. df = 10 (P =	0.04):	$l^2 = 47\%$						-
Test for overall effect: 2									-4 -2 0 2 4	
Test for subgroup diffe		<u> </u>	0.88).	$l^2 = 0\%$					Favours Metformin Favours Placebo	
Dist. of hiss leaves										

Risk of bias legend

1.8 Total testosterone [nmol/I]

Study or Subgroup Mean [mmol/l] SD[mmol/l] Total Weight V, Random, 95% Cl V/, Random, 95% Cl Chou 2003 1.59 0.67 14 2.25 0.87 16 6.0% -0.65 [-1.21, -0.11] Eisenhardt 2006 1.57 0.25 19 1.72 0.4 19 6.7% -0.05 [-0.36, 0.06] Hening 2002 2.74 1.07 2.6 2.81 0.78 7 4.5% -0.07 [-0.26, 0.04] Hoeger 2004 2.26 1.05 5 2.18 0.78 7 4.5% -0.07 [-0.26, 0.04] Ling aih 2019 - O 1.3 0.5 17 1.5 1 27 6.2% -0.20 [-0.65, 0.25] Lind 2006 2.51 0.64 16 2.26 0.33 0.25 [-0.14] 140 43.8% -0.21 [-0.65, 0.25] Macie 2004 - O 3.73 0.79 8 3.52 1.55 6 3.8% -0.21 [-0.33, 0.05] 1 Ballargeon 2004 1.2 0.6 1.6 0		Met	formin		Pla	cebo			Mean Difference	Mean Difference	Risk of Bias
Chou 2003 1 59 0 67 14 2.25 0.87 16 6.07 $0.66 + 1.21 - 0.11$ Eisenhardt 2006 1.57 0.25 19 1.72 0.4 19 6.7% -0.15 [0.36, 0.06] Hoeger 2004 2.26 1.05 5 2.18 0.79 7 4.6% -0.06 [+1.21, -0.11] Hoeger 2004 2.26 1.05 5 2.18 0.79 7 4.6% -0.05 [+0.8, 0.41] Hoeger 2004 2.26 1.06 5 2.18 0.79 7 4.6% -0.02 [-1.89, 0.37] Lingsiah 2019 - 0 1.3 0.5 17 1.5 1 27 6.2% -0.20 [-0.65, 0.26] Lingsiah 2019 - 0 3.73 0.79 8 3.52 1.55 6 3.8% 0.21 [+1.5, 1.57] Subtotal (95% CI) 111 Heterogeneity: Tau ² = 0.01; Ch ² = 8.24, df = 7 (P = 0.31); P = 15% Test for overall effect: Z = 1.47 (P = 0.4) 1.8.2 BMI<-25kg/m2 Bailargene 2004 1.28 0.73 28 4.16 0.76 30 6.4% -2.88 [-3.26, -2.50] Heterogeneity: Tau ² = 0.01; Ch ² = 8.24, df = 7 (P = 0.31); P = 15% Test for overall effect: Z = 1.47 (P = 0.4) 1.8.2 BMI<-25kg/m2 Bailargene 2004 1.28 0.73 28 4.16 0.76 30 6.4% -0.40 [-0.67, -0.13] Ng 2001 1.3 0.5 8 1.7 0.7 7 5.5% -0.40 [-1.02, 0.22] Palomba 2007 5.2 1.73 14 5.2 1.73 13 3.9% -0.04 [-1.02, 0.22] Palomba 2007 5.2 1.73 14 5.2 1.73 13 3.9% -0.04 [-1.02, 0.22] Palomba 2007 5.2 1.73 14 5.2 1.73 13 3.9% -0.06 [-1.41, 0.04] 94 27.5% -0.87 [-2.15, 0.41] 1.84 BMI<-and-25kg/m2 1.84 BMI<-and-25kg/m2 Ketly 2002 3.2 0.95 10 3.4 1.58 10 4.3% -0.20 [-1.34, 0.94] Maciel 2004 -NO 2.25 0.68 7 3.57 0.83 8 5.4% -1.32 [-2.06, 0.56] Total (95% CI) 92 Heterogeneity: Tau ² = 0.16; Ch ² = 13.87, df = 4 (P = 0.0001); P = 97% Test for overall effect: Z = 1.99 (P = 0.05) Total (95% CI) 92 Heterogeneity: Tau ² = 0.56; Ch ² = 13.87, df = 4 (P = 0.00001); P = 91% Test for overall effect: Z = 1.99 (P = 0.05) Total (95% CI) 92 Heterogeneity: Tau ² = 0.56; Ch ² = 13.87, df = 4 (P = 0.00001); P = 91% Test for overall effect: Z = 1.99 (P = 0.02) Total (95% CI) 92 Heterogeneity: Tau ² = 0.56; Ch ² = 13.80, df = 17 (P < 0.00001); P = 91% Test for overall effect: Z = 2.33 (P = 0.02) Total (95% CI) 0 23 Heterogeneity: Tau ² = 0.56; Ch ² = 13.87, df = 4 (P = 0.00001); P = 91% Test for overall effect: Z = 2.33 (P = 0.02) To	Study or Subgroup	Mean [nmol/l]	SD[nmol/l]	Total	Mean [nmol/l]	SD[nmol/l]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Eisenhardt 2006 1 57 0 25 19 1.72 Herming 2002 2 .74 1.07 26 2.81 1 0.94 39 6.1% - 0.07 [0.58, 0.44] 1 0.94 39 6 .1% - 0.07 [0.58, 0.44] - 0.76 [1.89, 0.37] Lingaiah 2019 - 0 1 .3 0.5 17 1.5 1 27 6.2% - 0.20 [-0.65, 0.25] Lord 2006 2 .51 0.64 16 2 .26 0 .61 16 6 .3.% - 0.25 [0.18, 0.68] Maciel 2004 - 0 3 .73 0.79 8 3 .52 Lord 2006 2 .51 0.64 16 2 .26 0 .61 16 6 .3.% - 0.25 [0.18, 0.68] Maciel 2004 - 0 3 .73 0.79 8 - 1.47 (P = 0.31); P = 15% Test for overail effect: Z = 1.47 (P = 0.31); P = 15% Test for overail effect: Z = 1.37 (A = 0.73 28 - 1.47 (P = 0.31); P = 15% Test for overail effect: Z = 1.33 (P = 0.73 28 - 1.73 14 5.2 - 1.73 1.42 10 - 4.9% - 0.48 [1.40, 0.44] 	1.8.1 BMIÓ25kg/m2	1724C C2							58. C.1917		
Fiering 2002 2.74 107 26 2.81 0.94 39 6.1% -0.07 [0.8, 0.4] Hoeger 2004 2.26 1.05 5 2.18 0.79 7 4.5% 0.08 [-1.01, 1.17] Hoeger 2008 1.72 1.08 6 2.48 1.17 10 4.4% -0.76 [-1.89, 0.37] Lingsiah 2019 - 0 1.3 0.5 17 1.5 1 27 6.2% -0.20 [0.65, 0.25] Lord 2006 2.51 0.64 16 2.26 0.61 16 6.3% 0.25 [0.18, 0.84] Maciel 2004 - 0 3.73 0.79 8 3.52 1.55 6 3.8% 0.21 [-1.15, 1.57] Heterogeneity: Tau ² = 0.01; Ch ² = 8.24, df = 7 (P = 0.31); P = 15% Test for overall effect: Z = 1.47 (P = 0.14) 1.8.2 BMI<25Kg/m2 Baillargeon 2004 1.28 0.73 28 4.16 0.76 30 6.4% -2.88 [-3.26, 2.50] Lingsiah 2019 - NO 1.2 0.6 40 1.6 0.6 34 6.6% -0.40 [-0.67, 0.13] Ng 2001 1.3 0.5 8 1.7 0.7 7 5.8% -0.40 [-0.7, 0.13] Ng 201 1.3 0.5 8 1.7 0.7 7 5.8% -0.40 [-1.02, 0.22] Palomba 2007 5.2 1.73 14 5.2 1.73 13 3.9% 0.00 [-1.31, 1.31] Romueld 2010 1.53 0.52 13 2.01 1.42 10 4.9% -0.48 [-1.40, 0.44] 94 27.5% -0.48 [-1.40, 0.44] 95 2017 2.88 0.68 23 2.88 0.68 27 6.4% 0.79 [-1.39, 0.56] Naka 2011 2.65 0.7 15 3.44 0.66 14 6.1% -0.79 [-1.99, 0.56] Total (95% C1) 2.31 0.83 37 2.46 0.66 37 6.5% 0.01 [-3.4, 0.34] Heterogeneity: Tau ² = 0.15, Ch ² = 1.37, df = 4 (P = 0.0001); P = 97% Test for overall effect: Z = 1.39 (Ch ² = 13.67, df = 4 (P = 0.0005); P = 71% Test for overall effect: Z = 1.39 (Ch ² = 13.67, df = 4 (P = 0.0005); P = 71% Test for overall effect: Z = 1.39 (Ch ² = 1.99 (P = 0.05) Total (95% C1) 306 Heterogeneity: Tau ² = 0.59; Ch ² = 193.90, df = 17 (P < 0.00001); P = 91% Test for overall effect: Z = 2.33 (P = 0.02) Test for overall effect: Z = 2.33 (P = 0.02) Test for overall effect: Z = 2.33 (P = 0.02) Test for overall effect: Z = 2.33 (P = 0.02) Test for overall effect: Z = 2.33 (P = 0.02) Test for overall effect: Z = 2.33 (P = 0.02) Test for overall effect: Z = 2.33 (P = 0.02) Test for overall effect: Z = 2.33 (P = 0.02) Heterogeneity: Tau ² = 0.59; Ch ² = 193.90, df = 17 (P < 0.00001); P	Chou 2003	1.59	0.67	14	2.25	0.87	16	6.0%	-0.66 [-1.21, -0.11]		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Eisenhardt 2006	1.57	0.25	19	1.72	0.4	19	6.7%	-0.15 [-0.36, 0.06]		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Fleming 2002	2.74	1.07	26	2.81	0.94	39	6.1%	-0.07 [-0.58, 0.44]		
Lingaiah 2019 - 0 1.3 0.5 17 1.5 1 27 6.2% -0.20 [-0.65, 0.25] Lord 2006 2.51 0.64 16 2.26 0.61 16 6.3% 0.25 [-0.18, 0.68] Maciel 2004 - 0 3.73 0.79 8 3.52 1.5 6 3.8% 0.21 [-1.15, 1.57] Subtotal (95% CI) 111 140 43.8% -0.14 [-0.33, 0.05] Heterogeneity: Tau" = 0.01; Ch" = 8.24, df = 7 (P = 0.31); P = 15% Test for overall effect: Z = 1.47 (P = 0.14) 1.8.2 BMI<25kg/m2 Bailargeon 2004 1.28 0.73 28 4.16 0.76 30 6.4% -2.88 [-3.26, -2.50] 4 Lingaiah 2019 - NO 1.2 0.6 40 1.6 0.6 34 6.6% -0.40 [-0.67, 0.13] Ng 2001 1.3 0.5 8 1.7 0.7 7 5.8% -0.40 [-1.02, 0.22] Palomba 2007 5.2 1.73 14 5.2 1.73 13 3.9% 0.00 [-1.31, 1.31] Ng 2001 1.53 0.52 1.3 2.01 1.42 94 27.5% -0.48 [-4.0, 0.44] Subtotal (95% CI) 103 142 94 27.5% -0.48 [-1.40, 0.44] Heterogeneity: Tau" = 1.97; Ch" = 117/04, df = 4 (P < 0.00001); P = 97% Test for overall effect: Z = 1.33 (P = 0.18) 1.8.4 BMI<and>25kg/m2</and> Kelly 2002 3.2 0.95 10 3.4 1.58 10 4.3% -0.20 [-1.34, 0.94] Maciel 2004 - NO 2.25 0.68 7 3.57 0.83 8 5.4% -0.32 [-2.08, 0.56] Trolle 2017 2.88 0.68 2.3 2.88 0.68 2.7 6.4% 0.00 [-0.38, 0.38] 1.8.4 BMI<and>25kg/m2</and> Kelly 2020 3.2 0.95 10 3.44 0.66 14 6.1% -0.79 [-1.29, 0.29] Trolle 2017 2.88 0.68 2.3 2.88 0.68 2.7 6.4% 0.00 [-0.38, 0.38] 1.8.4 BMI<and>25kg/m2</and> Heterogeneity: Tau" = 0.59; Ch" = 13.67, df = 4 (P = 0.008); P = 71% Test for overall effect: Z = 1.39 (P = 0.008); P = 71% Test for overall effect: Z = 1.30 (P = 0.008); P = 71% Test for overall effect: Z = 2.33 (P = 0.02) Total (95% CI) 92 Heterogeneity: Tau" = 0.59; Ch" = 13.67, df = 4 (P = 0.008); P = 71% Test for overall effect: Z = 2.33 (P = 0.02) Total (95% CI) 92 Heterogeneity: Tau" = 0.59; Ch" = 13.67, df = 4 (P = 0.00001); P = 91% Test for overall effect: Z = 2.33 (P = 0.02) Total (95% CI) 92 Heterogeneity: Tau" = 0.59; Ch" = 13.67, df = 4 (P = 0.00001); P = 91% Test for overall effect: Z = 2.33 (P = 0.02) Test for subroput differences: Ch" = 2.64, df = 2 (P = 0.27), P = 24.1%	Hoeger 2004	2.26	1.05	5	2.18	0.79	7	4.5%	0.08 [-1.01, 1.17]		
Lor 2006 2.51 0.64 16 2.26 0.61 16 6.3% 0.25 [0.18, 0.68] Maciel 2004 - O 3.73 0.79 8 3.52 1.55 6 3.8% 0.21 [1.15, 1.57] Heterogeneity: Tau ² = 0.01; Ch ² = 8.24, df = 7 (P = 0.31); P = 15% Test for overall effect: Z = 1.47 (P = 0.14) 1.8.2 BMI<25kg/m2 Bailargeon 2004 1.28 0.73 28 4.16 0.76 30 6.4% -2.88 [-3.26, -2.50] Lingaiah 2019 - NO 1.2 0.6 40 1.6 0.6 34 6.6% -0.40 [-0.67, -0.13] Ng 2001 1.3 0.5 8 1.7 0.7 7 5.8% -0.40 [-1.02, 0.22] Palomba 2007 5.2 1.73 14 5.2 1.73 13 3.9% Subtotal (95% Cl) 103 Heterogeneity: Tau ² = 1.97; Ch ² = 117.04, df = 4 (P < 0.00011); P = 97% Test for overall effect: Z = 1.33 (P = 0.18) 1.8.4 BMI<and>25kg/m2</and> Kelly 2002 3.2 0.95 10 3.4 1.58 10 4.3% -0.20 [-1.34, 0.94] Maciel 2004 - NO 2.25 0.68 7 3.57 0.83 8 5.4% -0.302 [-1.34, 0.94] Maciel 2004 - NO 2.25 0.68 7 3.57 0.83 8 5.4% -0.302 [-1.34, 0.94] Maciel 2004 - NO 2.25 0.68 7 3.57 0.83 8 5.4% -0.302 [-1.34, 0.94] Trolle 2017 2.88 0.68 23 2.88 0.68 27 6.4% 0.00 [-0.38, 0.38] Trolle 2010 2.31 0.83 37 2.46 0.66 37 6.5% -0.15 [-0.49, 0.19] Subtotal (95% Cl) 92 Heterogeneity: Tau ² = 0.59; Ch ² = 193.90, df = 17 (P < 0.00001); P = 91% Test for overall effect: Z = 1.99 (P = 0.02) Total (95% Cl) 92 Total (95% Cl) 94 Heterogeneity: Tau ² = 0.49; Ch ² = 193.90, df = 17 (P < 0.00001); P = 91% Test for overall effect: Z = 1.99 (P = 0.02) Total (95% Cl) 94 Heterogeneity: Tau ² = 0.49; Ch ² = 193.90, df = 17 (P < 0.00001); P = 91% Test for overall effect: Z = 2.33 (P = 0.02) Total (95% Cl) 94 Heterogeneity: Tau ² = 0.49; Ch ² = 193.90, df = 17 (P < 0.00001); P = 91% Test for overall effect: Z = 2.33 (P = 0.02) Total (95% Cl) 94 Heterogeneity: Tau ² = 0.49; Ch ² = 1.92, P = 2.09 Heterogeneity: Tau ² = 0.49; Ch ² = 1.92, P = 0.02) Total (95% Cl) 95 Total (95% Cl) 94 Heterogeneity: Tau ² = 0.49; Ch ² = 1.92, P = 2.79, P = 2.41%	Hoeger 2008	1.72	1.08	6	2.48	1.17	10	4.4%	-0.76 [-1.89, 0.37]		
$\begin{array}{c} \text{Maciel 2004 - 0} & 3.73 & 0.79 & 8 & 3.52 \\ \text{Subtotal (95\% Cl)} & 111 & 140 & 43.8\% & 0.21 \left[+1.15, 1.57 \right] \\ \text{Heterogeneily:} Tau^2 = 0.01; Ch^2 = 8.24, df = 7 (P = 0.31); P = 15\% \\ \text{Test for overall effect: Z = 1.47 (P = 0.14)} \\ \hline 1.8.2 \text{BMI} < 25 kg/m2 \\ \text{Bailargeon 2004} & 1.28 & 0.73 & 28 & 4.16 & 0.76 & 30 & 6.4\% & -2.88 \left[3.26, -2.50 \right] \\ \text{Lingaiah 2019 - NO & 1.2 & 0.6 & 40 & 1.6 & 0.6 & 34 & 6.6\% & -0.40 \left[-0.67, -0.13 \right] \\ \text{Ng 2001} & 1.3 & 0.5 & 8 & 1.7 & 0.7 & 7 & 5.8\% & -0.40 \left[-1.02, 0.22 \right] \\ \text{Palomba 2007} & 5.2 & 1.73 & 14 & 5.2 & 1.73 & 13 & 3.9\% & 0.00 \left[-1.31, 1.31 \right] \\ \text{Subtotal (95\% Cl)} & 103 & 103 & 94 & 27.5\% & -0.87 \left[-2.15, 0.41 \right] \\ \text{Heterogeneity: Tau^2 = 1.97; Ch^2 = 117.04, df = 4 (P < 0.00001); P = 97\% \\ \text{Test for overall effect: Z = 1.33 (P = 0.18)} \\ \text{18.4 BMI < and> 25 kg/m2 \\ \text{Maciel 2004 - NO & 2.25 & 0.68 & 7 & 3.57 & 0.38 & 8 & 5.4\% & -0.20 \left[-1.34, 0.94 \right] \\ \text{Maciel 2001 & 2.31 & 0.83 & 37 & 2.46 & 0.66 & 37 & 6.4\% & 0.000 \left[-0.38, 0.38 \right] \\ \text{Total (95\% Cl)} & 2.68 & 0.68 & 2.3 & 2.288 & 0.66 & 27 & 6.4\% & 0.00 \left[-0.38, 0.38 \right] \\ \text{Total (95\% Cl)} & 306 \\ \text{Heterogeneity: Tau^2 = 0.59; Ch^2 = 133.67, df = 4 (P = 0.0001); P = 91\% \\ \text{Test for overall effect: Z = 1.39 (P = 0.05)} \\ \text{Total (95\% Cl)} & 306 \\ \text{Total (95\% Cl)} & 2.54, df = 2 (P = 0.27), P = 24.1\% \\ \end{array}$	Lingaiah 2019 - O	1.3	0.5	17	1.5	1	27	6.2%	-0.20 [-0.65, 0.25]		
Subtotal (95% CI) 111 140 43.8% -0.14 [-0.33, 0.05] Heterogeneity: Tau ² = 0.01; Ch ² = 8.24, df = 7 (P = 0.31); P = 15% Test for overall effect: Z = 1.47 (P = 0.14) 1.8.2 BMI<25kg/m2 Baillargeon 2004 1.28 0.73 28 4.16 0.76 30 6.4% -2.88 [-3.26, -2.50] Lingaiah 2019 - NO 1.2 0.6 40 1.6 0.6 34 6.6% -0.40 [-0.67, -0.13] Ng 2001 1.3 0.5 8 1.7 0.7 7 5.8% -0.40 [-1.02, 0.22] Palomba 2007 5.2 1.73 14 5.2 1.73 13 3.9% 0.00 [-1.31, 1.31] Romuldi 2010 1.53 0.52 13 2.01 1.42 10 4.9% -0.48 [-1.40, 0.44] Subtotal (95% CI) 103 94 27.5% -0.48 [-1.40, 0.44] Heterogeneity: Tau ² = 1.97; Ch ² = 117.04, df = 4 (P < 0.00001); P = 97% Test for overall effect: Z = 1.33 (P = 0.18) 1.8.4 BMI <and>25kg/m2 Kelly 2002 3.2 0.95 10 3.4 1.58 10 4.3% -0.20 [-1.34, 0.94] Maciel 2004 - NO 2.25 0.68 7 3.57 0.83 8 5.4% -1.32 [-2.08, 0.56] Total (95% CI) 2.31 0.83 37 2.46 0.66 37 6.5% -0.15 [-0.49, 0.19] Subtotal (95% CI) 92 96 28.7% -0.45 [-0.48, -0.01] Heterogeneity: Tau² = 0.59; Ch² = 139.30, df = 17 (P < 0.00001); P = 91% Test for overall effect: Z = 1.39 (P = 0.02) Total (95% CI) 306 330 100.0% -0.47 [-0.86, -0.07] Heterogeneity: Tau² = 0.59; Ch² = 139.0, df = 17 (P < 0.00001); P = 91% Test for overall effect: Z = 2.33 (P = 0.27), P = 24.1%</and>	Lord 2006	2.51	0.64	16	2.26	0.61	16	6.3%	0.25 [-0.18, 0.68]		
Heterogeneity: Tau ² = 0.01; Ch ² = 8.24, df = 7 (P = 0.31); P = 15% Test for overall effect: Z = 1.47 (P = 0.14) 1.8.2 BMI<25kg/m2 Bailargeon 2004 1.28 0.73 28 4.16 0.6 34 6.6% -0.40 [-0.67, -0.13] Ng 2001 1.3 0.5 8 1.7 0.7 7 5.8% -0.40 [-1.02, 0.22] Palomba 2007 5.2 1.73 14 5.2 1.73 13 3.9% 0.00 [-1.31, 1.31] Subtotal (95% Cl) 1.53 0.52 13 2.01 1.42 10 4.9% -0.48 [-1.40, 0.41] Heterogeneity: Tau ² = 1.97; Ch ² = 117.04, df = 4 (P < 0.00001); P = 97% Test for overall effect: Z = 1.33 (P = 0.18) 1.8.4 BMI<and>25kg/m2</and> Kelly 2002 3.2 0.95 10 3.4 1.58 10 4.3% -0.20 [-1.34, 0.94] Maciel 2004 - NO 2.25 0.68 7 3.57 0.83 8 5.4% -1.32 [-2.08, 0.56] Naka 2011 2.65 0.7 15 3.44 0.66 37 6.5% -0.15 [-0.49, 0.19] Maciel 2007 2.88 0.68 23 2.88 0.68 27 6.4% 0.00 [-0.38, 0.38] Trolle 2010 2.31 0.83 37 2.46 0.66 37 6.5% -0.15 [-0.49, 0.19] Subtotal (95% Cl) 92 96 28.7% -0.45 [-0.89, -0.01] Heterogeneity: Tau ² = 0.16; Ch ² = 13.67, df = 4 (P = 0.008); P = 71% Test for overall effect: Z = 1.99 (P = 0.05) Total (95% Cl) 306 330 100.0% -0.47 [-0.86, -0.07] Heterogeneity: Tau ² = 0.59; Ch ² = 193.90, df = 17 (P < 0.0001); P = 91% Test for overall effect: Z = 1.99 (P = 0.02) Total (95% Cl) 306 330 100.0% -0.47 [-0.86, -0.07] Heterogeneity: Tau ² = 0.59; Ch ² = 193.90, df = 17 (P < 0.0001); P = 91% Test for overall effect: Z = 2.33 (P = 0.02) Total (95% Cl) 306 330 100.0% -0.47 [-0.86, -0.07] Heterogeneity: Tau ² = 0.59; Ch ² = 193.90, df = 17 (P < 0.0001); P = 91% Test for overall effect: Z = 2.33 (P = 0.02) Total (95% Cl) 306 330 100.0% -0.47 [-0.86, -0.07] Heterogeneity: Tau ² = 0.59; Ch ² = 193.90, df = 17 (P < 0.0001); P = 91% Test for overall effect: Z = 2.33 (P = 0.02) Total (95% Cl) 306 330 100.0% -0.47 [-0.86, -0.07] Heterogeneity: Tau ² = 0.59; Ch ² = 193.90, df = 17 (P < 0.0001); P = 24.1%	Maciel 2004 - O	3.73	0.79	8	3.52	1.55	6	3.8%	0.21 [-1.15, 1.57]		
Test for overall effect: $Z = 1.47$ (P = 0.14) 1.8.2 BMI<25kg/m2 Bailargeon 2004 1.28 0.73 28 4.16 0.76 30 6.4% -2.88 [3.26, -2.50] Lingalah 2019 - NO 1.2 0.6 40 1.6 0.6 34 6.6% -0.40 [-0.67, -0.13] Ng 2001 1.3 0.5 8 1.7 0.7 7 5.8% -0.40 [-1.02, 0.22] Pelomba 2007 5.2 1.73 14 5.2 1.73 13 3.9% 0.00 [-1.31, 1.31] Romualdi 2010 1.53 0.52 13 2.01 1.42 10 4.9% -0.48 [-1.40, 0.44] Subtotal (95% CI) 103 94 27.5% -0.87 [-2.15, 0.41] Heterogeneity: Tau ² = 1.97; Ch ² = 117.04, df = 4 (P < 0.00001); P = 97% Test for overall effect: Z = 1.33 (P = 0.18) 1.8.4 BMI<and>255 kg/m2</and> Kelly 2002 3.2 0.95 10 3.4 1.58 10 4.3% -0.20 [-1.34, 0.94] Maciel 2004 - NO 2.25 0.68 7 3.57 0.83 8 5.4% -1.32 [-2.08, -0.56] Naka 2011 2.65 0.7 15 3.444 0.66 14 6.1% -0.79 [-1.29, -0.29] Trolle 2010 2.31 0.83 37 2.46 0.66 37 6.5% -0.15 [-0.49, 0.19] Subtotal (95% CI) 92 96 28.7% -0.45 [-0.49, 0.01] Heterogeneity: Tau ² = 0.16; Ch ² = 13.87, df = 4 (P = 0.008); P = 71% Test for overall effect: Z = 1.99 (P = 0.05) Total (95% CI) 306 330 100.0% -0.47 [-0.86, -0.07] Heterogeneity: Tau ² = 0.59; Ch ² = 193.90, df = 17 (P < 0.00001); P = 91% Test for overall effect: Z = 1.99 (P = 0.05) Total (95% CI) 306 330 100.0% -0.47 [-0.86, -0.07] Heterogeneity: Tau ² = 0.46, df = 2 (P = 0.27), P = 24.1%	Subtotal (95% CI)			111			140	43.8%	-0.14 [-0.33, 0.05]	•	
1.8.2 BMI<25kg/m2 Baillargeon 2004 1.28 0.73 28 4.16 0.76 30 6.4% -2.88 [-3.26, -2.50] Lingaiah 2019 - NO 1.2 0.6 40 1.6 0.6 34 6.6% -0.40 [-0.67, -0.13] Ng 2001 1.3 0.5 8 1.7 0.7 7 5.8% -0.40 [-1.02, 0.22] Palomba 2007 5.2 1.73 14 5.2 1.73 13 3.9% -0.48 [-1.40, 0.44] Subtotal (95% CI) 103 94 27.5% -0.87 [-2.15, 0.41] Heterogeneity: Tau ² = 1.97; Ch ² = 117.04, df = 4 ($P < 0.00001$); $P = 97\%$ Trest for overall effect: $Z = 1.33$ ($P = 0.18$) 1.8.4 BMI<and>25kg/m2</and> Kelly 2002 3.2 0.95 10 3.4 1.58 10 4.3% -0.20 [-1.34, 0.94] Maciel 2004 - NO 2.25 0.68 7 3.57 0.83 8 5.4% -1.32 [-2.08, 0.56] Naka 2011 2.65 0.7 15 3.44 0.68 14 6.1% -0.79 [-1.29, 0.29] Trolle 2007 2.88 0.68 23 2.88 0.68 27 6.4% 0.00 [-0.38, 0.38] Trolle 2010 2.31 0.83 37 2.46 0.66 37 6.5% -0.15 [-0.49, 0.19] Subtotal (95% CI) 92 Heterogeneity: Tau ² = 0.16; Ch ² = 13.67, df = 4 ($P = 0.008$); $P = 71\%$ Test for overall effect: $Z = 1.39$ ($P = 0.05$) Total (95% CI) 306 330 100.0% -0.47 [-0.86, -0.07] Heterogeneity: Tau ² = 0.59; Ch ² = 193.90, df = 17 ($P < 0.00001$); $P = 91\%$ Test for overall effect: $Z = 1.39$ ($P = 0.02$) Total (95% CI) 306 330 100.0% -0.47 [-0.86, -0.07] Heterogeneity: Tau ² = 0.59; Ch ² = 193.90, df = 17 ($P < 0.00001$); $P = 91\%$ Test for overall effect: $Z = 1.39$ ($P = 0.02$) Total (95% CI) 306 330 100.0% -0.47 [-0.86, -0.07] Heterogeneity: Tau ² = 0.59; Ch ² = 193.90, df = 17 ($P < 0.00001$); $P = 91\%$ Test for overall effect: $Z = 2.33$ ($P = 0.02$) Total (95% CI) 306 330 100.0% -0.47 [-0.86, -0.07]	Heterogeneity: Tau ² = (0.01; Chi ² = 8.24	, df = 7 (P = 0	.31); l ²	= 15%						
Baillargeon 2004 1.28 0.73 28 4.16 0.76 30 6.4% -2.88 [-3.26, -2.50] 4 Lingaiah 2019 · NO 1.2 0.6 40 1.6 0.6 34 6.6% -0.40 [-0.57, -0.13] Ng 2001 1.3 0.5 8 1.7 0.7 7 5.8% -0.40 [-0.57, -0.13] Palomba 2007 5.2 1.73 14 5.2 1.73 13 3.9% 0.00 [-1.31, 1.31] Romualdi 2010 1.53 0.52 13 2.01 1.42 10 4.9% -0.48 [-1.40, 0.44] Subtotal (95% Cl) 103 94 27.5% -0.87 [-2.15, 0.41] Heterogeneity: Tau ² = 1.97; Chi ² = 117.04, df = 4 (P < 0.00001); P = 97% Test for overall effect: $Z = 1.33$ (P = 0.18) 1.8.4 BMI<and>25kg/m2</and> Kelly 2002 3.2 0.95 10 3.4 1.58 10 4.3% -0.20 [-1.34, 0.94] Maciel 2004 · NO 2.25 0.68 7 3.57 0.83 8 5.4% -1.32 [-2.08, 0.56] Naka 2011 2.65 0.7 15 3.44 0.68 14 6.1% 0.079 [-1.29, -0.29] Trolle 2007 2.88 0.68 23 2.88 0.68 27 6.4% 0.00 [-0.38, 0.38] Trolle 2010 2.31 0.83 37 2.46 0.66 37 6.5% -0.15 [-0.49, 0.19] 96 28.7% -0.45 [-0.89, -0.01] Heterogeneity: Tau ² = 0.16; Chi ² = 13.67, df = 4 (P = 0.008); P = 71% Test for overall effect: $Z = 1.99$ (P = 0.05) Total (95% Cl) 306 330 100.0% -0.47 [-0.86, -0.07] Heterogeneity: Tau ² = 0.16; Chi ² = 13.67, df = 4 (P = 0.27), P = 24.1%	Test for overall effect: 2	Z = 1.47 (P = 0.1	4)								
Lingaiah 2019 - NO 1.2 0.6 40 1.6 0.6 34 6.6% -0.40 [0.67, -0.13] Ng 2001 1.3 0.5 8 1.7 0.7 7 5.8% -0.40 [-1.02, 0.22] Palomba 2007 5.2 1.73 14 5.2 1.73 13 3.9% 0.00 [-1.31, 1.31] Romuali 2010 1.53 0.52 13 2.01 1.42 10 4.9% -0.48 [-1.40, 0.44] Subtotal (95% Cl) 103 94 27.5% -0.87 [-2.15, 0.41] Heterogeneity: Tau ² = 1.97; Chi ² = 117.04, df = 4 (P < 0.00001); I ² = 97% Test for overall effect: Z = 1.33 (P = 0.18) 1.8.4 BMI <ard>25kg/m2 Kelly 2002 3.2 0.95 10 3.4 1.58 10 4.3% -0.20 [-1.34, 0.94] Maciel 2004 - NO 2.25 0.68 7 3.57 0.83 8 5.4% -1.32 [-2.08, -0.56] Naka 2011 2.65 0.7 15 3.44 0.68 14 6.1% -0.79 [-1.29, -0.29] Trolle 2010 2.31 0.83 37 2.46 0.66 37 6.5% -0.15 [-0.49, 0.19] Subtotal (95% Cl) 92 96 28.7% -0.45 [-0.89, -0.01] Heterogeneity: Tau² = 0.16; Chi² = 13.67, df = 4 (P = 0.008); I² = 71% Test for overall effect: Z = 1.39 (P = 0.05) Total (95% Cl) 306 330 100.0% -0.47 [-0.86, -0.07] Heterogeneity: Tau² = 0.59; Chi² = 13.90, df = 17 (P < 0.00001); I² = 91% Test for overall effect: Z = 2.33 (P = 0.02) Total (95% Cl) 306 330 100.0% -0.47 [-0.86, -0.07] Heterogeneity: Tau² = 0.59; Chi² = 13.90, df = 17 (P < 0.00001); I² = 91% Test for subgroup differences: Chi² = 2.64, df = 2 (P = 0.27), I² = 24.1%</ard>	1.8.2 BMI<25kg/m2										
Lingaiah 2019 - NO 1.2 0.6 40 1.6 0.6 34 6.6% -0.40 [0.67, -0.13] Ng 2001 1.3 0.5 8 1.7 0.7 7 5.8% -0.40 [-1.02, 0.22] Palomba 2007 5.2 1.73 14 5.2 1.73 13 3.9% 0.00 [-1.31, 1.31] Romuali 2010 1.53 0.52 13 2.01 1.42 10 4.9% -0.48 [-1.40, 0.44] Subtotal (95% Cl) 103 94 27.5% -0.87 [-2.15, 0.41] Heterogeneity: Tau ² = 1.97; Chi ² = 117.04, df = 4 (P < 0.00001); I ² = 97% Test for overall effect: Z = 1.33 (P = 0.18) 1.8.4 BMI <ard>25kg/m2 Kelly 2002 3.2 0.95 10 3.4 1.58 10 4.3% -0.20 [-1.34, 0.94] Maciel 2004 - NO 2.25 0.68 7 3.57 0.83 8 5.4% -1.32 [-2.08, -0.56] Naka 2011 2.65 0.7 15 3.44 0.68 14 6.1% -0.79 [-1.29, -0.29] Trolle 2010 2.31 0.83 37 2.46 0.66 37 6.5% -0.15 [-0.49, 0.19] Subtotal (95% Cl) 92 96 28.7% -0.45 [-0.89, -0.01] Heterogeneity: Tau² = 0.16; Chi² = 13.67, df = 4 (P = 0.008); I² = 71% Test for overall effect: Z = 1.39 (P = 0.05) Total (95% Cl) 306 330 100.0% -0.47 [-0.86, -0.07] Heterogeneity: Tau² = 0.59; Chi² = 13.90, df = 17 (P < 0.00001); I² = 91% Test for overall effect: Z = 2.33 (P = 0.02) Total (95% Cl) 306 330 100.0% -0.47 [-0.86, -0.07] Heterogeneity: Tau² = 0.59; Chi² = 13.90, df = 17 (P < 0.00001); I² = 91% Test for subgroup differences: Chi² = 2.64, df = 2 (P = 0.27), I² = 24.1%</ard>	Baillargeon 2004	1.28	0.73	28	4.16	0.76	30	6.4%	-2.88 [-3.26, -2.50]	•	
Ng 2001 1.3 0.5 8 1.7 0.7 7 5.8% -0.40 [-1.02, 0.22] Palomba 2007 5.2 1.73 14 5.2 1.73 13 3.9% 0.00 [-1.31, 1.31] Romualdi 2010 1.53 0.52 13 2.01 1.42 10 4.9% -0.48 [-1.40, 0.44] Subtotal (95% CI) 103 94 27.5% -0.87 [-2.15, 0.41] -0.87 [-2.15, 0.41] Heterogeneity: Tau ² = 1.97; Ch ² = 117.04, df = 4 (P < 0.00001); l ² = 97% 1.84 BMI <and>>25kg/m2 Kelly 2002 3.2 0.95 10 3.4 1.58 10 4.3% -0.20 [-1.34, 0.94] Makeil 2004 - NO 2.25 0.68 7 3.57 0.83 8 5.4% -1.32 [-2.08, 0.56] Naka 2011 2.65 0.7 15 3.44 0.68 27 6.4% 0.00 [-0.38, 0.38] Trolle 2007 2.88 0.68 23 2.88 0.66 37 6.5% -0.15 [-0.49, 0.19] Subtotal (95% Cl) 92 96 28.7% -0.45 [-0.89, -0.01] -2 -1 0<</and>	Lingaiah 2019 - NO	1.2	0.6	40	1.6	0.6	34	6.6%	-0.40 [-0.67, -0.13]		
Palomba 2007 5.2 1.73 14 5.2 1.73 13 3.9% 0.00 [-1.31, 1.31] Romualdi 2010 1.53 0.52 13 2.01 1.42 10 4.9% -0.48 [-1.40, 0.44] Subtotal (95% Cl) 103 94 27.5% -0.87 [-2.15, 0.41] -0.87 [-2.15, 0.41] Heterogeneity: Tau ² = 1.97; Chi ² = 117.04, df = 4 (P < 0.00001); l ² = 97% 94 27.5% -0.87 [-2.15, 0.41] 1.84 BMI <and>25kg/m2 </and>											
Subtotal (95% CI) 103 Heterogeneity: Tau ² = 1.97; Chi ² = 117.04, df = 4 (P < 0.00001); l ² = 97% Test for overall effect: Z = 1.33 (P = 0.18) 1.8.4 BMI <and>25kg/m2 Kelly 2002 3.2 0.95 10 3.4 1.58 10 4.3% -0.20 [-1.34, 0.94] Maciel 2004 - NO 2.25 0.68 7 3.57 0.83 8 5.4% -1.32 [-2.08, -0.56] Naka 2011 2.65 0.7 15 3.44 0.68 14 6.1% -0.79 [-1.29, -0.29] Trolle 2007 2.88 0.68 23 2.88 0.68 27 6.4% 0.00 [-0.38, 0.38] Trolle 2010 2.31 0.83 37 2.46 0.66 37 6.5% -0.15 [-0.49, 0.19] Subtotal (95% CI) 92 Heterogeneity: Tau² = 0.16; Chi² = 13.67, df = 4 (P = 0.008); l² = 71% Test for overall effect: Z = 1.99 (P = 0.05) Total (95% CI) 306 Heterogeneity: Tau² = 0.59; Chi² = 193.90, df = 17 (P < 0.00001); l² = 91% Test for overall effect: Z = 2.33 (P = 0.02) Test for subgroup differences: Chi² = 2.64, df = 2 (P = 0.27), l² = 24.1%</and>			1.73	14	5.2	1.73	13				
Subtotal (95% CI) 103 Heterogeneity: Tau ² = 1.97; Chi ² = 117.04, df = 4 (P < 0.00001); l ² = 97% Test for overall effect: Z = 1.33 (P = 0.18) 1.8.4 BMI <and>25kg/m2 Kelly 2002 3.2 0.95 10 3.4 1.58 10 4.3% -0.20 [-1.34, 0.94] Maciel 2004 - NO 2.25 0.68 7 3.57 0.83 8 5.4% -1.32 [-2.08, -0.56] Naka 2011 2.65 0.7 15 3.44 0.68 14 6.1% -0.79 [-1.29, -0.29] Trolle 2007 2.88 0.68 23 2.88 0.68 27 6.4% 0.00 [-0.38, 0.38] Trolle 2010 2.31 0.83 37 2.46 0.66 37 6.5% -0.15 [-0.49, 0.19] Subtotal (95% CI) 92 96 28.7% -0.45 [-0.89, -0.01] Heterogeneity: Tau² = 0.16; Chi² = 13.67, df = 4 (P = 0.008); l² = 71% Test for overall effect: Z = 1.99 (P = 0.05) Total (95% CI) 306 330 100.0% -0.47 [-0.86, -0.07] Heterogeneity: Tau² = 0.59; Chi² = 193.90, df = 17 (P < 0.00001); l² = 91% Test for overall effect: Z = 2.33 (P = 0.22) Test for subgroup differences: Chi² = 2.64, df = 2 (P = 0.27), l² = 24.1%</and>	Romualdi 2010	1.53	0.52	13	2.01	1.42	10	4.9%	-0.48 [-1.40, 0.44]		
Test for overall effect: $Z = 1.33 (P = 0.18)$ 1.8.4 BMI <and>25kg/m2 Kelly 2002 3.2 0.95 10 3.4 1.58 10 4.3% -0.20 [-1.34, 0.94] Maciel 2004 - NO 2.25 0.68 7 3.57 0.83 8 5.4% -1.32 [-2.08, -0.56] Naka 2011 2.65 0.7 15 3.44 0.68 14 6.1% -0.79 [-1.29, -0.29] Trolle 2007 2.88 0.68 23 2.88 0.68 27 6.4% 0.00 [-0.38, 0.38] Trolle 2010 2.31 0.83 37 2.46 0.66 37 6.5% -0.15 [-0.49, 0.19] Subtotal (95% CI) 92 96 28.7% -0.45 [-0.89, -0.01] Heterogeneity: Tau² = 0.16; Chi² = 13.67, df = 4 (P = 0.008); l² = 71% Test for overall effect: Z = 1.99 (P = 0.05) Total (95% CI) 306 330 100.0% -0.47 [-0.86, -0.07] Heterogeneity: Tau² = 0.59; Chi² = 193.90, df = 17 (P < 0.00001); l² = 91% Test for overall effect: Z = 2.33 (P = 0.22) Test for subgroup differences: Chi² = 2.64, df = 2 (P = 0.27), l² = 24.1%</and>	Subtotal (95% CI)			103			94	27.5%			
Kelly 2002 3.2 0.95 10 3.4 1.58 10 4.3% -0.20 [-1.34, 0.94] Maciel 2004 - NO 2.25 0.68 7 3.57 0.83 8 5.4% -1.32 [-2.08, -0.56] Naka 2011 2.65 0.7 15 3.44 0.68 14 6.1% -0.79 [-1.29, -0.29] Trolle 2007 2.88 0.68 23 2.88 0.68 27 6.4% 0.00 [-0.38, 0.38] Trolle 2010 2.31 0.83 37 2.46 0.66 37 6.5% -0.15 [-0.49, 0.19] Subtotal (95% CI) 92 96 28.7% -0.45 [-0.89, -0.01] -0.45 [-0.89, -0.01] Heterogeneity: Tau ² = 0.16; Chi ² = 13.67, df = 4 (P = 0.008); l ² = 71% 330 100.0% -0.47 [-0.86, -0.07] Heterogeneity: Tau ² = 0.59; Chi ² = 193.90, df = 17 (P < 0.00001); l ² = 91% 330 100.0% -0.47 [-0.86, -0.07] Test for overall effect: Z = 2.33 (P = 0.02) Test for overall effect: Z = 2.64, df = 2 (P = 0.27), l ² = 24.1% 330 100.0% -0.47 [-0.86, -0.07]	5 ,			< 0.000	01); l² = 97%						
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	1.8.4 BMI <and>25kg/r</and>	n2									
Naka 2011 2.65 0.7 15 3.44 0.68 14 6.1% $-0.79 [-1.29, -0.29]$ Trolle 2007 2.88 0.68 23 2.88 0.68 27 6.4% 0.00 [-0.38, 0.38] Trolle 2010 2.31 0.83 37 2.46 0.66 37 6.5% -0.15 [-0.49, 0.19] Subtotal (95% CI) 92 96 28.7% -0.45 [-0.89, -0.01] Heterogeneity: Tau ² = 0.16; Chi ² = 13.67, df = 4 (P = 0.008); l ² = 71% 330 100.0% -0.47 [-0.86, -0.07] Total (95% CI) 306 330 100.0% -0.47 [-0.86, -0.07] -2 -1 0 1 2 Test for overall effect: Z = 2.33 (P = 0.02) 306 330 100.0% -0.47 [-0.86, -0.07] -2 -1 0 1 2 Test for overall effect: Z = 2.33 (P = 0.02) Test for subgroup differences: Chi ² = 2.64, df = 2 (P = 0.27), l ² = 24.1% 330 100.0% -0.47 [-0.86, -0.07] Metformin <placebo< th=""></placebo<>	Kelly 2002	3.2	0.95	10	3.4	1.58	10	4.3%	-0.20 [-1.34, 0.94]		
Naka 2011 2.65 0.7 15 3.44 0.68 14 6.1% -0.79 [-1.29, -0.29] Trolle 2007 2.88 0.68 23 2.88 0.68 27 6.4% 0.00 [-0.38, 0.38] Trolle 2010 2.31 0.83 37 2.46 0.66 37 6.5% -0.15 [-0.49, 0.19] Subtotal (95% CI) 92 96 28.7% -0.45 [-0.89, -0.01] Heterogeneity: Tau ² = 0.16; Chi ² = 13.67, df = 4 (P = 0.008); l ² = 71% 330 100.0% -0.47 [-0.86, -0.07] Total (95% CI) 306 330 100.0% -0.47 [-0.86, -0.07] Heterogeneity: Tau ² = 0.59; Chi ² = 193.90, df = 17 (P < 0.00001); l ² = 91% 330 100.0% -0.47 [-0.86, -0.07] Test for overall effect: Z = 2.33 (P = 0.02) Test for subgroup differences: Chi ² = 2.64, df = 2 (P = 0.27), l ² = 24.1% 330 100.0% -0.47 [-0.86, -0.07]	Maciel 2004 - NO	2.25	0.68	7	3.57	0.83	8	5.4%	-1.32 [-2.08, -0.56]		
Trolle 2010 2.31 0.83 37 2.46 0.66 37 6.5% -0.15 [-0.49, 0.19] Subtotal (95% Cl) 92 96 28.7% -0.45 [-0.89, -0.01] Heterogeneity: Tau ² = 0.16; Chi ² = 13.67, df = 4 (P = 0.008); l ² = 71% 306 330 100.0% -0.47 [-0.86, -0.07] Total (95% Cl) 306 330 100.0% -0.47 [-0.86, -0.07] -2 -1 0 1 2 Test for overall effect: Z = 2.33 (P = 0.02) 306 330 100.0% -0.47 [-0.86, -0.07] -2 -1 0 1 2 Test for overall effect: Z = 2.33 (P = 0.02) 306 330 100.0% -0.47 [-0.86, -0.07] -2 -1 0 1 2 Test for subgroup differences: Chi ² = 2.64, df = 2 (P = 0.27), l ² = 24.1% 330 100.0% -0.47 [-0.86, -0.07] -2 -1 0 1 2 Metformin Placebo Metformin Placebo -2 -1 0 1 2	Naka 2011	2.65	0.7	15	3.44	0.68	14	6.1%			
Subtotal (95% Cl) 92 96 28.7% -0.45 [- $\overline{0.89}$, -0.01] Heterogeneity: Tau ² = 0.16; Chi ² = 13.67, df = 4 (P = 0.008); l ² = 71% -2 -10 -2 Test for overall effect: Z = 1.99 (P = 0.05) 306 330 100.0% -0.47 [- 0.86 , -0.07] Heterogeneity: Tau ² = 0.59; Chi ² = 193.90, df = 17 (P < 0.00001); l ² = 91% -2 -1 0 1 2 Test for overall effect: Z = 2.33 (P = 0.02) Test for subgroup differences: Chi ² = 2.64, df = 2 (P = 0.27), l ² = 24.1% -4 -4 -10 1 2	Trolle 2007	2.88	0.68	23	2.88	0.68	27	6.4%	0.00 [-0.38, 0.38]		
Heterogeneity: Tau ² = 0.16; Chi ² = 13.67, df = 4 (P = 0.008); l ² = 71% Test for overall effect: Z = 1.99 (P = 0.05) Total (95% Cl) 306 330 100.0% -0.47 [-0.86, -0.07] Heterogeneity: Tau ² = 0.59; Chi ² = 193.90, df = 17 (P < 0.00001); l ² = 91% Test for overall effect: Z = 2.33 (P = 0.02) Test for subgroup differences: Chi ² = 2.64, df = 2 (P = 0.27), l ² = 24.1%	Trolle 2010	2.31	0.83	37	2.46	0.66	37	6.5%	-0.15 [-0.49, 0.19]		
Test for overall effect: Z = 1.99 (P = 0.05) Total (95% Cl) 306 Heterogeneity: Tau ² = 0.59; Chi ² = 193.90, df = 17 (P < 0.00001); l ² = 91% Test for overall effect: Z = 2.33 (P = 0.02) Test for subgroup differences: Chi ² = 2.64, df = 2 (P = 0.27), l ² = 24.1%	Subtotal (95% CI)			92			96	28.7%	-0.45 [-0.89, -0.01]	•	
Total (95% CI) 306 330 100.0% -0.47 [-0.86, -0.07] Heterogeneity: Tau ² = 0.59; Chi ² = 193.90, df = 17 (P < 0.00001); l ² = 91% -2 -1 0 1 2 Test for overall effect: Z = 2.33 (P = 0.02) Test for subgroup differences: Chi ² = 2.64, df = 2 (P = 0.27), l ² = 24.1% -0.47 [-0.86, -0.07] -2 -1 0 1 2	Heterogeneity: Tau ² = (0.16; Chi ² = 13.6	7, df = 4 (P =	0.008);	l ² = 71%						
Heterogeneity: Tau ² = 0.59; Chi ² = 193.90, df = 17 (P < 0.00001); l ² = 91% Test for overall effect: Z = 2.33 (P = 0.02) Test for subgroup differences: Chi ² = 2.64, df = 2 (P = 0.27), l ² = 24.1%	Test for overall effect: 2	Z = 1.99 (P = 0.0	5)								
Test for overall effect: Z = 2.33 (P = 0.02) -2 -1 0 1 2 Test for subgroup differences: Chi ² = 2.64, df = 2 (P = 0.27), l ² = 24.1% Metformin Placebo	Total (95% CI)			306			330	100.0%	-0.47 [-0.86, -0.07]	•	
Test for overall effect: Z = 2.33 (P = 0.02) -2 -1 0 1 2 Test for subgroup differences: Chi ² = 2.64, df = 2 (P = 0.27), l ² = 24.1% Metformin Placebo	Heterogeneity: Tau ² = (0.59; Chi ² = 193.	90, df = 17 (F	< 0.00	001); l² = 91%						<u> </u>
Test for subgroup differences: Chi ² = 2.64, df = 2 (P = 0.27), l ² = 24.1%											2
			Sector and an and an and an and	= 0.27).	l ² = 24.1%					Metornin Placebo	
	01		naanse tot in the Mill								

1.9 Androstenedione (nmol/l)

	Me	tformi	n	PI	acebo			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	1.0
1.9.1 BMI≥25										10
Lingaiah 2019 - O	14.5	5.7	17	17.9	8	27	15.5%	-3.40 [-7.46, 0.66]		
Maciel 2004 - O	8.03	2.97	8	7.33	3.42	6	18.1%	0.70 [-2.72, 4.12]		
Subtotal (95% CI)			25			33	33.6%	-1.20 [-5.21, 2.81]		
Heterogeneity: Tau ² =	4.74; Cl	ni² = 2.	29, df =	= 1 (P =	0.13);	$I^2 = 56$	%			
Test for overall effect:	Z = 0.59) (P = (0.56)							
1.9.2 BMI<25										
Lingaiah 2019 - NO Subtotal (95% CI)	14.6	5.7	40 40	20	8.1	34 34	18.9% 18.9%	-5.40 [-8.65, -2.15] -5.40 [-8.65, -2.15]		
	- Parala Ia		40			34	10.9%	-5.40 [-6.65, -2.15]		
Heterogeneity: Not ap		· /D - /	0.004							
Test for overall effect:	Z = 3.26	6 (P = (J.001)							
1.9.3 BMI <and>25kg/</and>	/m2									
Maciel 2004 - NO	4.89	1.85	7	8.03	4.92	8	17.0%	-3.14 [-6.81, 0.53]		
Palomba 2007	5.94	1.05	14	6.28	1.05	13	30.4%	-0.34 [-1.13, 0.45]	+	
Subtotal (95% CI)			21			21	47.5%	-1.14 [-3.62, 1.34]	-	
Heterogeneity: Tau ² =	2.08; CI	ni² = 2.	13, df =	= 1 (P =	0.14);	$ ^2 = 53$	%			
Test for overall effect:	Z = 0.90) (P = (0.37)							
Total (95% CI)			86			88	100.0%	-2.06 [-4.29, 0.17]	-	
Heterogeneity: Tau ² =	4.09; CI	ni² = 12	2.87, df	= 4 (P	= 0.01); l ² = 6	9%		-10 -5 0 5 10	<u></u>
Test for overall effect:	Z = 1.81	(P=0	0.07)						Favours Metformin Favours Placebo	
Test for subgroup diffe	erences:	Chi ² =	4.62, 0	lf = 2 (F	9 = 0.1	0), l² =	56.7%			
Risk of bias legend										

1.10 Fasting insulin [pmol/l]

	Met	formin		Pla	icebo			Mean Difference	Mean Di	fference	Risk of Bias
Study or Subgroup	Mean [pmol/l]	SD[pmol/l]	Total	Mean [pmol/I]	SD[pmol/l]	Total	Weight	IV, Random, 95% CI	IV, Rando	m, 95% CI	10
1.10.1 BMIÓ25kg/m2											
Chou 2003	274.65	38.89	14	217.7	19.79	16	9.7%	56.95 [34.39, 79.51]			
Eisenhardt 2006	140.63	19.1	19	145.83	13.89	19	11.1%	-5.20 [-15.82, 5.42]		ł	
Fleming 2002	116.67	67.36	26	127.78	85.41	39	7.5%	-11.11 [-48.38, 26.16]		-	
Hoeger 2004	116.04	73.61	5	121.53	41.67	7	3.8%	-5.49 [-77.02, 66.04]			
Hoeger 2008	137.5	72.22	6	202.8	170.14	10	1.7%	-65.30 [-185.55, 54.95]	· · · · · ·		
Lingaiah 2019 - O	84.03	40.97	17	104.17	54.86	27	8.8%	-20.14 [-48.56, 8.28]			
Lord 2006	120.49	61.81	16	106.67	43.75	16	7.5%	13.82 [-23.29, 50.93]	·	-	
Maciel 2004 - O	146.53	64.58	8	161.1	84.72	6	3.2%	-14.57 [-95.80, 66.66]			
Subtotal (95% CI)			111			140	53.2%	2.62 [-21.79, 27.02]	•		
Heterogeneity: Tau ² =	736.82; Chi ² = 29	9.14, df = 7 (P	= 0.00	01); l² = 76%							
Test for overall effect:	Z = 0.21 (P = 0.8	3)									
1.10.2 BMI<25kg/m2											
Lingaiah 2019 - NO	40.28	19.44	40	53.47	45.14	34	10.5%	-13.19 [-29.52, 3.14]		t i i i i i i i i i i i i i i i i i i i	
Subtotal (95% CI)			40			34	10.5%	-13.19 [-29.52, 3.14]	•	1	
Heterogeneity: Not app	olicable										
Test for overall effect:	Z = 1.58 (P = 0.1	1)									
1.10.3 BMI <and>25kg</and>											
Maciel 2004 - NO	43.75	10.97	7	97.92	27.36	8	9.9%	-54.17 [-74.80, -33.54]	-		
Naka 2011	68.75	31.94	15	81.25	33.33	14	9.5%	-12.50 [-36.29, 11.29]		F	
Trolle 2007	65	57.5	23	65.69	58.06	27	8.2%	-0.69 [-32.81, 31.43]		_	
Trolle 2010	404.17	343.06	30	597.22	397.01	30		-193.05 [-380.81, -5.29]	+		
Zahra 2017	97.9	64.58	20	129.17	44.44	20	7.9%	-31.27 [-65.63, 3.09]		t	
Subtotal (95% CI)			95			99	36.3%	-28.96 [-56.07, -1.84]	•		
Heterogeneity: Tau ² =	580.88; Chi ² = 13	3.45, df = 4 (P	= 0.00	9); l² = 70%							
Test for overall effect:	Z = 2.09 (P = 0.0)	4)									
Total (95% CI)			246			273	100.0%	-10.39 [-27.43, 6.65]	•		
Heterogeneity: Tau ² =	650.49: Chi ² = 60).52. df = 13 (P < 0.0	0001): l ² = 79%				-5 - 1 - 5	+		
Test for overall effect:			2.0							0 100	200
Test for subgroup diffe	(,	= 0 24)	$l^2 = 30.9\%$					Metformin	Placebo	

Test for subgroup differences: $\dot{C}hi^2$ = 2.89, df = 2 (P = 0.24), l^2 = 30.9% Risk of bias legend

1.11 Fasting glucose [mmol/l]

	Met	formin		Pla	acebo			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup		SD [mmol/I]	Total	Mean [mmol/l]	SD [mmol/I]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
1.11.1 BMIÓ25kg/m2										
Chou 2003	5.02	0.67	14	5.07	0.61	16	1.7%	-0.05 [-0.51, 0.41]		
Eisenhardt 2006	4.61	0.31	19	4.82	0.37	19	7.9%	-0.21 [-0.43, 0.01]		
Fleming 2002	5.05	0.64	26	4.95	0.45	39	4.6%	0.10 [-0.18, 0.38]		
Heidari 2019	4.86	0.52	29	5.07	0.51	13	3.3%	-0.21 [-0.55, 0.13]		
Hoeger 2004	5.26	0.73	5	5.9	1	7	0.4%	-0.64 [-1.62, 0.34]		
Hoeger 2008	4.71	0.7	6	4.8	0.3	10	1.1%	-0.09 [-0.68, 0.50]		
Lingaiah 2019 - O	5.1	0.3	17	5.3	0.3	27	11.2%	-0.20 [-0.38, -0.02]		
Lord 2006	5.03	0.53	16	5.05	0.48	16	3.0%	-0.02 [-0.37, 0.33]		
Maciel 2004 - O	4.7	0.72	8	4.69	0.77	6	0.6%	0.01 [-0.78, 0.80]		
Onalan 2005 - O1	4.53	0.56	7	4.43	0.6	9	1.1%	0.10 [-0.47, 0.67]		
Onalan 2005 - O2	4.58	0.71	6	4.55	0.45	6	0.8%	0.03 [-0.64, 0.70]		
Subtotal (95% CI)			153			168	35.6%	-0.13 [-0.23, -0.02]	•	
Heterogeneity: Tau ² =	0.00; Chi ² = 6.34,	df = 10 (P = 0	.79); l²	= 0%						
Test for overall effect:	Z = 2.41 (P = 0.02	2)								
1.11.2 BMI<25kg/m2										
Baillargeon 2004	4.68	0.7	28	4.45	0.75	30	2.7%	0.23 [-0.14, 0.60]		
Lingaiah 2019 - NO	4.9	0.4	40	5	0.4	34	11.1%	-0.10 [-0.28, 0.08]		
Ng 2001	5.1	0.3	8	5.1	0.5	7	2.1%	0.00 [-0.42, 0.42]		
Onalan 2005 - NO	4.08	0.26	15	4.16	0.58	16	3.8%	-0.08 [-0.39, 0.23]		
Subtotal (95% CI)			91			87	19.5%	-0.04 [-0.18, 0.10]	•	
Heterogeneity: Tau ² = Test for overall effect:			17); l² =	0%						
1.11.4 BMI <and>25kg</and>	ı/m2									
Bodur 2018	4.35	0.34	17	4.59	0.25	15	8.8%	-0.24 [-0.45, -0.03]		
Maciel 2004 - NO	4.55	0.62	7	4.3	0.23	8	1.6%	0.25 [-0.24, 0.74]		
Naka 2011	4.83	0.33	15	4.94	0.28	14	7.5%	-0.11 [-0.33, 0.11]		
Trolle 2007	5.29	0.52	23	5.29	0.52	27	4.4%	0.00 [-0.29, 0.29]		
Trolle 2010	5.22	0.44	29	5.44	0.15	29	12.9%	-0.22 [-0.39, -0.05]		
Zahra 2017	5.6	0.29	20	5.86	0.34	20	9.6%	-0.26 [-0.46, -0.06]		
Subtotal (95% CI)			111			113	44.8%	-0.17 [-0.27, -0.07]	•	
Heterogeneity: Tau ² =	0.00; Chi ² = 6.05,	df = 5 (P = 0.3)	30); l ² =	17%						
Test for overall effect:										
Total (95% CI)			355			368	100.0%	-0.13 [-0.19, -0.07]	•	
Heterogeneity: Tau ² =	0.00: Chi ² = 17.5	2. df = 20 (P =	0.62): 1	$^{2} = 0\%$						
Test for overall effect:				_ /0					-1 -0.5 0 0.5 1	
Test for subgroup diffe			0.34) 1	$^{2} = 7.2\%$					Metformin Placebo	
Risk of bias legend		10, a. 2 (i -	0.04), 1							
THAN OF DIAS REGETIC										

1.12HOMA-IR

	Me	tformi	n	PI	acebo			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
1.12.1 BMI≥25										
Eisenhardt 2006	4.13	0.68	19	4.22	0.72	19	22.1%	-0.09 [-0.54, 0.36]	+	
Lingaiah 2019 - O	2.8	1.4	17	3.6	1.9	27	11.1%	-0.80 [-1.78, 0.18]		
Lord 2006	3.86	1.92	18	3.44	1.29	16	9.6%	0.42 [-0.67, 1.51]		
Subtotal (95% CI)			54			62	42.9%	-0.15 [-0.68, 0.37]	•	
Heterogeneity: Tau ² =	0.07; Cł	ni² = 2.	81, df =	: 2 (P =	0.25);	$I^2 = 29^9$	%			
Test for overall effect:	Z = 0.57	(P=0).57)							
1.12.2 BMI<25										
Lingaiah 2019 - NO	1.3	0.6	40	1.8	1.7	34	18.2%	-0.50 [-1.10, 0.10]		
Subtotal (95% CI)			40			34	18.2%	-0.50 [-1.10, 0.10]	•	
Heterogeneity: Not app	olicable									
Test for overall effect:	Z = 1.63	(P=0	0.10)							
1.12.3 BMI>and<25kg	J/m2								1. P.S.	
Bodur 2018	1.18		17		0.59	15	22.3%	-1.02 [-1.46, -0.58]	-	
Trolle 2007	2.24		23	2.25		27	7.9%	-0.01 [-1.26, 1.24]		
Trolle 2010		6.46	24	2.86	9.4	24	0.8%	-1.21 [-5.77, 3.35]		
Zahra 2017	3.5	2.3	20	4.8	1.7	20	7.9%	-1.30 [-2.55, -0.05]		
Subtotal (95% CI)			84			86	38.9%	-0.95 [-1.34, -0.56]	•	
Heterogeneity: Tau ² =				S & .	0.46);	$I^2 = 0\%$,			
Test for overall effect:	Z = 4.74	(P < (0.00001)						
Total (95% CI)			178			182	100.0%	-0.50 [-0.91, -0.09]	•	
Heterogeneity: Tau ² =	0.15; Cł	ni² = 13	8.94, df	= 7 (P =	= 0.05)	; l ² = 50	0%		-4 -2 0 2 4	
Test for overall effect:	Z = 2.39	(P=0	0.02)						Favours Metformin Favours Placebo	
Test for subgroup diffe	rences:	Chi² =	5.89, d	f = 2 (P	= 0.05	5), l² = (66.1%			
Risk of bias legend										

1.13 Total cholesterol [mmol/l]

		formin			acebo			Mean Difference	Mean Difference Risk of E
Study or Subgroup		SD [mmol/I]	Total	Mean [mmol/I]	SD [mmol/l]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.13.1 BMIÓ25kg/m2									
Chou 2003	4.16	0.52	14	5.09	1.4	16	5.1%	-0.93 [-1.67, -0.19]	
Fleming 2002	4.61	0.82	26	4.93	0.96	39	10.3%	-0.32 [-0.76, 0.12]	
Heidari 2019	4.38	0.68	29	4.42	0.63	13	10.7%	-0.04 [-0.46, 0.38]	
Hoeger 2008	3.76	0.65	6	4.06	1.38	10	3.1%	-0.30 [-1.30, 0.70]	
Karimzadeh 2007	4.89	1.52	100	5.19	1.11	10	5.0%	-0.30 [-1.05, 0.45]	
Lord 2006	4.78	0.82	16	5.65	1.15	16	5.6%	-0.87 [-1.56, -0.18]	
Maciel 2004 - O	4.85	0.77	8	4.28	1.12	6	2.9%	0.57 [-0.47, 1.61]	
Onalan 2005 - O1	4.4	0.44	7	5.03	0.98	9	5.3%	-0.63 [-1.35, 0.09]	
Onalan 2005 - O2	4.48	0.74	6	5.36	0.73	6	4.2%	-0.88 [-1.71, -0.05]	
Subtotal (95% CI)			212			125	52.2%	-0.41 [-0.68, -0.14]	•
Heterogeneity: Tau ² = Test for overall effect:			.16); l² =	= 32%					
rest for overall effect:	Z = 2.94 (P = 0.00)	33)							
1.13.2 BMI<25kg/m2									-
Ng 2001	4.5	0.9	8	5.2	1.6	7	1.8%	-0.70 [-2.04, 0.64]	
Onalan 2005 - NO	4.23	0.76	15	4.47	0.43	16	10.3%	-0.24 [-0.68, 0.20]	
Romualdi 2010	3.91	0.58	13	3.71	0.74	10	7.7%	0.20 [-0.36, 0.76]	
Subtotal (95% CI)			36			33	19.8%	-0.11 [-0.48, 0.26]	-
Heterogeneity: Tau ² =			82); l ² =	12%					
Test for overall effect:	Z = 0.58 (P = 0.56	6)							
1.13.4 BMI <and>25kg</and>	J/m2								
Maciel 2004 - NO	4.33	0.79	7	3.81	0.84	8	4.3%	0.52 [-0.31, 1.35]	
Naka 2011	4.5	0.65	15	4.66	0.41	14	11.5%	-0.16 [-0.55, 0.23]	
Trolle 2010	4.86	0.76	36	4.91	0.84	36	12.2%	-0.05 [-0.42, 0.32]	
Subtotal (95% CI)			58			58	28.0%	-0.04 [-0.31, 0.23]	•
Heterogeneity: Tau ² =	0.00; Chi ² = 2.13,	df = 2 (P = 0.3	84); I ² =	6%					
Test for overall effect:	Z = 0.28 (P = 0.78	3)							
Total (95% CI)			306			216	100.0%	-0.24 [-0.43, -0.05]	•
Heterogeneity: Tau ² =	0.04: Chi ² = 20 46	6. df = 14 (P =	0.12): 12	= 32%					
Test for overall effect:			0), 1	OL /O					-2 -1 0 1 2
Test for subaroup diffe		the second	0 14) 12	= 48 9%					Metformin Placebo
source and and and		, u - z (i -	0.17,1	10.070					

Risk of bias legend

1.14 LDL [mmol/l]

		formin			acebo			Mean Difference	Mean Difference	Risk of Bia
Study or Subgroup		SD [mmol/I]	Total	Mean [mmol/l]	SD [mmol/l]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
1.14.1 BMIÓ25kg/m2										
Chou 2003	2.57	0.48	14	3.3	1.42	16	3.4%	-0.73 [-1.47, 0.01]		
Heidari 2019	2.63	0.51	29	2.6	0.52	13	11.2%	0.03 [-0.31, 0.37]		
Hoeger 2008	2.38	0.4	6	2.95	0.7	10	5.8%	-0.57 [-1.11, -0.03]		
Karimzadeh 2007	3.67	0.91	100	3.77	0.86	100	15.7%	-0.10 [-0.35, 0.15]		
Lord 2006	2.87	0.85	16	3.84	1.15	16	3.8%	-0.97 [-1.67, -0.27]		
Maciel 2004 - O	2.97	0.76	8	2.87	0.97	6	2.2%	0.10 [-0.84, 1.04]		
Onalan 2005 - O1	2.5	0.8	7	2.98	0.43	9	4.2%	-0.48 [-1.14, 0.18]		
Onalan 2005 - O2	1.89	1.28	6	2.92	1	6	1.2%	-1.03 [-2.33, 0.27]	· · · · · · · · · · · · · · · · · · ·	
Subtotal (95% CI)			186			176	47.7%	-0.35 [-0.62, -0.08]	•	
Heterogeneity: Tau ² =	0.06; Chi ² = 13.40), df = 7 (P = 0	.06); l ²	= 48%					222 TO	
Test for overall effect:	Z = 2.52 (P = 0.01	1)								
1.14.2 BMI<25kg/m2										
Onalan 2005 - NO	2.46	0.71	15	2.46	0.51	16	8.0%	0.00 [-0.44, 0.44]		
Palomba 2007	1.6	0.6	14	1.8	0.8	13	5.9%	-0.20 [-0.74, 0.34]		
Romualdi 2010	2.27	0.38	13	2.31	0.27	10	14.6%	-0.04 [-0.31, 0.23]	-	
Subtotal (95% CI)			42			39	28.5%	-0.06 [-0.26, 0.15]	+	
Heterogeneity: Tau ² =			34); l² =	0%						
Test for overall effect:	Z = 0.52 (P = 0.61	1)								
1.14.4 BMI <and>25kg</and>	j/m2									
Kelly 2002	2.4	1.89	10	2.8	1.58	10	0.9%	-0.40 [-1.93, 1.13]		
Maciel 2004 - NO	2.59	0.86	7	2.02	0.73	8	2.9%	0.57 [-0.24, 1.38]		
Naka 2011	2.82	0.7	15	2.97	0.39	14	8.8%	-0.15 [-0.56, 0.26]		
Trolle 2010	3.08	0.61	36	3.08	0.84	36	11.2%	0.00 [-0.34, 0.34]	- <u>+</u> -	
Subtotal (95% CI)			68			68	23.8%	-0.01 [-0.26, 0.23]	•	
Heterogeneity: Tau ² =	0.00; Chi ² = 2.66,	df = 3 (P = 0.4)	15); l ² =	0%						
Test for overall effect:	Z = 0.10 (P = 0.92	2)								
Total (95% CI)			296			283	100.0%	-0.16 [-0.30, -0.01]	•	
Heterogeneity: Tau ² =	0.02; Chi ² = 19.07	, df = 14 (P =	0.16); F	² = 27%						_
Test for overall effect:									-2 -1 0 1 2 Metformin Placebo	
Test for subgroup diffe		See and conservation a	0.15). 1	² = 47.9%					wettormin Placebo	
Diele of king Jammed		· · · · ·	-,, .							

Risk of bias legend

Melin *et al.*

1.15 HDL [mmol/l]

	Met	formin		Pla	acebo			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [mmol/l]	SD [mmol/l]	Total	Mean [mmol/l]	SD [mmol/l]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
1.15.1 BMIÓ25kg/m2										
Chou 2003	1	0.28	14	1.08	0.23	16	9.1%	-0.08 [-0.26, 0.10]		
Heidari 2019	1.18	0.31	29	1.32	0.56	13	6.0%	-0.14 [-0.46, 0.18]		
Hoeger 2008	1.13	0.49	6	1.13	0.23	10	4.5%	0.00 [-0.42, 0.42]		
Karimzadeh 2007	0.86	0.26	100	0.68	0.25	100	11.7%	0.18 [0.11, 0.25]	-	
Lord 2006	1.26	0.25	16	1.27	0.19	16	9.9%	-0.01 [-0.16, 0.14]		
Maciel 2004 - O	1.18	0.39	8	0.86	0.19	6	6.2%	0.32 [0.01, 0.63]		
Onalan 2005 - O1	0.51	0.22	7	0.56	0.22	9	8.3%	-0.05 [-0.27, 0.17]		
Onalan 2005 - O2 Subtotal (95% CI)	0.43	0.18	6 186	0.56	0.11	6 176	9.5% 65.2%	-0.13 [-0.30, 0.04] 0.01 [-0.11, 0.14]		
Heterogeneity: Tau ² = 0	102° Chi ² = 23.38	df = 7 (P = 0)		$^{2} = 70\%$						
Test for overall effect: Z			.001), 1	1070						
1.15.2 BMI<25kg/m2										
Onalan 2005 - NO	0.75	0.17	15	1.03	0.27	16	9.8%	-0.28 [-0.44, -0.12]		
Romualdi 2010	1.3	0.3	13	1.25	0.39	10	6.6%	0.05 [-0.24, 0.34]		
Subtotal (95% CI)			28			26	16.4%	-0.14 [-0.46, 0.18]		
Heterogeneity: Tau ² = 0); I ² =	74%						
Test for overall effect: Z	z = 0.85 (P = 0.40))								
1.15.4 BMI <and>25kg/</and>	'm2									
Maciel 2004 - NO	0.99	0.3	7	1.49	0.51	8	4.5%	-0.50 [-0.92, -0.08]		
Naka 2011	1.16	0.23	15	1.11	0.18	14	10.0%	0.05 [-0.10, 0.20]		
Trolle 2007	1.27	1.47	23	1.27	1.43	27	1.6%	0.00 [-0.81, 0.81]		
Trolle 2010	1.27	1.47	36	1.27	1.43	36	2.2%	0.00 [-0.67, 0.67]		
Subtotal (95% CI)			81			85	18.3%	-0.11 [-0.42, 0.20]		
Heterogeneity: Tau ² = 0		· · · · · · · · · · · · · · · · · · ·	2); I ² =	49%						
Test for overall effect: Z	2 = 0.70 (P = 0.48	3)								
Total (95% CI)			295			287	100.0%	-0.03 [-0.14, 0.08]	•	
Heterogeneity: Tau ² = 0		· · · ·	0.0000	1); l² = 73%					-1 -0.5 0 0.5	+
Test for overall effect: Z									Metformin Placebo	4
Test for subgroup differ	ences: Chi ² = 1.1	14, df = 2 (P =	0.56), l ^a	² = 0%						
Risk of bias legend										

1.16 Triglycerides [mmol/l]

		formin			icebo			Mean Difference	Mean Difference	Risk of Bia
Study or Subgroup	Mean [mmol/l]	SD [mmol/l]	Total	Mean [mmol/l]	SD [mmol/l]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
1.16.1 BMIÓ25kg/m2										
Chou 2003	1.3	0.33	14	1.45	0.19	16	11.0%	-0.15 [-0.35, 0.05]		
Fleming 2002	1.62	0.97	26	1.4	0.49	39	4.4%	0.22 [-0.18, 0.62]		
Heidari 2019	1.24	0.54	29	1.08	0.34	13	7.8%	0.16 [-0.11, 0.43]	+	
Hoeger 2008	0.81	0.24	6	0.98	0.28	10	8.2%	-0.17 [-0.43, 0.09]		
Karimzadeh 2007	2.16	0.63	100	2.32	0.6	100	12.4%	-0.16 [-0.33, 0.01]		
Lord 2006	1.44	0.71	16	1.34	0.62	16	3.5%	0.10 [-0.36, 0.56]		
Maciel 2004 - O	1.52	0.98	8	1.21	0.45	6	1.4%	0.31 [-0.46, 1.08]		
Onalan 2005 - O1	1.71	0.4	7	1.87	0.37	9	4.8%	-0.16 [-0.54, 0.22]		
Onalan 2005 - O2	1.21	0.47	6	2.08	0.3	6	3.7%	-0.87 [-1.32, -0.42]	←	
Subtotal (95% CI)			212			215	57.2%	-0.10 [-0.27, 0.06]	•	
Heterogeneity: Tau ² = 0			.009); 1	2 = 61%						
Test for overall effect: Z	z = 1.20 (P = 0.23	3)								
1.16.2 BMI<25kg/m2										
Ng 2001	0.9	0.4	8	1.2	0.7	7	2.3%	-0.30 [-0.89, 0.29]		
Onalan 2005 - NO	1.51	0.22	15	1.61	0.37	16	10.2%	-0.10 [-0.31, 0.11]		
Romualdi 2010	0.75	0.15	13	0.78	0.15	10	15.4%	-0.03 [-0.15, 0.09]	-	
Subtotal (95% CI)			36			33	27.9%	-0.06 [-0.16, 0.05]	•	
Heterogeneity: Tau ² = 0	0.00; Chi ² = 1.00,	df = 2 (P = 0.6	61); I ² =	0%						
Test for overall effect: 2	z = 1.04 (P = 0.30	0)								
1.16.4 BMI <and>25kg/</and>	/m2									
Kelly 2002	2.5	1.26	10	2.6	0.95	10	0.9%	-0.10 [-1.08, 0.88]		
Maciel 2004 - NO	0.3	0.8	7	0.68	0.36	8	2.0%	-0.38 [-1.02, 0.26]		
Naka 2011	1.16	0.44	15	1.23	0.66	14	4.2%	-0.07 [-0.48, 0.34]		
Trolle 2010	1.16	0.63	36	1.37	0.52	36	7.9%	-0.21 [-0.48, 0.06]		
Subtotal (95% CI)			68			68	15.0%	-0.19 [-0.39, 0.02]	•	
Heterogeneity: Tau ² = 0	0.00; Chi ² = 0.72,	df = 3 (P = 0.8)	87); l ² =	0%						
Test for overall effect: Z	z = 1.78 (P = 0.08	3)								
Fotal (95% CI)			316			316	100.0%	-0.11 [-0.20, -0.02]	•	
Heterogeneity: Tau ² = 0	0.01; Chi ² = 23.42	2, df = 15 (P =	0.08); 1	2 = 36%						
Test for overall effect: Z									-1 -0.5 0 0.5 1 Metformin Placebo	
Test for subgroup differ			0.53), l ⁱ	² = 0%					Metionnin Placebo	
Risk of bias legend										

1.17 CRP [Nmol/I] Metformin Placebo Mean Difference Mean Difference **Risk of Bias** Mean [Nmol/I] SD[Nmol/I] Total Mean [Nmol/I] SD[Nmol/I] Total Weight IV, Random, 95% CI IV, Random, 95% CI Study or Subgroup -3.43 [-5.41, -1.45] 15 99.2% Bodur 2018 2.19 5.62 3.43 2 17 Hoeger 2008 -13.33 [-35.82, 9.16] 26.67 19.05 6 40 26.67 10 0.8% Total (95% CI) 23 25 100.0% -3.51 [-5.48, -1.53] Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 1 (P = 0.39); I² = 0% -10 -5 5 10 ò Test for overall effect: Z = 3.49 (P = 0.0005) Favours Metformin Favours Placebo

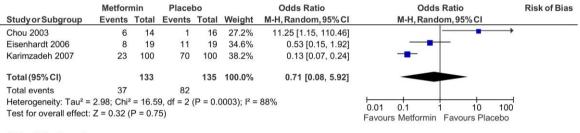
Risk of bias legend

1.18 PAI-1 [ng/ml]

	Met	formin		Pla	icebo			Mean Difference		Mean Diffe	erence	Risk of Bias
Study or Subgroup	Mean [ng/ml]	SD[ng/ml]	Total	Mean [ng/ml]	SD[ng/ml]	Total	Weight	IV, Random, 95% CI		IV, Random	, 95% CI	
Bodur 2018	9.59	2.65	17	14.59	2.5	15	99.8%	-5.00 [-6.79, -3.21]				
Hoeger 2008	45.4	32.2	6	48	45.9	10	0.2%	-2.60 [-40.98, 35.78]	•			>
Total (95% CI)			23			25	100.0%	-4.99 [-6.78, -3.21]		•		
Heterogeneity: Tau ² =	0.00; Chi ² = 0.0	1, df = 1 (P =	0.90);	² = 0%					-20	-10 0	10	20
Test for overall effect:	Z = 5.49 (P < 0.0	00001)								rs Metformin F		

Risk of bias legend

1.19 Oligomenorrhea



Risk of bias legend

1.20 Amenorrhea

	Metfor	min	Place	00		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
Chou 2003	4	14	11	16	45.2%	0.18 [0.04, 0.87]		
Eisenhardt 2006	4	19	9	19	54.8%	0.30 [0.07, 1.23]		
Total (95% CI)		33		35	100.0%	0.24 [0.08, 0.68]	•	
Total events	8		20					
Heterogeneity: Tau ² =	0.00; Chi2	² = 0.20	, df = 1 (F	P = 0.65	5); l ² = 0%			
Test for overall effect:	Z = 2.67 ((P = 0.0	08)				0.01 0.1 1 10 1 Favours Metfromin Favours Placeb	00

Risk of bias legend

1.21 Regular period

	Metfor	min	Place	00		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	
Chou 2003	4	14	4	16	51.7%	1.20 [0.24, 6.06]		
Eisenhardt 2006	8	19	2	19	48.3%	6.18 [1.10, 34.70]		
Total (95% CI)		33		35	100.0%	2.65 [0.53, 13.23]	-	
Total events	12		6					
Heterogeneity: Tau ² =	0.62; Chi ²	= 1.85	, df = 1 (F	P = 0.17	7); l ² = 46°	%		_
Test for overall effect:	Z = 1.19 (P = 0.2	24)				0.02 0.1 1 10 50 Favours Placebo Favours Metform	hin

Risk of bias legend

1.22 Cycle duration (d)

	Me	tformi	n	PI	acebo	,		Mean Difference	Mean D	ifference	Risk o
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Rando	om, 95% CI	
Maciel 2004 - NO	36.4	4.9	7	79.8	16.3	6	67.4%	-43.40 [-56.94, -29.86]			
Maciel 2004 - O	79.9	17.6	8	107.5	24	6	32.6%	-27.60 [-50.35, -4.85]			
Total (95% CI)			15			12	100.0%	-38.25 [-52.77, -23.74]	•		
Heterogeneity: Tau ² = Test for overall effect				100 C 100	= 0.24); I² = 2	7%		-100 -50 Favours Metformin	0 50 Favours Pla	100 cebo

Risk of bias legend

1.23 Adverse effects

	Metform	nin	Place	bo		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
1.23.1 BMI≥25								
Fleming 2002	15	26	5	39	27.9%	9.27 [2.74, 31.39]		
Heidari 2019	1	33	0	15	8.2%	1.43 [0.06, 37.17]		
Ng 2001	5	8	1	7	12.0%	10.00 [0.78, 128.77]		
Subtotal (95% CI)		67		61	48.2%	7.75 [2.73, 21.99]		
Total events	21		6					
Heterogeneity: Tau ² = 0	.00; Chi ²	= 1.16,	df = 2 (P	= 0.56); l² = 0%			
Test for overall effect: Z	2 = 3.85 (F	P = 0.00	001)					
1.23.2 BMI<25								
Palomba 2007	0	14	0	13		Not estimable		
Subtotal (95% CI)		14		13		Not estimable		
Total events	0		0					
Heterogeneity: Not appl	icable							
Test for overall effect: N		able						
1.23.3 BMI>and<25kg/	m2							
Morin-Papunen 2012	11	160	4	160	28.9%	2.88 [0.90, 9.24]	⊢ ∎	
Trolle 2007	29	50	2	50	22.9%	33.14 [7.24, 151.82]		
Subtotal (95% CI)	0.000	210	-	210	51.8%	9.29 [0.83, 104.29]		
Total events	40		6					
Heterogeneity: Tau ² = 2	.57: Chi ²	= 6.37.	df = 1 (P)	= 0.01): ² = 84%			
Test for overall effect: Z								
Total (95% CI)		291		284	100.0%	7.67 [2.74, 21.46]	•	
Total events	61		12					
Heterogeneity: Tau ² = 0	.60; Chi ²	= 7.48.		= 0.11); l² = 46%			-
Test for overall effect: Z							0.005 0.1 1 10 200)
Test for subgroup differ	•		,	(P = 0.	89), l ² = 09	%	Favours Metformin Favours Placebo	
Risk of bias legend					,,. •,			

Figure 2. Continued

However, this effect was not observed in adults with a BMI of <25 kg/m² or in adolescents. We also found evidence (ranging from very low to moderate certainty) that the reduction of WHR, fasting glucose, HOMA-IR, total cholesterol, LDL cholesterol, triglycerides, CRP, and PAI-1 was larger with metformin compared to placebo, with the effect on lipids and fasting glucose being more pronounced in the subgroup with $BMI > 25 \text{ kg/m}^2$. Regarding hyperandrogenism, metformin reduced total testosterone compared with placebo or lifestyle (very low certainty) and lowered FAI in the subgroup with $BMI < 25 \text{ kg/m}^2$, with no change in hirsutism (moderate certainty). Adults using metformin also experienced shortening of the menstrual cycle (very low certainty) compared to those using placebo. Women using metformin had a 7.7-fold risk of adverse gastrointestinal effects (nausea, vomiting, diarrhea, and abdominal pain) compared to women using placebo (moderate certainty).

Metformin and anthropometrics

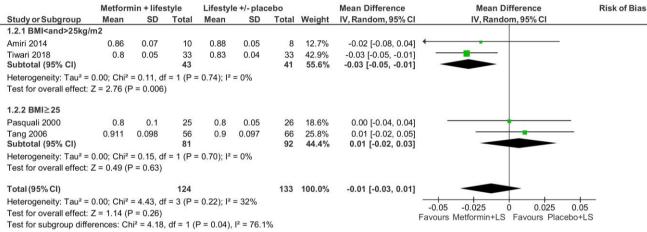
Studies have suggested that metformin might reduce weight through appetite regulatory pathways in the brain, leading to decreased food uptake.⁵⁰ This is particularly important as weight is a primary concern for women with PCOS⁵¹ because weight gain and obesity exacerbate insulin resistance and increase the risk of type 2 diabetes and cardiometabolic diseases in women with PCOS.⁵² In our systematic review, metformin was found to be superior to placebo in lowering BMI in women with a BMI of ≥ 25 kg/m² (moderate certainty). For women with PCOS and a BMI of < 25 kg/m², no significantly increased benefit of metformin use was observed regarding BMI (moderate certainty). The low number of relatively small studies (70 vs 69 participants altogether) could, however, affect this result. A recent study showed that women with PCOS gained more weight annually compared to women

1 Metformin+LS vs placebo+LS

1.1 Weight [kg]

	Metform	nin + lifest	yle	Lifestyl	e +/- place	bo		Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [kg]	SD [kg]	Total	Mean [kg]	SD [kg]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
1.1.1 BMI <and>25kg/i</and>	m2									
Tiwari 2018 Subtotal (95% CI)	55.12	9.9	33 33	59.84	8.83	33 33	51.8% 51.8%	-4.72 [-9.25, -0.19] -4.72 [-9.25, -0.19]	-	
Heterogeneity: Not app	olicable									
Test for overall effect:	Z = 2.04 (P =	0.04)								
1.1.2 BMI≥25										
Pasquali 2000	94	17	10	97	18	8	4.0%	-3.00 [-19.33, 13.33]		
Gambineri 2006	88	14	20	93	16	19	11.9%	-5.00 [-14.46, 4.46]		
Tang 2006	99.9	15	56	99.2	17.3	66	32.3%	0.70 [-5.03, 6.43]		
Subtotal (95% CI)			86			93	48.2%	-1.01 [-5.71, 3.68]	-	
Heterogeneity: Tau ² =	0.00; Chi ² =	1.08, df = 2	2(P = 0.)	58); l ² = 0%						
Test for overall effect:	Z = 0.42 (P =	0.67)								
Total (95% CI)			119			126	100.0%	-2.93 [-6.19, 0.33]	•	
Heterogeneity: Tau ² =	0.00; Chi ² = 2	2.33, df = 3	B(P = 0.	51); l ² = 0%						20
Test for overall effect:	Z = 1.76 (P =	0.08)							-20 -10 0 10 Metformin+ lifestyle Lifestyle +/- plac	
Test for subgroup diffe	rences: Chi ²	= 1.24, df	= 1 (P =	$0.26), I^2 = 12$	9.5%				Medonnin+ mescyle Ellestyle +/- plac	ebu
Risk of bias legend				325.5						

1.2 WHR



Risk of bias legend

1.3 BMI [kg/m2]

	Metforn	nin + lifestyle		Lifestyl	e +/- placebo			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [kg/m2]	SD [kg/m2]	Total	Mean [kg/m2]	SD [kg/m2]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
1.3.1 BMI <and>25kg/</and>	/m2									
Ladson 2011	38	7.8	22	38.3	8	16	4.1%	-0.30 [-5.40, 4.80]		
Fux Otta 2010	31.53	4.98	14	34.16	4.95	15	8.1%	-2.63 [-6.25, 0.99]		
Amiri 2014	28.9	5	25	29.2	3.6	26	18.5%	-0.30 [-2.70, 2.10]		
Tiwari 2018 Subtotal (95% CI)	24.16	4.37	33 94	25.86	3.59	33 90	28.5% 59.2%	-1.70 [-3.63, 0.23] -1.29 [-2.63, 0.05]	•	
Heterogeneity: Tau ² =	0.00; Chi ² = 1.50), df = 3 (P = 0	.68); l ² =	0%					78	
Test for overall effect:	Z = 1.89 (P = 0.0	06)								
1.3.2 BMIÓ25kg/m2										
Hoeger 2004	41.72	9.18	5	40.63	7.98	8	1.1%	1.09 [-8.67, 10.85]		-
Pasquali 2000	36.4	7.4	10	38	6.2	8	2.7%	-1.60 [-7.88, 4.68]		
Gambineri 2006	33	5	20	35	5	19	10.8%	-2.00 [-5.14, 1.14]		
Tang 2006 Subtotal (95% CI)	37.1	5.04	56 91	37.4	6.3	66 101	26.2% 40.8%	-0.30 [-2.31, 1.71] -0.80 [-2.41, 0.82]	•	
Heterogeneity: Tau ² = Test for overall effect:			.80); I² =	0%						
Total (95% CI)			185			191	100.0%	-1.09 [-2.12, -0.06]	•	
Heterogeneity: Tau ² = Test for overall effect: Test for subgroup diffe <u>Risk of bias legend</u>	Z = 2.08 (P = 0.0	04)							-10 -5 0 5 1 Metformin+ lifestyle Lifestyle +/- pla	0 cebo

Figure 3. Forest plots presenting meta-analyses on different outcomes when comparing metformin and lifestyle to placebo and lifestyle. Abbreviations: CI: confidence interval; SD, standard deviation.

1.4 Hirsutism (FGS)

	Metform	in + lifes	style	Lifestyl	e +/- plac	cebo		Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	I IV, Random, 95% CI	
Amiri 2014	7.08	3.8	25	4.8	2.4	26	39.5%	2.28 [0.53, 4.03]]	
Gambineri 2006	10.9	8.6	20	8	5.1	19	18.0%	2.90 [-1.51, 7.31]]	
Tiwari 2018	3.46	2.66	33	4	3.34	33	42.5%	-0.54 [-2.00, 0.92]	g —	
Total (95% CI)			78			78	100.0%	1.19 [-1.13, 3.52]		
Heterogeneity: Tau ² =	2.76; Chi ² =	= 6.85, d	f = 2 (P =	= 0.03); l ²	= 71%				-4 -2 0 2 4	
Test for overall effect:	Z = 1.01 (P	= 0.31)							Favours Metformin+LS Favours Placebo	+LS

Risk of bias legend

1.5 SHBG (nmol/l)

	Metform	nin + lifes	style	Lifestyle	e +/- plac	ebo		Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Amiri 2014	26.9	18.9	25	24.14	11.3	26	19.0%	2.76 [-5.83, 11.35]		
Gambineri 2006	19.2	10.6	20	21.2	11.5	20	29.8%	-2.00 [-8.85, 4.85]		
Pasquali 2000	16.7	8.1	10	13.8	2.1	8	51.2%	2.90 [-2.33, 8.13]		
Total (95% CI)			55			54	100.0%	1.41 [-2.33, 5.15]		
Heterogeneity: Tau ² =	0.00; Chi ² :	= 1.36, d	f = 2 (P =	= 0.51); l ² =	= 0%				-10 -5 0 5	10
Test for overall effect:	Z = 0.74 (P	9 = 0.46)							-10 -5 0 5 Favours Placebo+LS Favours Metform	

Risk of bias legend

1.6 Total testosterone [Nmol/I]

	Metforn	nin + lifestyle		Lifestyle	e +/- placebo			Mean Difference	Mean Difference	Risk of Bia
Study or Subgroup	Mean [Nmol/I]	SD[Nmol/I]	Total	Mean [Nmol/I]	SD[Nmol/l]	Total	Weight	IV, Random, 95% C	IV, Random, 95% CI	
1.6.1 BMI <and>25kg/</and>	m2									
Amiri 2014	2.32	1.3	26	2.9	2.7	26	2.9%	-0.58 [-1.73, 0.57]		
Fux Otta 2010	2.65	0.49	14	3.06	0.83	15	12.7%	-0.41 [-0.90, 0.08]		
Tiwari 2018 Subtotal (95% CI)	1.5	0.47	33 73	1.54	0.43	33 74	32.7% 48.2%	-0.04 [-0.26, 0.18] -0.16 [-0.43, 0.11]		
Heterogeneity: Tau ² =	0.01; Chi ² = 2.46,	df = 2 (P = 0.2)	9); l ² = 1	9%						
Test for overall effect:	Z = 1.15 (P = 0.2	5)								
1.6.2 BMI≥25										
Gambineri 2006	1.77	1.01	20	1.73	0.59	20	11.9%	0.04 [-0.47, 0.55]		
Pasquali 2000	1.7	0.87	10	1.63	0.45	8	8.7%	0.07 [-0.55, 0.69]		
Tang 2006 Subtotal (95% CI)	1.9	0.6	56 86	2.3	0.7	66 94	31.2% 51.8%	-0.40 [-0.63, -0.17] -0.18 [-0.52, 0.16]		
Heterogeneity: Tau ² =	0.04; Chi ² = 3.75,	df = 2 (P = 0.1	5); l ² = 4	7%						
Test for overall effect:	Z = 1.06 (P = 0.2	9)								
Total (95% CI)			159			168	100.0%	-0.20 [-0.40, 0.01]	•	
Heterogeneity: Tau ² =	0.02; Chi ² = 7.65,	df = 5 (P = 0.1	8); l ² = 3	5%						
Test for overall effect:	Z = 1.91 (P = 0.0	6)	8577						-1 -0.5 0 0.5 1 Favours Metformin+LS Favours Placeb	0 1 5
Test for subgroup diffe	erences: Chi ² = 0.0	01, df = 1 (P = 0)	0.91), l ²	= 0%					Favours Menormint LS Favours Placed	UTLO

Risk of bias legend

1.7 Androstenedione [I	nmol/l] Metform	nin + lifestyle		Lifestyl	e +/- placebo			Mean Difference		Mea	n Differe	nce		Risk of Bias
Study or Subgroup	Mean [nmol/l]	SD[nmol/l]	Total	Mean [nmol/l]	SD[nmol/l]	Total	Weight	IV, Random, 95% C	1	IV, Ra	andom, 95	% CI		
Fux Otta 2010	9.01	4.22	14	10.34	5.03	15	40.7%	-1.33 [-4.70, 2.04]		-			
Gambineri 2006	11.59	4.29	20	10.3	3.91	20	59.3%	1.29 [-1.25, 3.83]		-	-		
Total (95% CI)			34			35	100.0%	0.22 [-2.30, 2.75]		+			
Heterogeneity: Tau ² =	1.11; Chi ² = 1.48	, df = 1 (P = 0.	22); l² =	32%					-10			5	10	
Test for overall effect:	Z = 0.17 (P = 0.8	6)								Metformin	+LS Fave	ours Pla		

Risk of bias legend

1.8 Fasting insulin [Pmol/l]

	Metform	in + lifestyle		Lifestyle	e +/- placebo			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [Pmol/I]	SD [Pmol/I]	Total	Mean [Pmol/I]	SD [Pmol/I]	Total	Weight	IV, Random, 95% C	IV, Random, 95% CI	
1.8.1 BMI <and>25kg</and>	J/m2									
Amiri 2014	95.14	49.31	25	83.4	70.14	15	27.6%	11.74 [-28.68, 52.16]		
Fux Otta 2010 Subtotal (95% CI)	65.42	35.63	14 39	106.32	37.22	15 30	33.3% 60.9%	-40.90 [-67.42, -14.38] -16.88 [-68.27, 34.51]		
Heterogeneity: Tau ² = Test for overall effect		and the second	- 0.03),	1 - 7070						
1.8.2 BMI≥25										
Gambineri 2006	97.22	34.22	20	76.39	48.61	20	33.5%	20.83 [-5.22, 46.88]	· +∎-	
Pasquali 2000 Subtotal (95% CI)	150	216.67	10 30	131.94	100	8 28	5.6% 39.1%	18.06 [-133.06, 169.18 20.75 [-4.92, 46.42]		
Heterogeneity: Tau ² = Test for overall effect		Contract of the second second	97); l² =	0%						
Total (95% CI)			69			58	100.0%	-2.40 [-41.04, 36.25]	-	
Heterogeneity: Tau ² =	= 984.22; Chi ² = 11	1.56, df = 3 (P	= 0.009)	; l² = 74%						
Test for overall effect	: Z = 0.12 (P = 0.9	0)							-100 -50 0 50 100 Favours Metformin+LS Favours Placebo+LS	2
Test for subgroup diff	ferences: Chi ² = 1.	65, df = 1 (P =	0.20), l ²	= 39.3%					Favours Mediornin -23 Favours Placeborts	2

Risk of bias legend

1.9 Fasting glucose [Mmol/I]

	Metform	nin + lifestyle		Lifestyl	e +/- placebo			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [Mmol/I]	SD[Mmol/I]	Total	Mean [Mmol/l]	SD[Mmol/I]	Total	Weight	IV, Random, 95% C	I IV, Random, 95% CI	
Amiri 2014	4.55	0.45	25	4.76	0.57	26	44.6%	-0.21 [-0.49, 0.07	1 - +	
Fux Otta 2010	4.73	0.62	14	4.94	0.6	15	20.6%	-0.21 [-0.65, 0.23	i —•+-	
Gambineri 2006	5.05	0.5	20	4.94	0.56	20	34.7%	0.11 [-0.22, 0.44	i 	
Total (95% CI)			59			61	100.0%	-0.10 [-0.31, 0.11]	•	
Heterogeneity: Tau ² =	0.01; Chi ² = 2.39,	df = 2 (P = 0.3	80); I ² = 1	6%					-1 -0.5 0 0.5 1	
Test for overall effect:	Z = 0.91 (P = 0.3	6)							Favours Metformin+LS Favours Placebo+	LS

Risk of bias legend

1.10 OGTT (Mg/dl/120min) [Mmol/I]

	Metforn	nin + lifestyle		Lifestyl	e +/- placebo			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [Mmol/I]	SD[Mmol/I]	Total	Mean [Mmol/I]	SD [Mmol/I]	Total	Weight	IV, Random, 95% C	I IV, Random, 95% CI	
Amiri 2014	6.22	1.69	25	5.31	1.74	26	47.9%	0.91 [-0.03, 1.85		
Fux Otta 2010	4.81	1.15	14	5.27	0.93	15	52.1%	-0.46 [-1.22, 0.30	·	
Total (95% CI)			39			41	100.0%	0.20 [-1.15, 1.54	-	
Heterogeneity: Tau ² =	0.75; Chi ² = 4.90,	df = 1 (P = 0.0	3); l ² = 8	30%						
Test for overall effect:	Z = 0.29 (P = 0.7	7)							Favours Metformin+LS Favours Placebo+LS	

Risk of bias legend

1.11 Total cholesterol [mmol/l]

	Metforn	nin + lifestyle		Lifestyl	e +/- placebo			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [mmol/l]	SD [mmol/l]	Total	Mean [mmol/l]	SD [mmol/l]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Amiri 2014	4.43	0.6	25	4.43	0.72	26	36.2%	0.00 [-0.36, 0.36]	_ + _	
Fux Otta 2010	4.1	0.76	14	4.78	0.74	15	28.6%	-0.68 [-1.23, -0.13]		
Tang 2006	5.14	1.03	56	4.88	1.15	66	35.2%	0.26 [-0.13, 0.65]		
Total (95% CI)			95			107	100.0%	-0.10 [-0.58, 0.38]		
Heterogeneity: Tau ² =	0.13; Chi ² = 7.62,	df = 2 (P = 0.0	2); l ² = 7	4%						-
Test for overall effect:	Z = 0.42 (P = 0.6	7)							-1 -0.5 0 0.5 1 Favours Metformin+LS Favours Placebo+L	S

Risk of bias legend

1.12 LDL [Mmol/I]

	Metforn	nin + lifestyle		Lifestyl	e +/- placebo			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [Mmol/I]	SD [Mmol/I]	Total	Mean [Mmol/I]	SD[Mmol/I]	Total	Weight	IV, Random, 95% C	IV, Random, 95% CI	
Amiri 2014	2.61	0.51	25	2.56	0.61	26	57.0%	0.05 [-0.26, 0.36]		
Fux Otta 2010	1.97	0.58	14	2.28	0.7	15	29.3%	-0.31 [-0.78, 0.16]		
Gambineri 2006	2.69	0.88	20	3.08	1.37	20	13.6%	-0.39 [-1.10, 0.32]		
Total (95% CI)			59			61	100.0%	-0.12 [-0.39, 0.16]	-	
Heterogeneity: Tau ² = Test for overall effect		and the second se	81); I ² = 1	4%					-1 -0.5 0 0.5 Favours Metformin+LS Favours Placebo	+

Risk of bias legend

1.13 HDL [Mmol/I]

	Metform	nin + lifestyle		Lifestyl	e +/- placebo			Mean Difference	Mean Difference Risk of Bia
Study or Subgroup	Mean [Mmol/I]	SD[Mmol/I]	Total	Mean [Mmol/I]	SD[Mmol/I]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Amiri 2014	1.07	0.29	25	1.21	0.24	26	35.4%	-0.14 [-0.29, 0.01]	
Fux Otta 2010	1.12	0.21	14	1.12	0.21	15	32.4%	0.00 [-0.15, 0.15]	
Gambineri 2006	1.16	0.21	20	1.22	0.28	20	32.2%	-0.06 [-0.21, 0.09]	
Total (95% CI)			59			61	100.0%	-0.07 [-0.16, 0.02]	-
Heterogeneity: Tau ² =	0.00; Chi ² = 1.70,	df = 2 (P = 0.4)	3); I ² = 0	0%					
Test for overall effect:	Z = 1.55 (P = 0.12	2)							-0.2 -0.1 0 0.1 0.2 Favours Metformin+LS Favours Placebo+LS

Risk of bias legend

1.14 Triglycerides [Mmol/I]

	Metform	nin + lifestyle		Lifestyl	e +/- placebo			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [Mmol/I]	SD [Mmol/I]	Total	Mean [Mmol/I]	SD[Mmol/I]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Amiri 2014	1.38	0.46	25	1.45	0.86	26	29.1%	-0.07 [-0.45, 0.31]		
Fux Otta 2010	1.3	0.8	14	1.4	0.7	15	13.7%	-0.10 [-0.65, 0.45]	• • •	
Gambineri 2006	1.1	0.41	20	1.14	0.73	20	30.6%	-0.04 [-0.41, 0.33]		
Tang 2006	2.04	1.01	56	1.78	1.21	66	26.6%	0.26 [-0.13, 0.65]		+
Total (95% CI)			115			127	100.0%	0.02 [-0.18, 0.23]		
Heterogeneity: Tau ² =	0.00; Chi ² = 1.93,	df = 3 (P = 0.5)	59); l ² = (0%						
Test for overall effect:	Z = 0.22 (P = 0.8	3)							-0.5 -0.25 0 0.25 0.5 Favours Metformin+LS Favours Placebo+LS	

Risk of bias legend

1.15 Menstrual cycles/6 months

	Metform	nin + life	style	Lifestyle	+/-plac	cebo		Mean Difference	Mean Difference Risl	k of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Gambineri 2006	4.3	1.5	20	3.2	1.2	20	78.9%	1.10 [0.26, 1.94]		
Hoeger 2004	2.4	2.55	5	2.13	2.1	8	7.9%	0.27 [-2.40, 2.94]		
Pasquali 2000	4.7	2.1	10	3.5	2.3	8	13.2%	1.20 [-0.86, 3.26]		
Total (95% CI)			35			36	100.0%	1.05 [0.30, 1.80]	-	
Heterogeneity: Tau ² =	0.00; Chi2 :	= 0.36, d	f = 2 (P =	= 0.83); l ² =	= 0%					
Test for overall effect:	Z = 2.75 (F	9 = 0.006)						-2 -1 0 1 2 Favours Placebo+LS Favours Metformin+LS	

Risk of bias legend

1.16 Adverse gastrointestinal effects

	Metformi	n+LS	Placebo	+LS		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	
Gambineri 2006	2	20	0	20	5.0%	5.54 [0.25, 123.08]		→
Ladson 2011	19	55	6	59	47.2%	4.66 [1.70, 12.81]		
Pasquali 2000	1	10	0	8	4.3%	2.68 [0.10, 75.12]		
Tang 2006	11	69	6	74	43.4%	2.15 [0.75, 6.17]		
Total (95% CI)		154		161	100.0%	3.28 [1.64, 6.57]	•	
Total events	33		12					
Heterogeneity: Tau ² =	0.00; Chi ² =	1.21, d	f = 3 (P =)	0.75); l ²	= 0%			100
Test for overall effect:	Z = 3.35 (P	= 0.000	8)				0.01 0.1 1 10 Favours Metformin+LS Favours Placebo	100 o+LS

Risk of bias legend

Figure 3. Continued

without PCOS.⁵³ In the light of these findings, non-obese women with PCOS could benefit from metformin treatment to prevent further weight gain.

Metformin and metabolic effects

From a mechanistic perspective, metformin is known to increase insulin sensitivity by inhibiting the production of hepatic glucose, as well as inhibiting gluconeogenesis and lipogenesis, resulting in a decrease in circulating insulin and glucose.⁵⁴ For insulin resistance-related outcomes, the reduction of fasting glucose and HOMA-IR (moderate certainty) is larger with metformin compared with placebo. Both lean and overweight women with PCOS have been found to have greater insulin resistance/hyperinsulinemia compared to women without PCOS,⁷ which is believed to explain the increased risk for diabetes observed in women with overweight and PCOS.^{55,56} In addition, our systematic review showed that the reduction of CRP and PAI-1 (very low certainty) was larger with metformin than placebo. Metformin has been shown to reduce CRP in both obese and non-obese women with PCOS.³⁰ CRP and PAI-1 are reliable markers of inflammation and sensitive predictors of cardiovascular morbidity.⁵⁷

Metformin and hyperandrogenism

Insulin suppresses hepatic SHBG secretion and acts on the ovary to promote thecal cell androgen synthesis⁵⁸ with the

1 Metformin versus lifestyle

1.1 BMI [kg/m2]

n [kg/m2]	00 11-01						Mean Difference	Mean Difference	Risk of Bias
	SD [kg/m2]	Total	Mean [kg/m2]	SD [kg/m2]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
35.7	8.6	6	34.9	7	8	11.7%	0.80 [-7.62, 9.22]	•	
36.15	5.29	6	40.63	7.98	8	17.2%	-4.48 [-11.44, 2.48]		
30.3	3.5	17	30.1	5.5	13	71.1%	0.20 [-3.22, 3.62]		
		29			29	100.0%	-0.53 [-3.42, 2.35]	•	
Chi ² = 1.51,	df = 2 (P = 0	.47); 12	= 0%						
36 (P = 0.72	2)							Metformin Lifestyle	
	36.15 30.3 Chi² = 1.51	36.15 5.29 30.3 3.5	36.15 5.29 6 30.3 3.5 17 29 Chi ² = 1.51, df = 2 (P = 0.47); l ²	36.15 5.29 6 40.63 30.3 3.5 17 30.1 29 Chi ² = 1.51, df = 2 (P = 0.47); l ² = 0%	36.15 5.29 6 40.63 7.98 30.3 3.5 17 30.1 5.5 29 Chi ² = 1.51, df = 2 (P = 0.47); i ² = 0%	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	36.15 5.29 6 40.63 7.98 8 17.2% -4.48 [-11.44, 2.48] 30.3 3.5 17 30.1 5.5 13 71.1% 0.20 [-3.22, 3.62] 29 29 100.0% -0.53 [-3.42, 2.35] Chi² = 1.51, df = 2 (P = 0.47); l² = 0%	$\begin{array}{cccccccccccccccccccccccccccccccccccc$

Risk of bias legend

1.2SHBG[(nmol/l)]

	Met	formin		Life	estyle			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [(nmol/l)]	SD [(nmol/l)]	Total	Mean [(nmol/l)]	SD [(nmol/l)]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Hoeger 2008	21.1	8.4	6	32	21.7	8	36.2%	-10.90 [-27.37, 5.57]		
Hoeger 2004	23.8	8.16	6	34.44	15.23	8	63.8%	-10.64 [-23.05, 1.77]		
Total (95% CI)			12			16	100.0%	-10.73 [-20.65, -0.82]	-	
Heterogeneity: Tau ² =	0.00; Chi ² = 0.00, 0	df = 1 (P = 0.98	B); I ² = 0)%				20 10 10 10 10 10 10 10 10 10 10 10 10 10	-20 -10 0 10 20	
Test for overall effect:	Z = 2.12 (P = 0.03))							-20 -10 0 10 20 Lifestyle Metformin	

Risk of bias legend

1.3 Total testosterone [nmol/l]

	Met	formin		Life	estyle			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [nmol/l]	SD[nmol/l]	Total	Mean [nmol/l]	SD[nmol/l]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Hoeger 2008	1.72	1.08	6	2.24	1.05	8	1.5%	-0.52 [-1.65, 0.61]		
Hoeger 2004	1.57	0.58	6	1.78	0.86	8	3.4%	-0.21 [-0.97, 0.55]		
Esfahanian 2013	0.5	0.18	17	0.66	0.21	13	95.1%	-0.16 [-0.30, -0.02]		
Total (95% CI)			29			29	100.0%	-0.17 [-0.31, -0.03]	•	
Heterogeneity: Tau ² =	0.00; Chi ² = 0.40	df = 2 (P = 0	.82); l ² :	= 0%					-1 -0.5 0 0.5 1	
Test for overall effect:	Z = 2.35 (P = 0.0	2)							Metformin Lifestyle	

Risk of bias legend

1.4 Fasting insulin [pmol/l]

	Met	formin		Lif	estyle			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [pmol/l]	SD[pmol/l]	Total	Mean [pmol/l]	SD[pmol/l]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Hoeger 2008	137.5	72.22	6	152.78	72.92	8	10.2%	-15.28 [-92.04, 61.48]		
Esfahanian 2013	79.86	43.06	17	63.19	29.17	13	89.8%	16.67 [-9.22, 42.56]		
Total (95% CI)			23			21	100.0%	13.41 [-11.13, 37.94]	-	
Heterogeneity: Tau ² = Test for overall effect: 2			.44); I²	= 0%					-50 -25 0 25 50 Metformin Lifestyle	_

Risk of bias legend

1.5 Fasting glucose [mmol/l]

	Met	formin		Lif	estyle			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [mmol/l]	SD [mmol/l]	Total	Mean [mmol/l]	SD [mmol/l]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Hoeger 2008	4.71	0.7	6	4.54	0.51	8	18.2%	0.17 [-0.49, 0.83]		
Hoeger 2004	4.74	0.38	6	5.07	0.58	8	28.9%	-0.33 [-0.83, 0.17]		
Esfahanian 2013	5.06	0.57	17	5.49	0.36	13	52.8%	-0.43 [-0.76, -0.10]	-	
Total (95% CI)			29			29	100.0%	-0.29 [-0.59, 0.01]	-	
Heterogeneity: Tau ² = Test for overall effect:			28); l² =	= 21%					-1 -0.5 0 0.5 Metformin Lifestyle	1

Risk of bias legend

Figure 4. Forest plots presenting meta-analyses on different outcomes when comparing metformin to lifestyle. Abbreviations: CI: confidence interval; SD, standard deviation.

1.6 Total cholesterol [mmol/l]

	Met	formin		Lif	estyle			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [mmol/l]	SD [mmol/l]	Total	Mean [mmol/I]	SD [mmol/l]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Esfahanian 2013	5.12	1.28	17	4.55	1.01	13	48.3%	0.57 [-0.25, 1.39]		
Hoeger 2008	3.76	0.65	6	4.04	0.8	8	51.7%	-0.28 [-1.04, 0.48]		
Total (95% CI)			23			21	100.0%	0.13 [-0.70, 0.96]		
Heterogeneity: Tau ² =	0.20; Chi ² = 2.22	, df = 1 (P = 0.	14); l² =	= 55%					-1 -0.5 0 0.5 1	
Test for overall effect:	Z = 0.31 (P = 0.76	6)							Metformin Lifestyle	

Risk of bias legend

1.7 LDL [mmol/l]

	Met	formin		Lif	estyle			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [mmol/l]	SD [mmol/l]	Total	Mean [mmol/l]	SD [mmol/l]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Esfahanian 2013	2.56	0.59	6	2.12	0.82	8	41.5%	0.44 [-0.30, 1.18]		
Hoeger 2008	2.38	0.4	17	2.62	0.84	13	58.5%	-0.24 [-0.73, 0.25]		
Total (95% CI)			23			21	100.0%	0.04 [-0.61, 0.70]		
Heterogeneity: Tau ² =	0.13; Chi ² = 2.25	, df = 1 (P = 0.	13); l² :	= 56%					-1 -0.5 0 0.5 1	
Test for overall effect:	Z = 0.13 (P = 0.90))							Metformin Lifestyle	

Risk of bias legend

1.8 HDL [mmol/l]

	Met	formin		Lif	estyle			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [mmol/l]	SD [mmol/l]	Total	Mean [mmol/l]	SD [mmol/l]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Esfahanian 2013	1.09	0.41	6	1.22	0.32	8	29.6%	-0.13 [-0.53, 0.27]		
Hoeger 2008	1.13	0.49	17	1.04	0.2	13	70.4%	0.09 [-0.17, 0.35]		
Total (95% CI)			23			21	100.0%	0.02 [-0.19, 0.24]	-	
Heterogeneity: Tau ² = Test for overall effect:			36); l² =	= 0%					-0.5 -0.25 0 0.25 0.5 Metformin Lifestyle	

Risk of bias legend

1.9 Triglycerides [mmol/l]

	Met	formin		Lif	estyle			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [mmol/l]	SD [mmol/l]	Total	Mean [mmol/l]	SD [mmol/l]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Esfahanian 2013	1.55	0.78	17	1.2	0.85	13	49.4%	0.35 [-0.24, 0.94]		
Hoeger 2008	0.81	0.24	6	1.24	0.77	8	50.6%	-0.43 [-1.00, 0.14]		
Total (95% CI)			23			21	100.0%	-0.04 [-0.81, 0.72]		
Heterogeneity: Tau ² =			06); l ² =	= 71%					-1 -0.5 0 0.5 1	
Test for overall effect:	Z = 0.12 (P = 0.91	1)							Metformin Lifestyle	

Risk of bias legend

1.10 CRP [nmol/I]

	Met	formin		Life	estyle			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean [nmol/l]	SD[nmol/l]	Total	Mean [nmol/l]	SD[nmol/l]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Hoeger 2008	2.8	2	6	3.8	3.6	8	15.2%	-1.00 [-3.96, 1.96]		
Esfahanian 2013	3.7	1.9	17	4.2	1.6	13	84.8%	-0.50 [-1.75, 0.75]		
Total (95% CI)			23			21	100.0%	-0.58 [-1.73, 0.58]	•	
Heterogeneity: Tau ² = Test for overall effect:			.76); I² :	= 0%					-4 -2 0 2 4 Metformin Lifestyle	

Risk of bias legend

Figure 4. Continued

net effect of increasing circulating free testosterone concentrations. Low SHBG levels are a feature of PCOS and associated co-morbidities including type 2 diabetes, insulin resistance, and obesity.⁵⁹ By enhancing insulin sensitivity, metformin indirectly decreases biochemical hyperandrogenism.⁶⁰ Indeed, we found metformin to be superior to placebo in lowering FAI in non-obese women with PCOS (moderate certainty). Metformin was also superior in lowering testosterone compared with placebo or lifestyle (very low certainty). The ability of metformin to reduce androgen levels in women with hyperandrogenic PCOS has been shown in previous studies, which have also suggested that the effect is more pronounced in non-obese women.⁶¹ However, metformin is similar to placebo regarding effects on SHBG and hirsutism (low and moderate certainty). This is in line with findings from the previous evidence-based guideline.²

Metformin and lipids

Women with PCOS have a more unfavorable lipid profile than women without PCOS.^{62,63} We found that overall, metformin was superior in lowering total cholesterol, LDL cholesterol, and triglycerides (low certainty) compared to placebo. Subanalyses according to BMI revealed that the effect of metformin on lipids was seen mainly in the subgroup of women with BMI ≥ 25 kg/m².

Metformin and menstrual cycles

Hyperandrogenism and hyperinsulinemia are associated with reproductive dysfunction such as anovulation in PCOS. Metformin has been used largely based on expert opinion to promote improved ovulatory function, increase menstrual cycle regularity and reproductive outcomes in women with PCOS.⁶⁰ Our meta-analyses showed that adults using metformin experienced shortening of the menstrual cycle and more menstrual cycles per 6 months (very low certainty). Bridger et al.³³ found that the number of adolescents with restored menses was also larger after metformin compared to placebo (very low certainty). These findings are consistent with previous systematic reviews comparing metformin to placebo with or without lifestyle.^{61,64,65}

Metformin and adverse gastrointestinal effects

Women using metformin had an increased risk of gastrointestinal adverse effects compared to placebo (moderate certainty). The reported adverse effects were mild and self-limited including nausea, vomiting, diarrhea, and abdominal pain but adverse effects were not systematically reported. Clinical experience of metformin use in other conditions has revealed that adverse effects can be minimized by starting metformin treatment at a lower dose such as 500 mg twice daily followed by weekly 500 mg increments until the maximum dose (2.5 g in adults and 2.0 g in adolescents) is achieved. Extended-release preparations may also decrease the gastrointestinal side effects.^{2,66}

With this systematic review, we advance knowledge updating the previous systematic review and guidelines² to demonstrate higher certainty evidence for effects on BMI, as well as confirming benefits of metformin on WHR, lipids, and glucose. Novel findings included establishing that metformin was also superior in lowering HOMA-IR, CRP, and PAI and shortening the menstrual cycle compared to placebo.

The main strength of this systematic review is that it is the most extensive, up to date review investigating the effect of metformin in women with PCOS with or without obesity, including both adults and adolescents. The results and conclusions are derived from International gold-standard evidence synthesis methodologies and will directly inform the 2023 internationally endorsed evidence-based guidelines in PCOS to guide clinical practice, with priorities defined by consumers, key scientific bodies, and experts in the field. The absence of larger studies on women with BMI $<25 \text{ kg/m}^2$ and adolescents with PCOS is a limitation and an area for future research. Other limitations include the risk of language bias, since studies conducted in languages other than English were excluded. We acknowledge that critical appraisal is subjective, which is why both ROB and grading assessments were conducted by two authors independently. Despite large sample sizes in our meta-analyses, certainty of evidence was low or very low for some outcomes. The key reason for this was the poorly described randomization process or lack of blinding in some of

the included RCTs, leading to a high ROB. Reporting of adverse effects in the RCTs was non-systematic.

In conclusion, whilst lifestyle intervention is fundamental in PCOS management, those with PCOS should be offered the option of metformin if outcomes align to patient priorities. Our systematic review shows clear benefits of metformin on anthropometric and metabolic outcomes compared with placebo. Metformin should be considered in adult women with PCOS and BMI ≥ 25 kg/m² for prevention of weight gain and management of weight and metabolic disorders. Metformin may be considered in adults with BMI < 25 kg/m² and adolescents with PCOS, acknowledging more limited evidence. Metformin has mild gastrointestinal side effects that are generally dose dependent and short-term. We acknowledge that the use of metformin in PCOS is evidence-based but off label.

This evidence informed the recommendations in the 2023 International PCOS Evidence-based Guideline, which recommends that health professionals need to inform women and discuss the evidence, possible concerns and side effects of metformin and regulators should be encouraged to consider approval of use of metformin in PCOS.

Acknowledgments

This systematic review is part of the ongoing 2023 update of the International Evidence-based PCOS Guideline update, led by H.T. Senior experts within the guideline working group included T.P., D.R., P.M.S., C.T.T., A.P., S.F.W., A.M., and HT. C.C.T. and A.M. are the evidence team leads for the PCOS Guideline update. J.M., M.F., and S.A. performed the search, screening, ROB, and GRADE assessments. J.M. and M.F. did the data extraction. J.M. drafted the first version of the manuscript, which was revised by the other authors. All authors critically reviewed and approved the final version of the manuscript.

Supplementary material

Supplementary material is available at European Journal of Endocrinology online.

Funding

J.M. received funding from Finska Läkaresällskapet and Orionin Tutkimussäätiö. M.F. received funding from the Iris foundation and Stiftelsen Handlanden Hjalmar Svenssons. A.M. and H.T. are supported by research fellowships from the National Health and Medical Research Council (NHMRC) of Australia. C.T.T. is supported by the Royal Australasian College of Physicians Foundation Roger Bartop Research Establishment Fellowship.

Conflict of interest: J.M. reports a postdoc research grant from Orion Research Foundation. D.R. reports an honorarium from Novo Nordisk for a lecture on PCOS and obesity. T.P. is on the editorial board of the *European Journal of Endocrinology* but was not involved in the review or editorial process of this paper. The other authors have no conflicts to declare.

Data availability

The data underlying this article is secondary, aggregated from already published work.

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