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Systematic Review and Meta Analysis

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

Johanna Melin,[1,2,*] Maria Forslund,[1,3] Simon Alesi,[1] Terhi Piltonen,[4] Daniela Romualdi,[5] Poli Mara Spritzer,[6] Chau Thien Tay,[1] Alexia Pena,[7] Selma Feldman Witchel,[8] Aya Mousa,[1,†] and Helena Teede[1,9,†]

[1]Monash Centre for Health Research and Implementation, School of public Health and Preventive Medicine, Monash University, Clayton, VIC 3168, Australia
[2]Department of Obstetrics and Gynecology, University of Helsinki, Helsinki University Hospital, 00014 Helsinki, Finland
[3]Department of Obstetrics and Gynecology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, 40530 Gothenburg, Sweden
[4]Department of Obstetrics and Gynecology, Research Unit of Clinical Medicine and Medical Research Centre, Oulu University Hospital, University of Oulu, 90014 Oulu, Finland
[5]Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, 00168 Rome, Italy
[6]Gynecological Endocrinology Unit, Division of Endocrinology, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS 90035-003, Brazil
[7]Discipline of Paediatics, The University of Adelaide and Robinson Research Institute, Adelaide, South Australia 5005, Australia
[8]Division of Pediatric Endocrinology, Department of Pediatrics, UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA 15224, United States
[9]Endocrine and Diabetes Units, Monash Health, Clayton, VIC 3169, Australia

***Corresponding author:** Johanna Melin, Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Level 1, 43-51 Kanooka Grove, Clayton, VIC 3168, Australia. Email: johanna.melin@hus.fi

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/m^2), 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.

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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 study[6] 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 review[13] 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 RoB2[16] 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

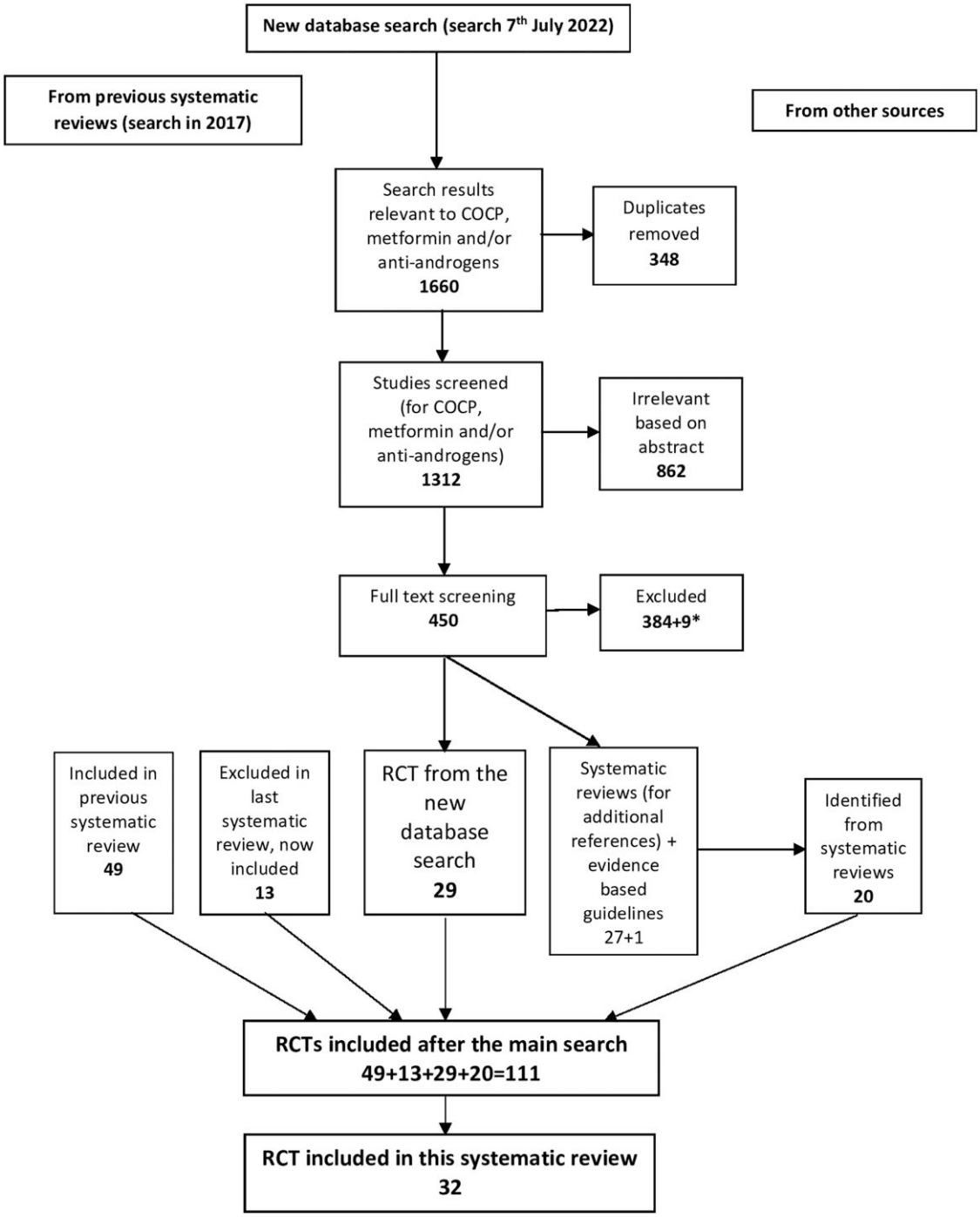


Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart of study selection. Abbreviations: COCP, combined oral contraceptive pill; RCT, randomized controlled study. * Included in COCP and/or anti-androgen questions, but not for metformin.

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/m^2 and those with BMI ≥ 25 kg/m^2. Studies using other BMI cutoffs were categorized as BMI $<$ or >25 kg/m^2. When meta-analyses could not be performed, study data are presented narratively.

Table 1. Characteristics of included studies.

Author, year, country	Population	Duration (months)	Sample size per group	Intervention details	Mean BMI (kg/m²)	Mean age (years)	Outcomes	Type of analysis and subgroup	ROB
Amiri et al. 2014 Iran	Adult women with PCOS	6	(1) LS + metformin = 25 (2) Placebo + LS = 26	LS + metformin 850 mg × 2/day	>19 and <35 kg/m²	18–40	WHR, BMI, SHBG, T, hirsutism	Meta BMI < or >25 Adults	ROB moderate
Baillargeon et al. 2004 Venezuela	Non-obese, adult women with PCOS	6	(1) Metformin = 28 (2) Placebo = 30	Metformin 850 mg × 1/day	(1) 24.6 ± 0.2 (2) 24.6 ± 0.2	(1) 27.7 ± 0.9 (2) 27.2 ± 0.9	Weight, whr, BMI, SHBG, T, DHEAS	Meta BMI<25 Adults	ROB moderate
Bodur et al. 2018 Turkey	Non-obese, adult women with PCOS	6	(1) Metformin = 29 (2) Placebo = 17	(1) Metformin 1700 mg/day	(1) 25.06 ± 3.08 (2) 23.82 ± 2.80	(1) 26.24 ± 3.96 (2) 29.18 ± 5.20	f-gluc, crp, PAI, HOMA-IR	Meta BMI < or >25 Adults	ROB high
Bridger et al. 2006 Canada	Adolescents with PCOS	3	(1) Metformin = 11 (2) Placebo = 10	Metformin 750 mg × 2/day	(1) 33.6 ± 5.6 (2) 30.81 ± 3.0	(1) 16.07 ± 0.97 (2) 16.08 ± 1.39	BMI, T, f-gluc, HOMA-IR, lipids, restored menses	Individual BMI < or >25 Adolescents	ROB low
Chou et al. 2003 Brazil	Adult, obese women with PCOS	3	(1) Metformin = 14 (2) Placebo = 16	Metformin 500 mg × 3/day	(1) 35.6 ± 4.9 (2) 37.4 ± 6	(1) 24 ± 5 (2) 24.5 ± 6.1	WHR, BMI, SHBG, T, f-insulin, f-gluc, lipids	Meta BMI≥25 Adults	ROB moderate
Eisenhardt et al. 2006 Germany	Adult, obese women with PCOS	3	(1) Metformin = 19 (2) Placebo 19	Metformin 500 mg × 3/day	(1) 28.9 (23.3–34.1)[a] (2) 32.4 (27.9 –37.5)[a]	(1) 27.0 (24.9 –30.7)[a] (2) 29.7 (26.8 –32.4)[a]	BMI, SHBG, T, f-insulin, f-gluc, HOMA, DHEAS	Meta BMI≥25 Adults	ROB moderate
Esfahanian et al. 2013 Iran	Adult, obese women with PCOS	3	(1) Metformin = 17 (2) LS = 13	Metformin 1000–2000 mg/day	(1) 31.1 ± 3.3 (2) 34.1 ± 5.4	(1) 21.9 ± 9.3 (2) 20 ± 4.6	BMI, WHR, T, DHEAS, f-insulin, f-gluc, lipids, HOMA, CRP, adverse effects	Meta BMI≥25 Adults	ROB high
Fleming et al. 2002 UK	Adult, obese women with PCOS	4	(1) Metformin = 26 (2) Placebo = 39	Metformin 850 mg × 2/day	(1) 34.2 (31.7–36.7)[a] (2) 35.0 (32.6–37.3)[a]	(1) 28.6 (26.9–30.3)[a] (2) 29.2 (27.5–30.7)[a]	BMI, SHBG, T, f-insulin, f-gluc, lipids	Meta BMI≥25 Adults	ROB high
Fux Otta et al. 2010 Argentina	Adult women with PCOS	4	(1) LS + metformin = 14 (2) LS + placebo = 15	LS + metformin 750 mg × 2/day	(1) 32.4 ± 6.7 (2) 35.6 ± 5.0	(1) 25.5 ± 4.8 (2) 24.7 ± 3.5	BMI	Meta BMI < or >25 Adults	ROB moderate
Gambineri et al. 2006 Italy	Adult, obese women with PCOS	6	(1) LS + metformin = 20 (2) LS + placebo = 20	LS + metformin 500 mg × 3/day	(1) 35 ± 4 (2) 37 ± 5	(1) 28 ± 8 (2) 26 ± 5	Weight, BMI, SHBG, T, hirsutism	Meta BMI≥25 Adults	ROB low
Heidari et al. 2019 USA	Adult, obese women with PCOS	3	(1) Metformin = 33 (2) Placebo = 15	Metformin 1500 mg/day	(1) 36.2 ± 10.3 (2) 37.7 ± 8.1	(1) 32.4 ± 7.5 (2) 33.1 ± 5.9	Weight, WHR, BMI, T, f-insulin, f-gluc, lipids, CRP, HOMA-IR	Meta and individual BMI≥25 Adults	ROB moderate
Hoeger et al. 2004 USA[a]	Adult, obese women with PCOS	6	(1) Metformin = 6 (2) LS + placebo = 8 (3) LS + metformin = 5 (4) Placebo = 7	(1) Metformin 850 mg × 2/day	(1) 37.1 ± 4.9 (2) 40 ± 7.4 (3) 41.7 ± 6.2 (4) 37.1 ± 4.6	(1) 29.5 ± 6.4 (2) 27.1 ± 4.3 (3) 30.4 ± 5.4 (4) 27.1 ± 4.5	BMI, SHBG, FAI, T, f-insulin, f-gluc	Meta BMI≥25 Adults	ROB moderate
Hoeger et al. 2008 USA	Adolescents, obese with PCOS	6	(1) Metformin = 6 (2) Placebo = 10 (3) LS = 8	(1) Metformin 850 mg × 2/day	(1) 35.0 ± 8.2 (2) 34.9 ± 6.7 (3) 36.0 ± 6.2	(1) 16 ± 1.7 (2) 15.4 ± 1.7 (3) 15.4 ± 1.2	BMI, hirsutism, SHBG, FAI, T, f-insulin, f-gluc, lipids, CRP, PAI	Meta BMI≥25 Adolescents	ROB moderate
Karimzadeh et al. 2007 Iran	Adult, obese women with PCOS	3	(1) Metformin = 100 (2) Placebo = 100	(1) Metformin 500 mg/day for 1 week and then 500 mg × 3/day	(1) 28.8 ± 3.2 (2) 29.5 ± 4.7	(1) 27.2 ± 6.8 (2) 28.6 ± 7.4	Lipids	Meta BMI≥25 Adults	ROB high
Kelly et al. 2002 UK (Crossover)	Adult women with PCOS	6	10 in total	(1) Metformin 500 mg/day to 500 mg × 3/day, over 3 weeks.	NR	NR	Hirsutism, SHBG, FAI, T, DHEAS	Meta BMI < or >25 Adults	ROB high
Ladson et al. 2011 USA	Adult women with PCOS	6	(1) LS + metformin = 22 (2) LS + placebo = 16	LS + metformin 500 mg × 4/day	(1) 38.0 ± 7.8 (2) 38.3 ± 8.0	(1) 29 ± 4.5 (2) 28.8 ± 4.6	BMI	Meta BMI < or >25 Adults	ROB high

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 BMI<25 BMI>25 Adults	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	Meta 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 Denmark	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, f-insulin, f-gluc, lipids, HOMA-IR	Meta BMI < or >25 Adults	ROB moderate
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]	Weight, T	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	Weight, BMI, f-insulin, f-gluc, HOMA-IR	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 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.
[a]Median and range (1–3 quartile).
[b]Mean (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.

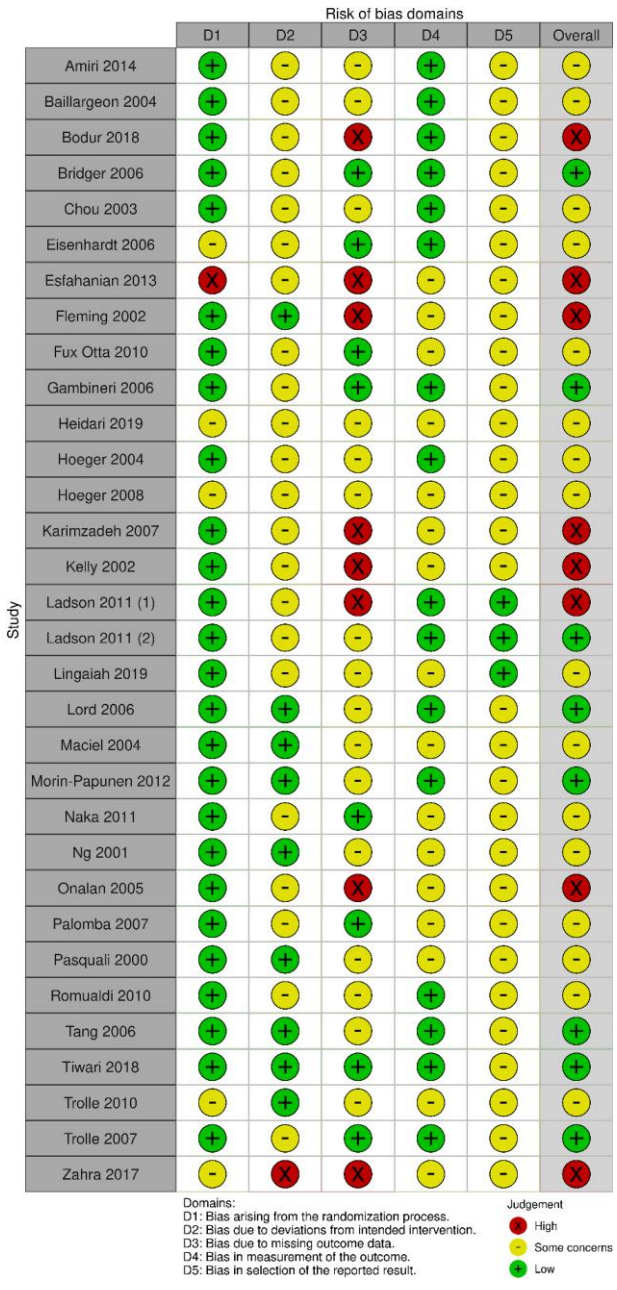
The majority of studies were on adult populations ($n = 29$ in adults, $n = 3$ in adolescents). The ROB in the included studies varied from low to high ROB ($n = 8$ high ROB, $n = 16$ moderate ROB, and $n = 8$ low ROB studies) and are reported in Table 2. Overall, evidence was mostly of moderate or low 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 one[33] 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/m^2), 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/m^2), 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 ≥ 25 kg/m^2, the reduction of BMI (MD −0.89, 95% CI −1.43 to −0.35 kg/m^2) (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. Forest 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/m^2) (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 ≥ 25 kg/m^2, one study[34] focused on adolescents.

Regarding critical outcomes, no significant difference in BMI was observed (MD −0.53, 95% CI −3.42 to 2.35 kg/m^2). 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/m^2 compared with placebo, with or without lifestyle change.

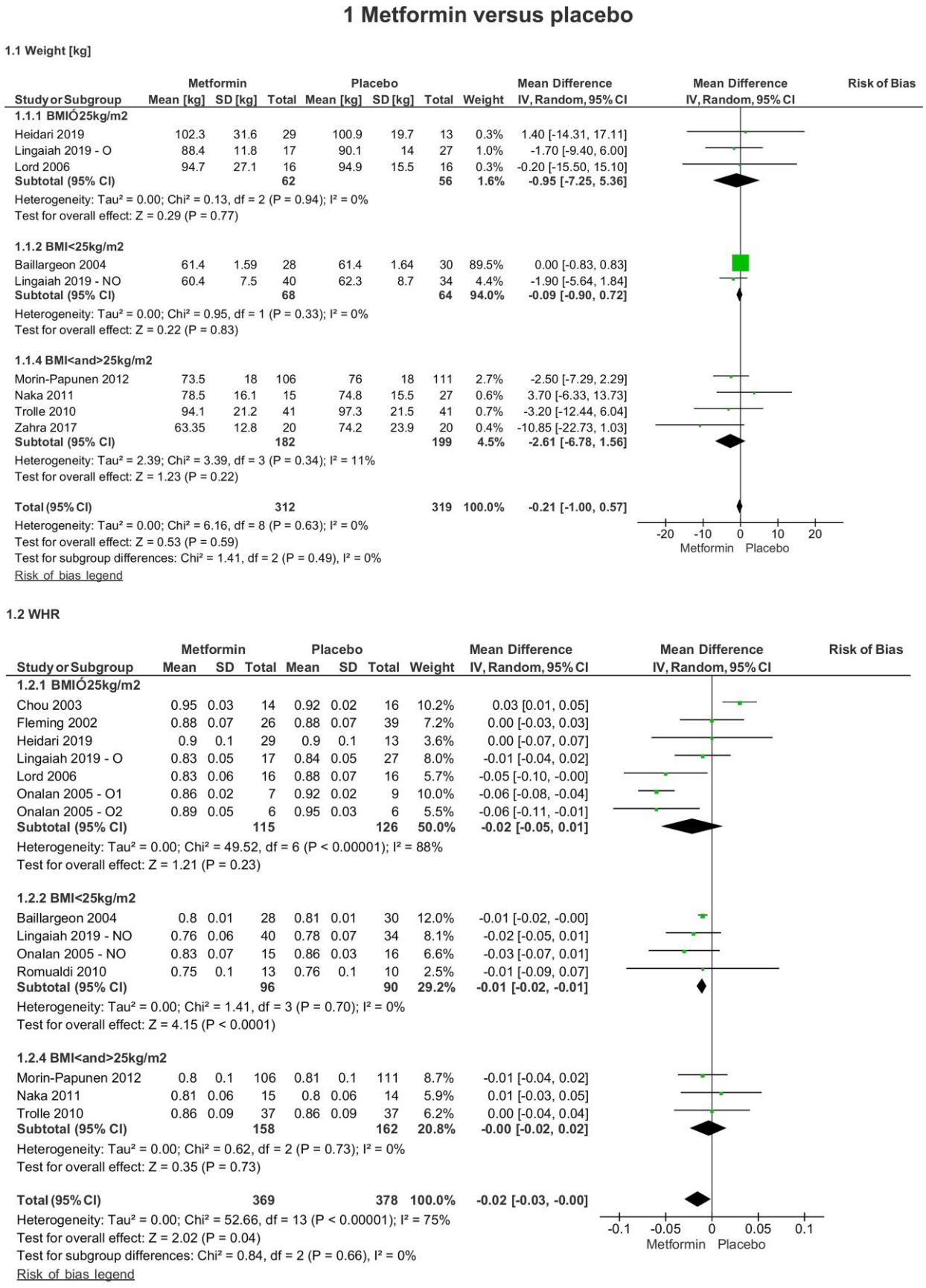
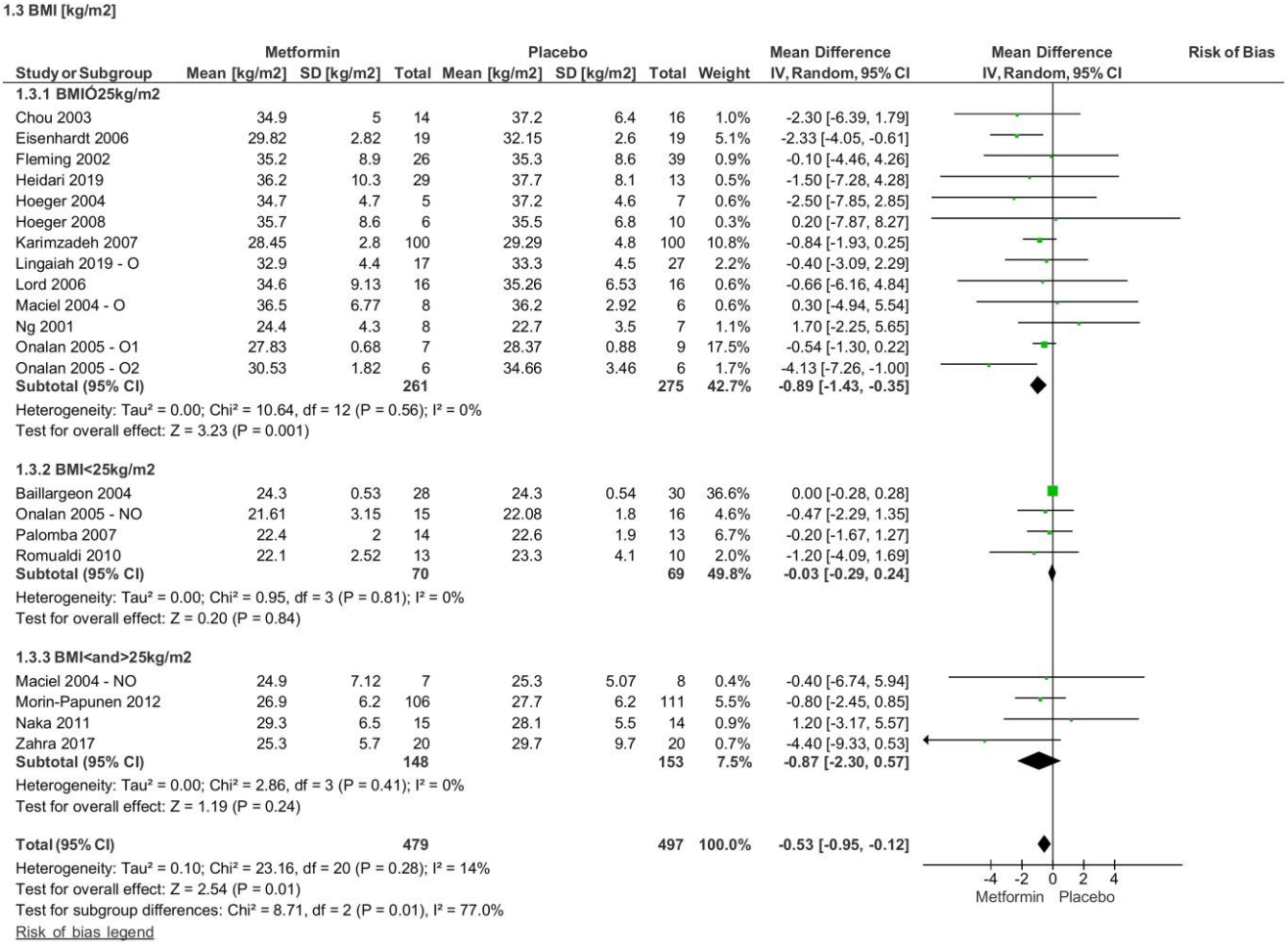


Figure 2. Forest plots presenting meta-analyses on different outcomes when comparing metformin to placebo. Abbreviations: CI: confidence interval; SD, standard deviation.



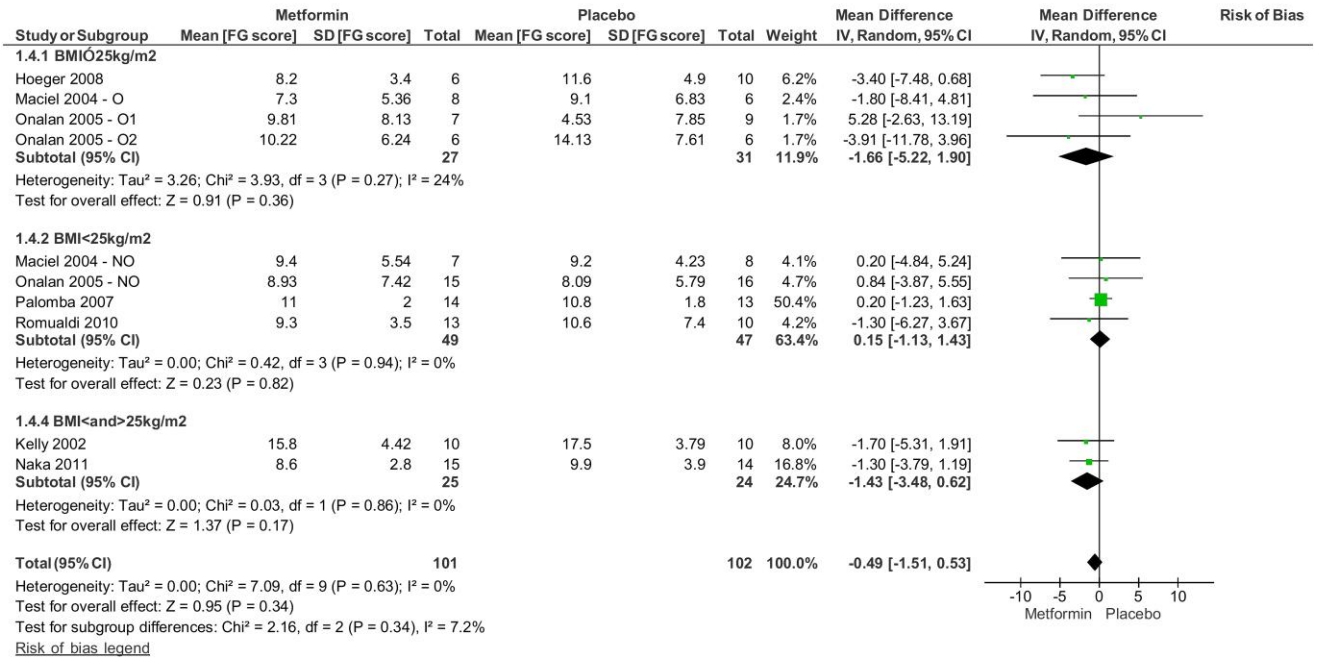
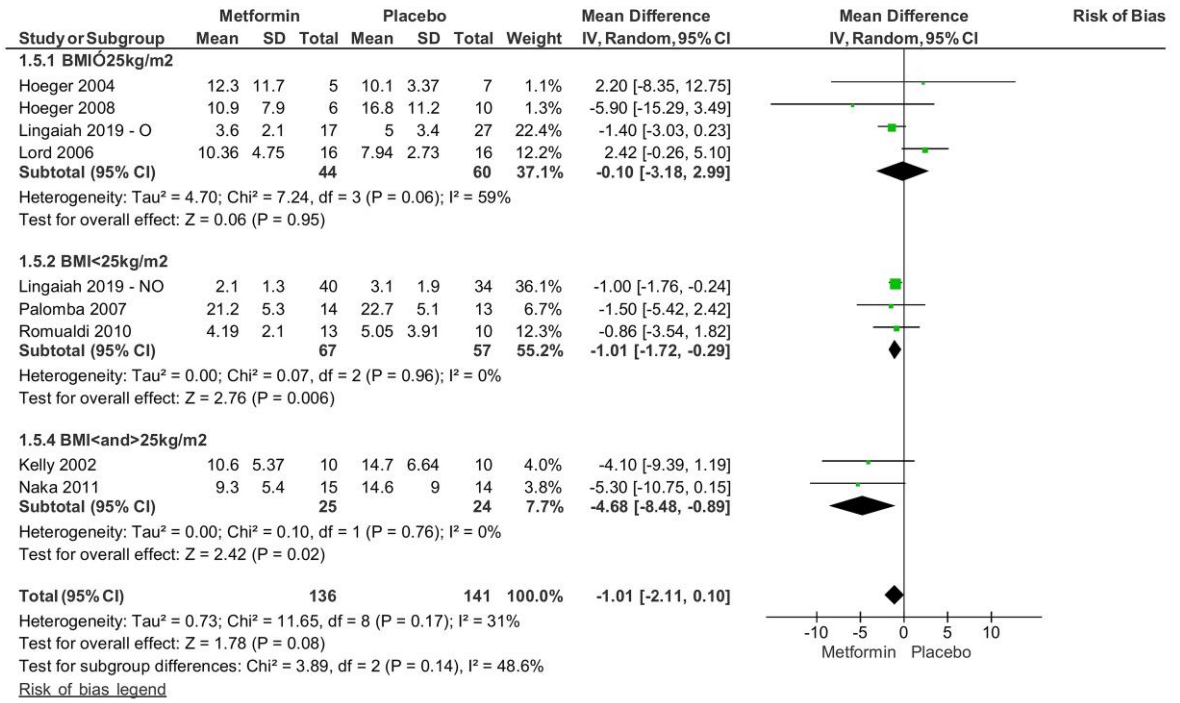


Figure 2. Continued

1.5 FAI



1.6 SHBG [nmol/l]

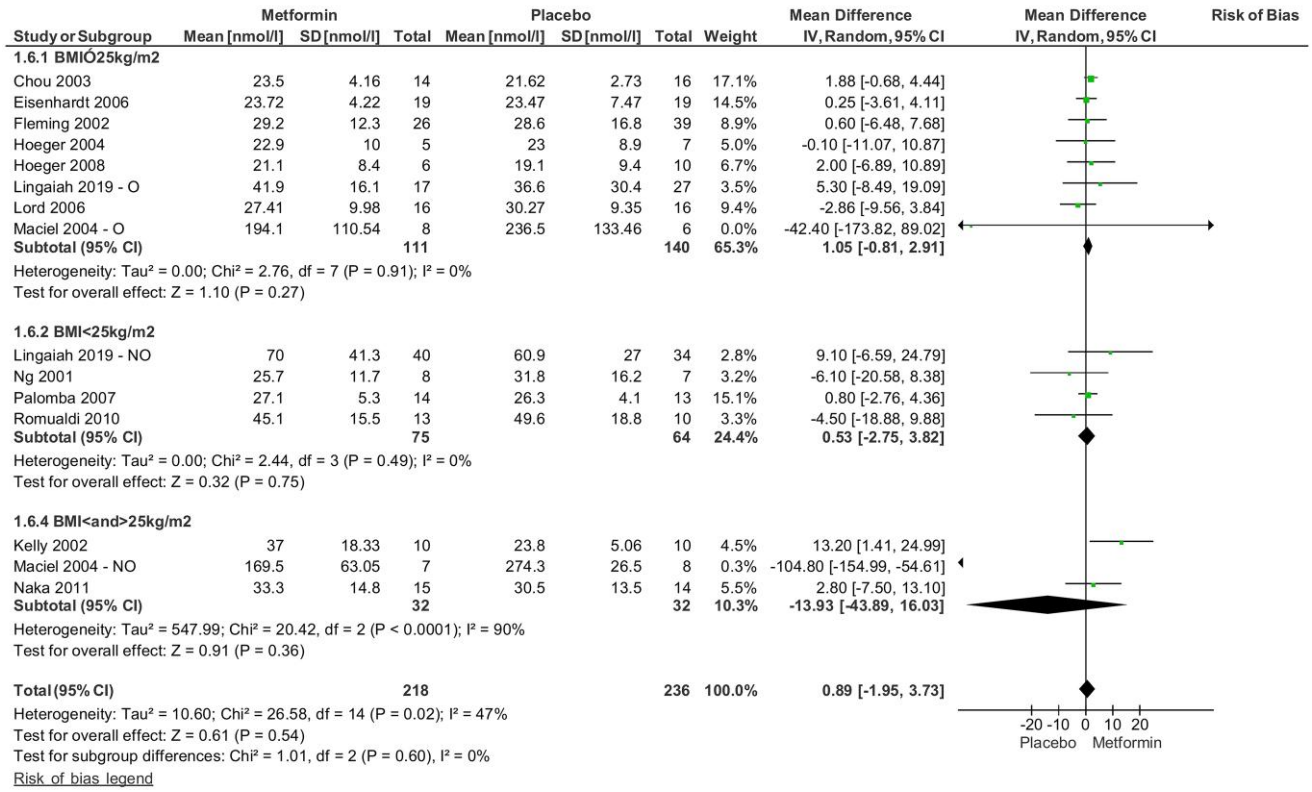
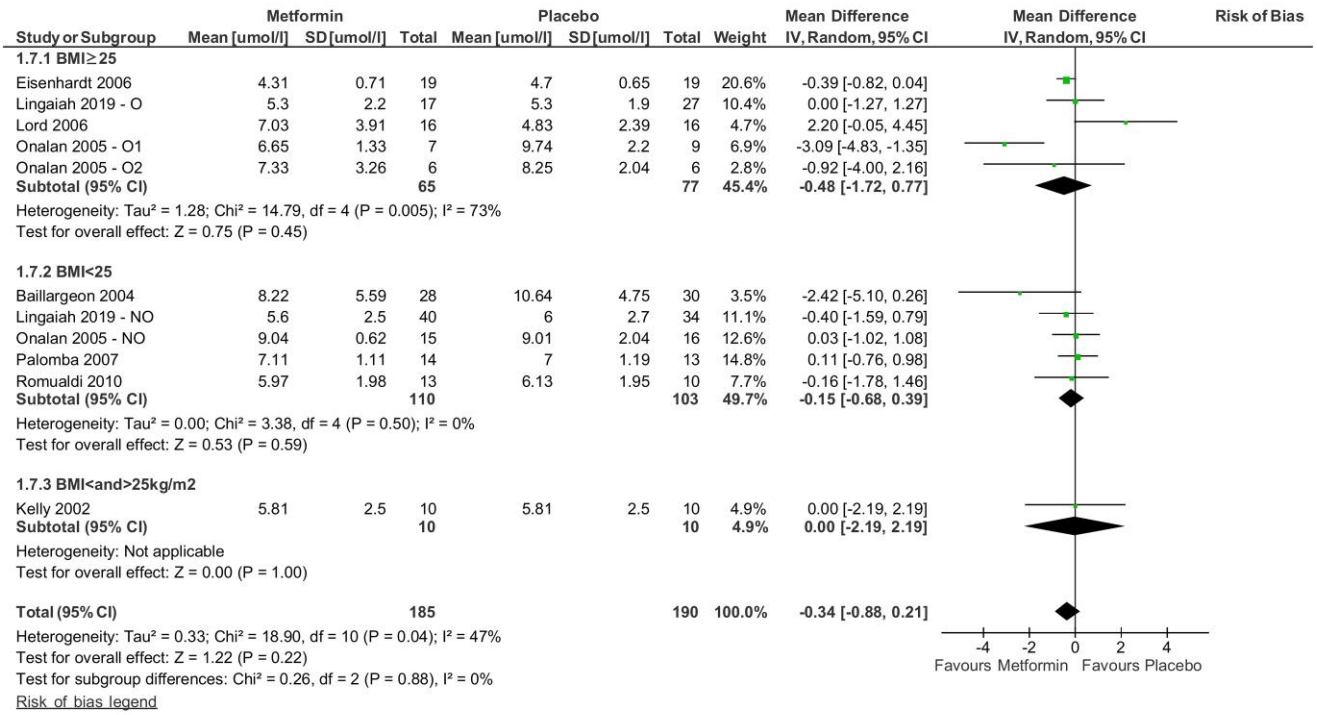


Figure 2. Continued

1.7 DHEAS [umol/l]



1.8 Total testosterone [nmol/l]

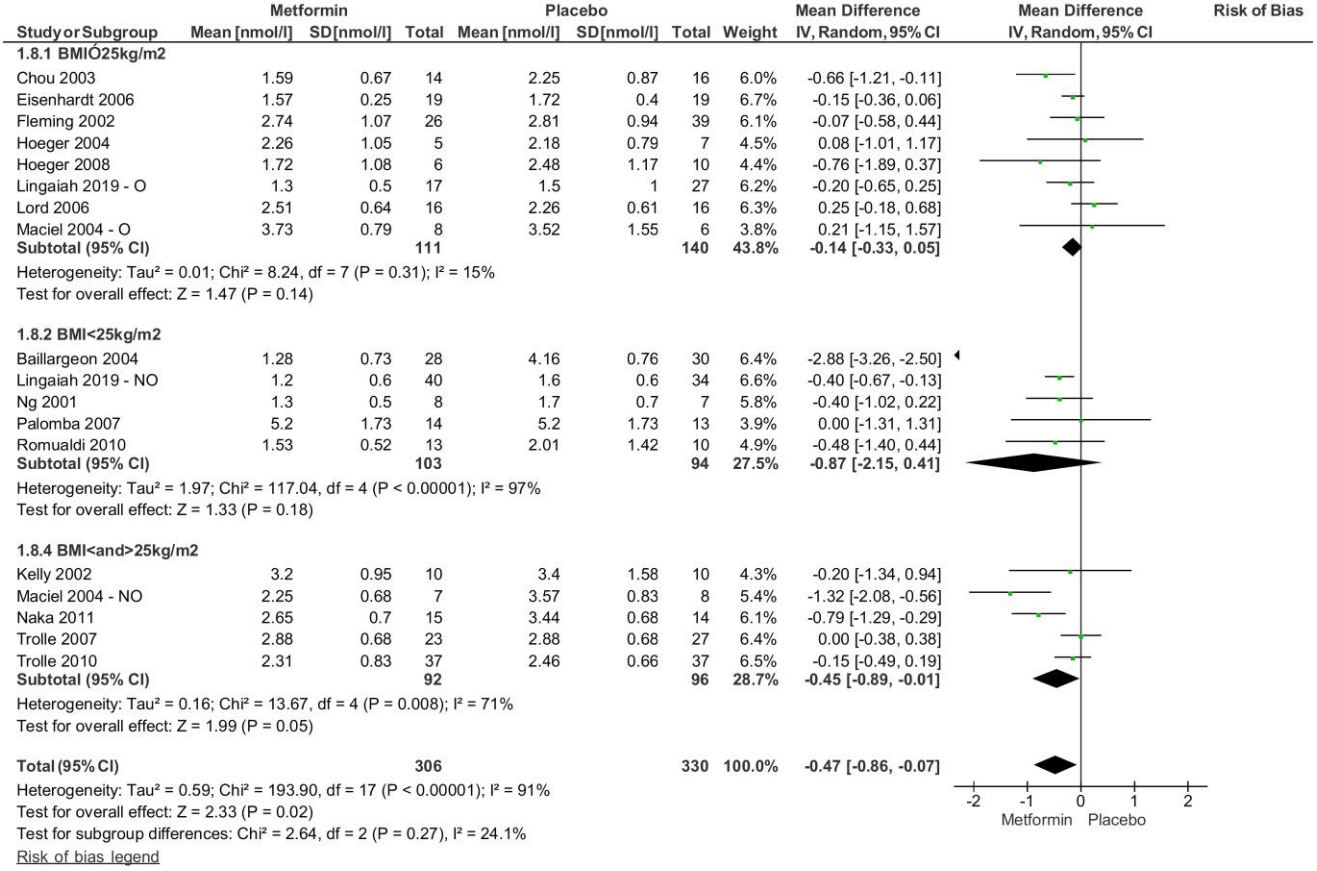
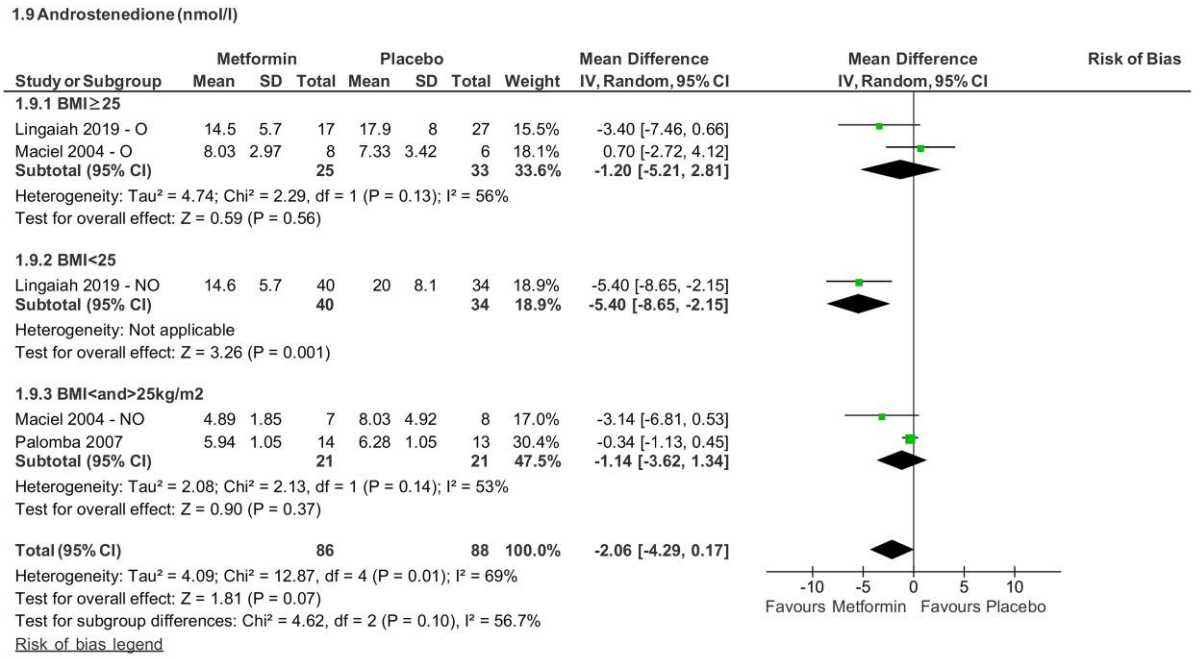


Figure 2. Continued



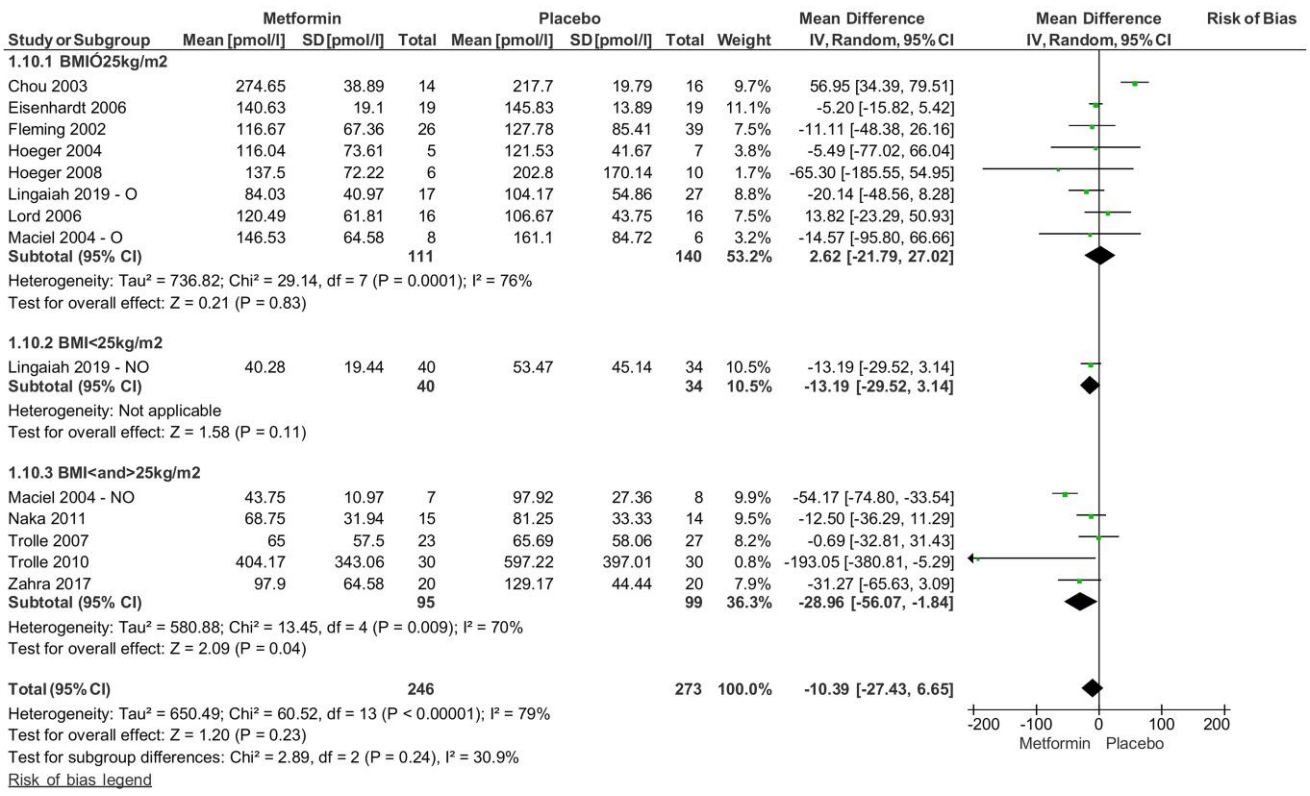
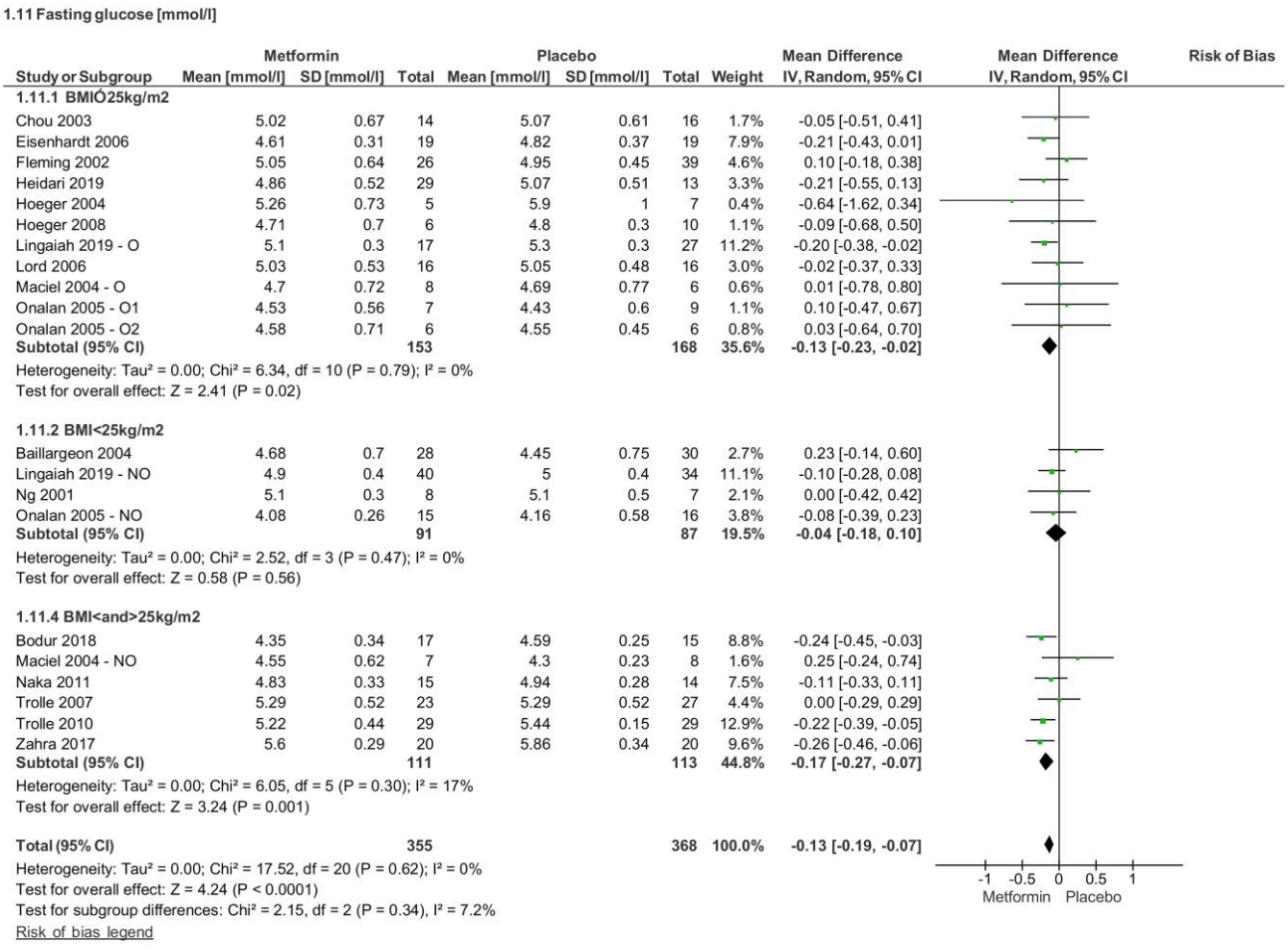


Figure 2. Continued



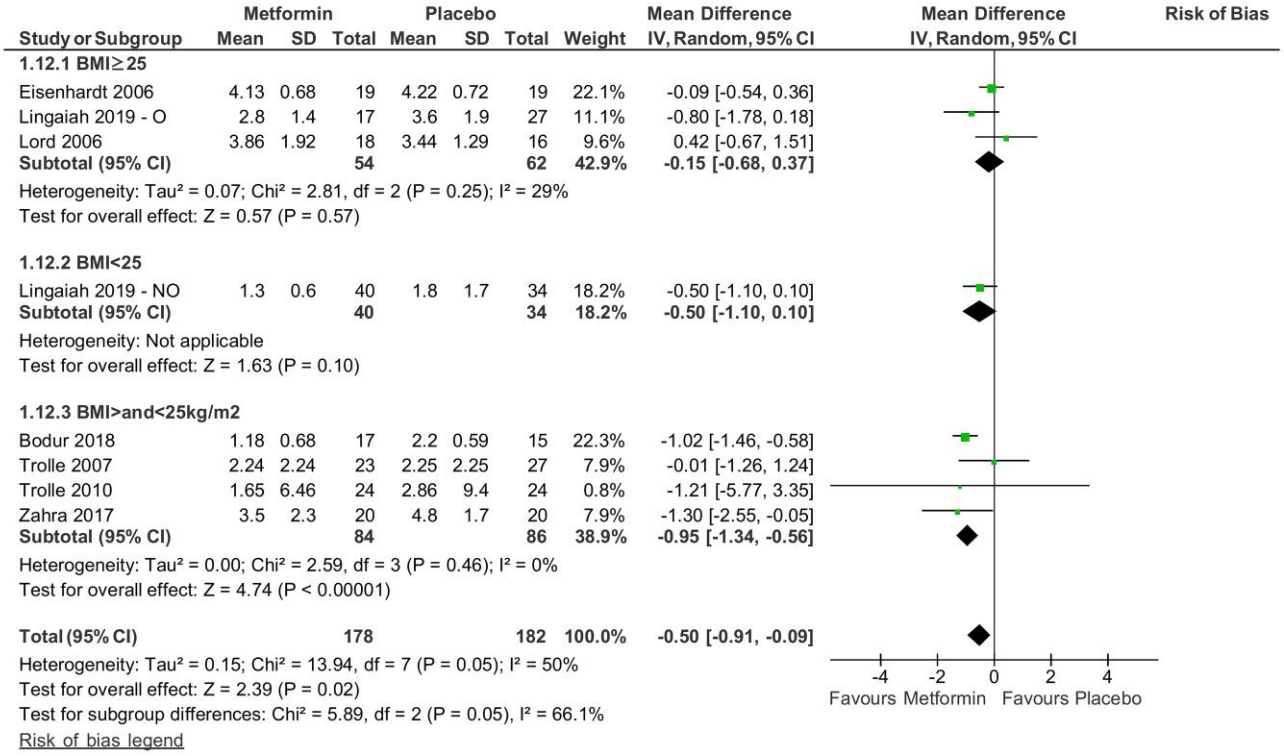
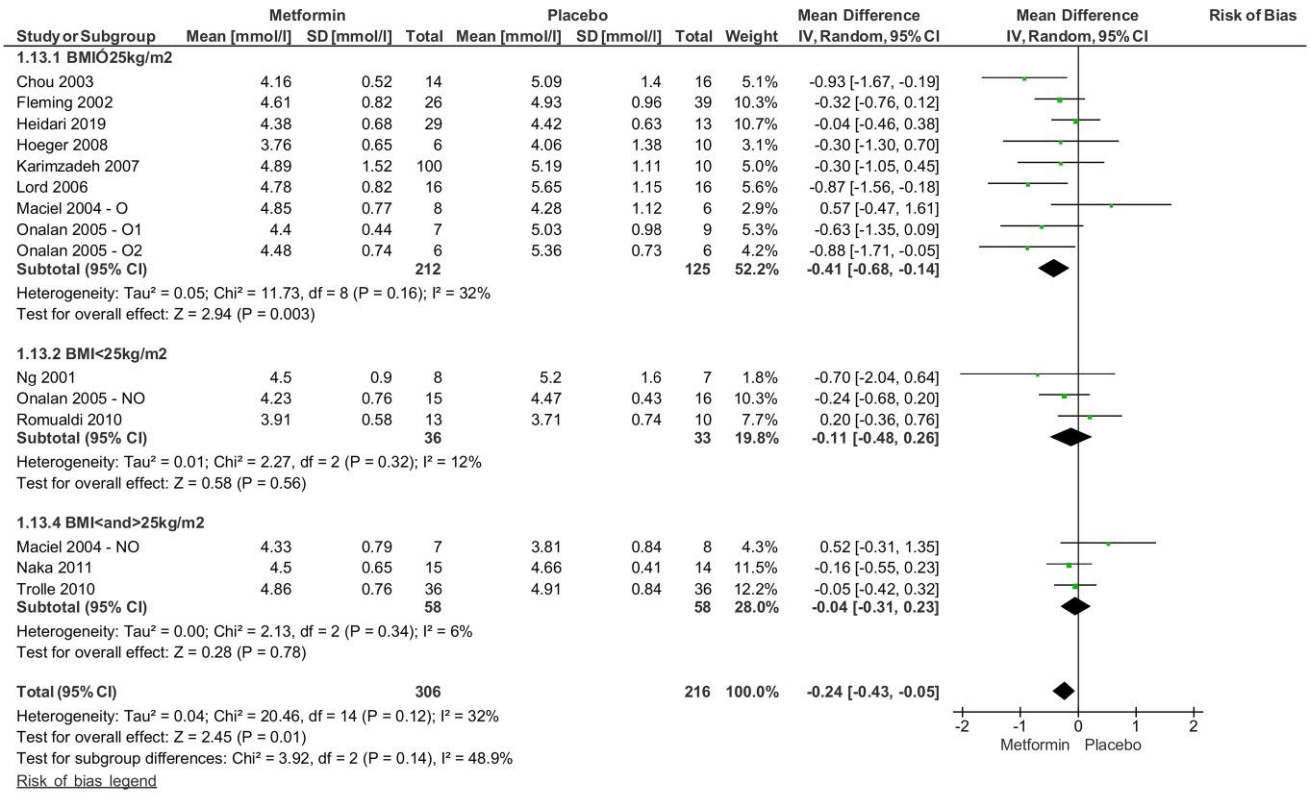


Figure 2. Continued

1.13 Total cholesterol [mmol/l]



1.14 LDL [mmol/l]

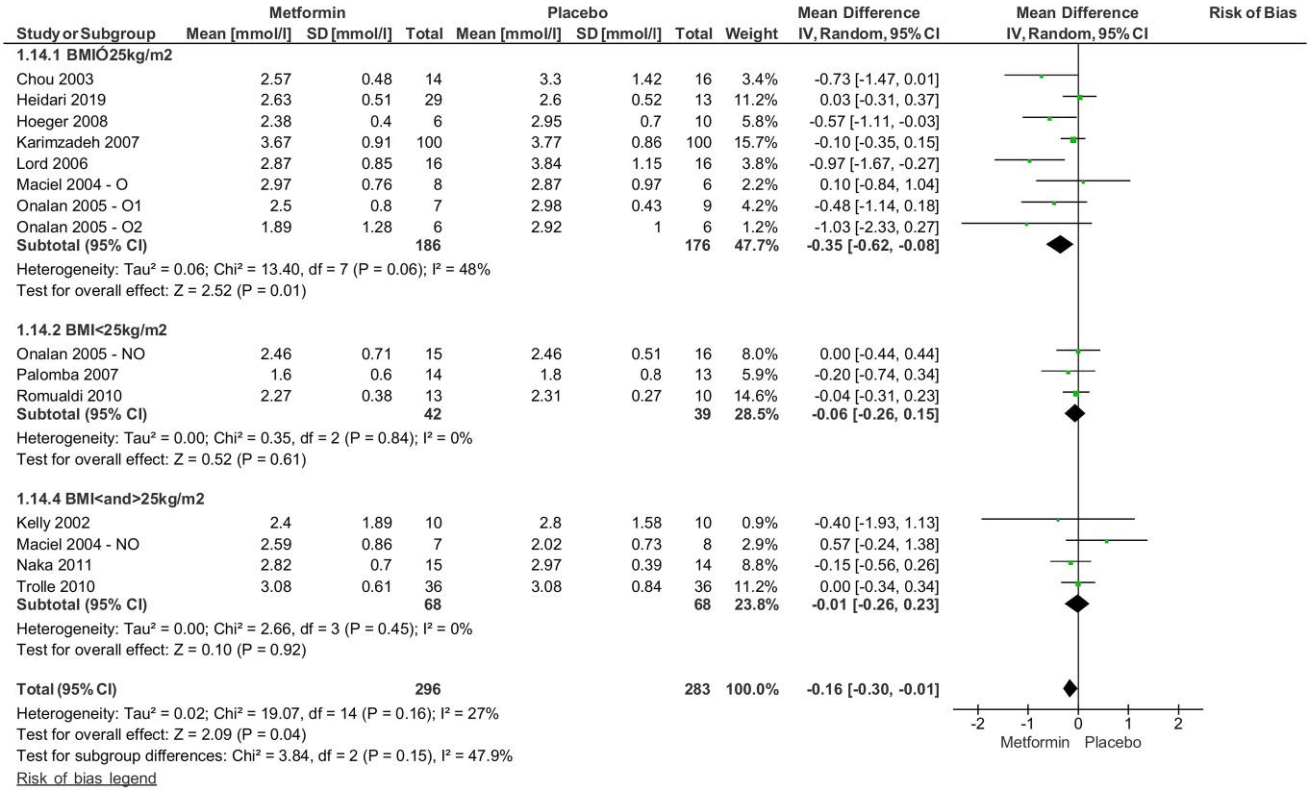


Figure 2. Continued

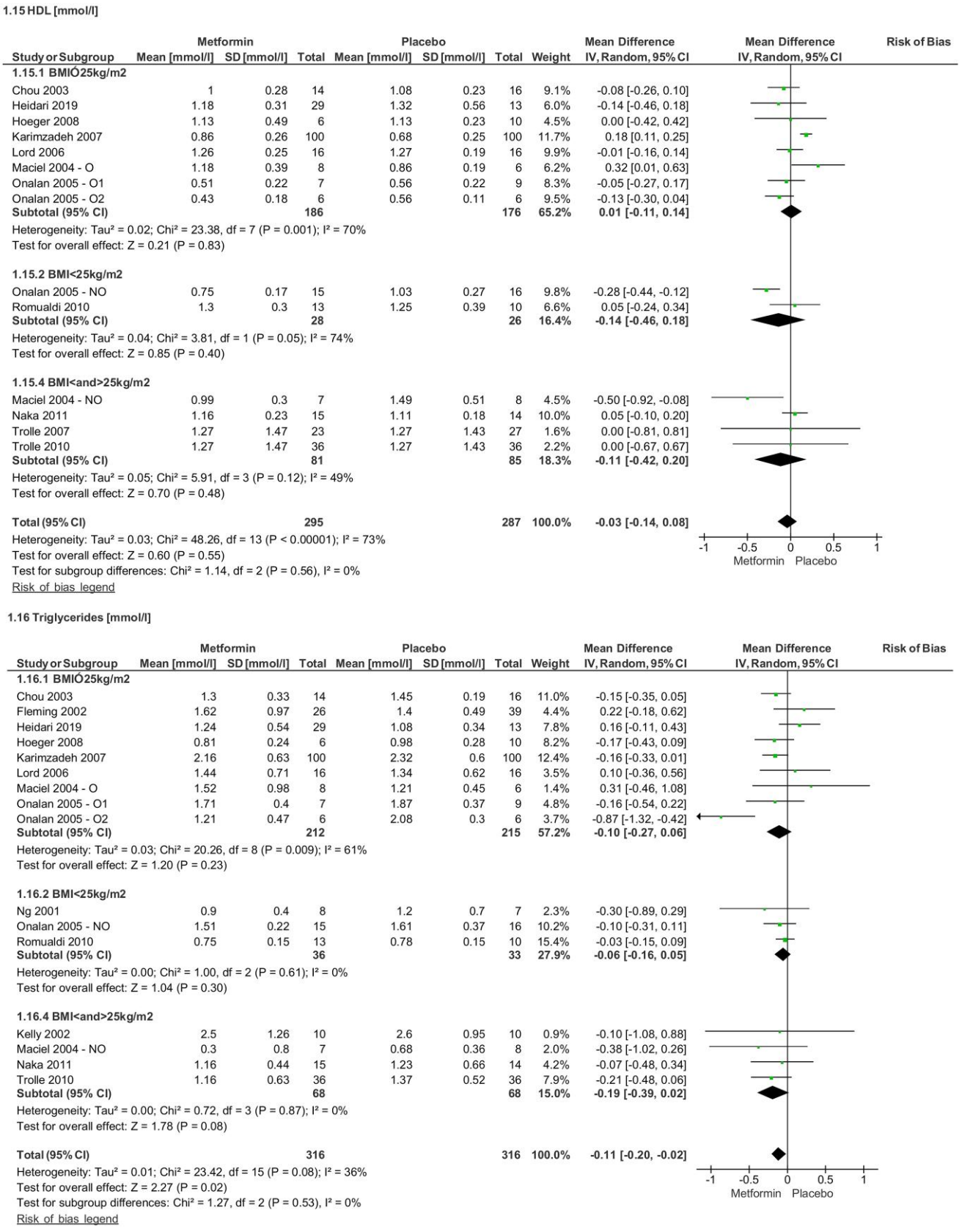


Figure 2. Continued

1.17 CRP [Nmol/l]

Study or Subgroup	Metformin Mean [Nmol/l]	Metformin SD[Nmol/l]	Metformin Total	Placebo Mean [Nmol/l]	Placebo SD[Nmol/l]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Bodur 2018	2.19	2	17	5.62	3.43	15	99.2%	-3.43 [-5.41, -1.45]
Hoeger 2008	26.67	19.05	6	40	26.67	10	0.8%	-13.33 [-35.82, 9.16]
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%
Test for overall effect: Z = 3.49 (P = 0.0005)

Mean Difference IV, Random, 95% CI
-10 -5 0 5 10
Favours Metformin Favours Placebo

Risk of Bias

Risk of bias legend

1.18 PAI-1 [ng/ml]

Study or Subgroup	Metformin Mean [ng/ml]	Metformin SD[ng/ml]	Metformin Total	Placebo Mean [ng/ml]	Placebo SD[ng/ml]	Placebo Total	Weight	Mean Difference 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: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 5.49 (P < 0.00001)

Mean Difference IV, Random, 95% CI
-20 -10 0 10 20
Favours Metformin Favours Placebo

Risk of Bias

Risk of bias legend

1.19 Oligomenorrhea

Study or Subgroup	Metformin Events	Metformin Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Chou 2003	6	14	1	16	27.2%	11.25 [1.15, 110.46]
Eisenhardt 2006	8	19	11	19	34.6%	0.53 [0.15, 1.92]
Karimzadeh 2007	23	100	70	100	38.2%	0.13 [0.07, 0.24]
Total (95% CI)		**133**		**135**	**100.0%**	**0.71 [0.08, 5.92]**
Total events	37		82			

Heterogeneity: Tau² = 2.98; Chi² = 16.59, df = 2 (P = 0.0003); I² = 88%
Test for overall effect: Z = 0.32 (P = 0.75)

Odds Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Favours Metformin Favours Placebo

Risk of Bias

Risk of bias legend

1.20 Amenorrhea

Study or Subgroup	Metformin Events	Metformin Total	Placebo Events	Placebo Total	Weight	Odds Ratio 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: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 2.67 (P = 0.008)

Odds Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Favours Metfromin Favours Placebo

Risk of Bias

Risk of bias legend

1.21 Regular period

Study or Subgroup	Metformin Events	Metformin Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
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: Tau² = 0.62; Chi² = 1.85, df = 1 (P = 0.17); I² = 46%
Test for overall effect: Z = 1.19 (P = 0.24)

Odds Ratio M-H, Random, 95% CI
0.02 0.1 1 10 50
Favours Placebo Favours Metformin

Risk of Bias

Risk of bias legend

Figure 2. Continued

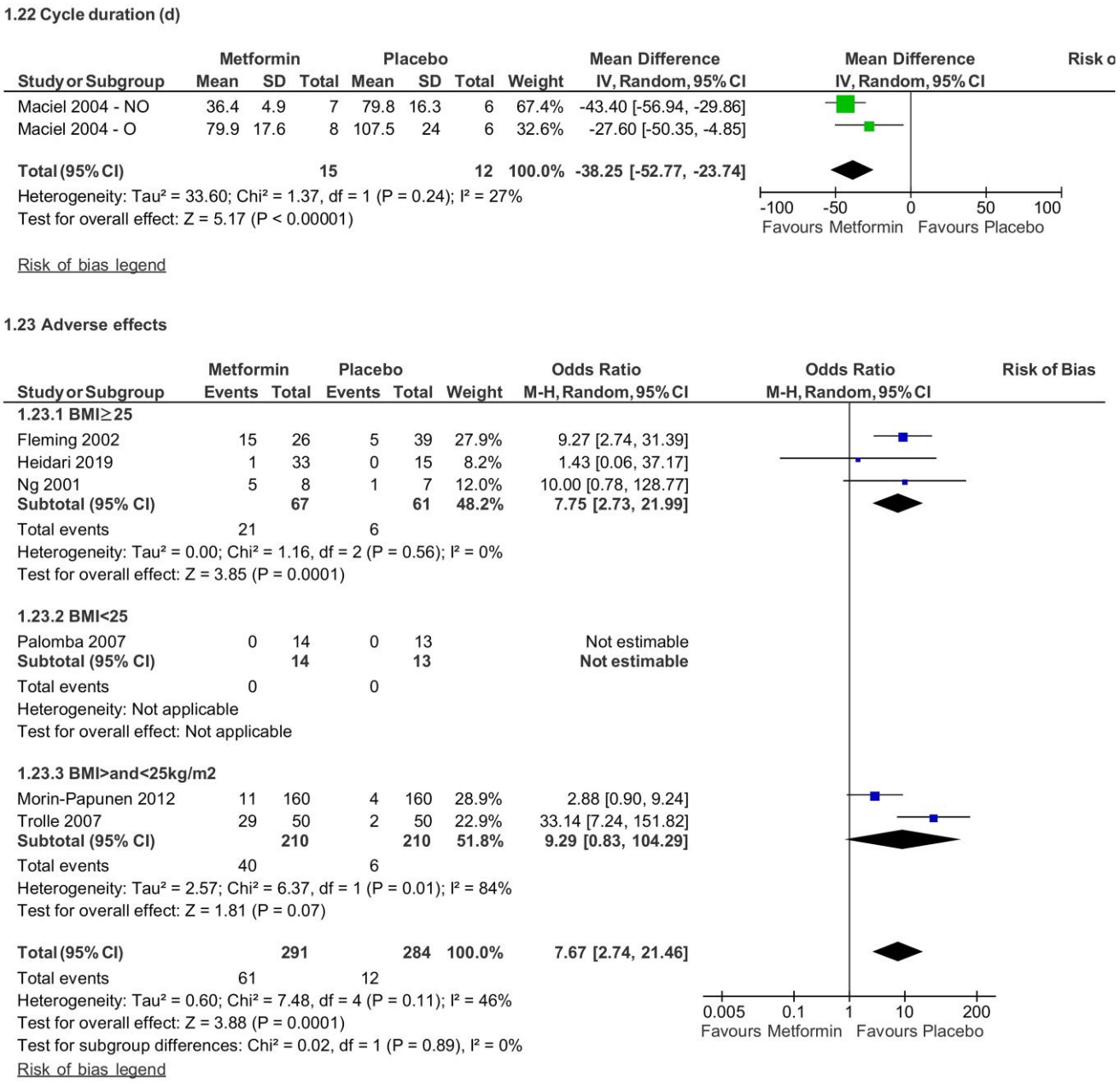


Figure 2. Continued

However, this effect was not observed in adults with a BMI of <25 kg/m^2 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 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 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 PCOS[51] 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/m^2 (moderate certainty). For women with PCOS and a BMI of <25 kg/m^2, 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

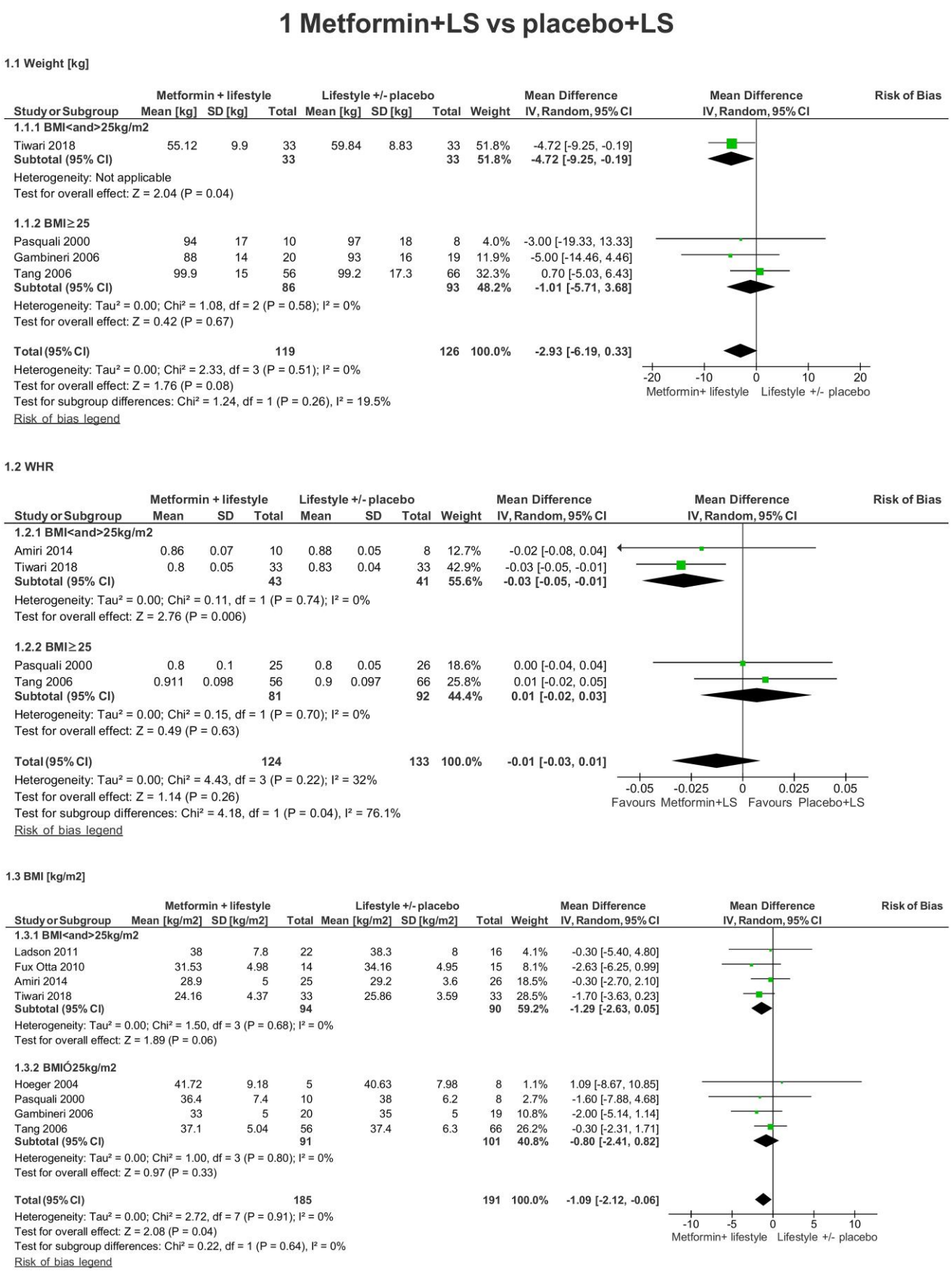


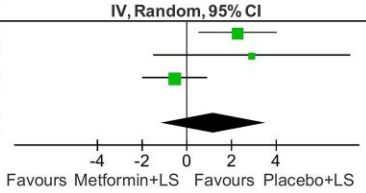
Figure 3. Forest plots presenting meta-analyses on different outcomes when comparing metformin and lifestyle to placebo and lifestyle. Abbreviations: CI: confidence interval; SD, standard deviation.

1.4 Hirsutism (FGS)

Study or Subgroup	Metformin + lifestyle Mean	SD	Total	Lifestyle +/- placebo Mean	SD	Total	Weight	Mean Difference 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]
Total (95% CI)			**78**			**78**	**100.0%**	**1.19 [-1.13, 3.52]**

Heterogeneity: Tau² = 2.76; Chi² = 6.85, df = 2 (P = 0.03); I² = 71%
Test for overall effect: Z = 1.01 (P = 0.31)

Risk of bias legend

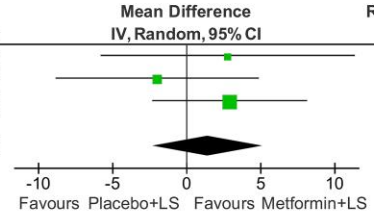


1.5 SHBG (nmol/l)

Study or Subgroup	Metformin + lifestyle Mean	SD	Total	Lifestyle +/- placebo Mean	SD	Total	Weight	Mean Difference 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: Tau² = 0.00; Chi² = 1.36, df = 2 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)

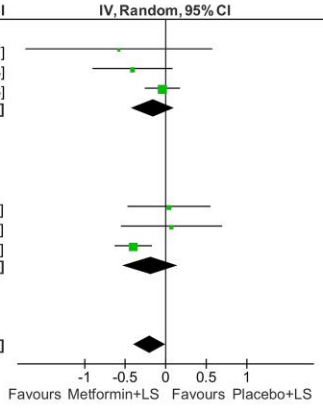
Risk of bias legend



1.6 Total testosterone [Nmol/l]

Study or Subgroup	Metformin + lifestyle Mean [Nmol/l]	SD [Nmol/l]	Total	Lifestyle +/- placebo Mean [Nmol/l]	SD [Nmol/l]	Total	Weight	Mean Difference IV, Random, 95% CI
1.6.1 BMI<and>25kg/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	1.5	0.47	33	1.54	0.43	33	32.7%	-0.04 [-0.26, 0.18]
Subtotal (95% CI)			**73**			**74**	**48.2%**	**-0.16 [-0.43, 0.11]**
Heterogeneity: Tau² = 0.01; Chi² = 2.46, df = 2 (P = 0.29); I² = 19%								
Test for overall effect: Z = 1.15 (P = 0.25)								
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	1.9	0.6	56	2.3	0.7	66	31.2%	-0.40 [-0.63, -0.17]
Subtotal (95% CI)			**86**			**94**	**51.8%**	**-0.18 [-0.52, 0.16]**
Heterogeneity: Tau² = 0.04; Chi² = 3.75, df = 2 (P = 0.15); I² = 47%								
Test for overall effect: Z = 1.06 (P = 0.29)								
Total (95% CI)			**159**			**168**	**100.0%**	**-0.20 [-0.40, 0.01]**
Heterogeneity: Tau² = 0.02; Chi² = 7.65, df = 5 (P = 0.18); I² = 35%								
Test for overall effect: Z = 1.91 (P = 0.06)								
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%								

Risk of bias legend



1.7 Androstenedione [nmol/l]

Study or Subgroup	Metformin + lifestyle Mean [nmol/l]	SD [nmol/l]	Total	Lifestyle +/- placebo Mean [nmol/l]	SD [nmol/l]	Total	Weight	Mean Difference IV, Random, 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: Tau² = 1.11; Chi² = 1.48, df = 1 (P = 0.22); I² = 32%
Test for overall effect: Z = 0.17 (P = 0.86)

Risk of bias legend

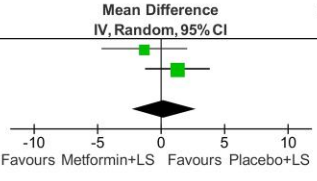
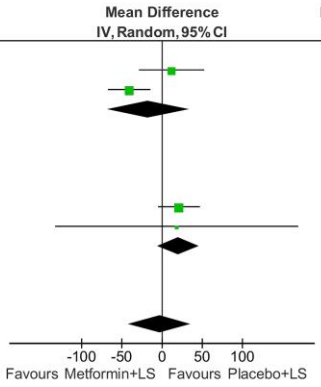


Figure 3. Continued

1.8 Fasting insulin [Pmol/l]

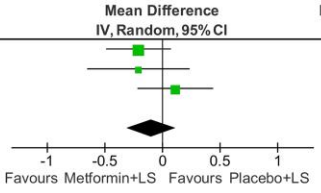
Study or Subgroup	Metformin + lifestyle Mean [Pmol/l]	SD [Pmol/l]	Total	Lifestyle +/- placebo Mean [Pmol/l]	SD [Pmol/l]	Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias
1.8.1 BMI<and>25kg/m2									
Amiri 2014	95.14	49.31	25	83.4	70.14	15	27.6%	11.74 [-28.68, 52.16]	
Fux Otta 2010	65.42	35.63	14	106.32	37.22	15	33.3%	-40.90 [-67.42, -14.38]	
Subtotal (95% CI)			**39**			**30**	**60.9%**	**-16.88 [-68.27, 34.51]**	
Heterogeneity: Tau² = 1081.35; Chi² = 4.56, df = 1 (P = 0.03); I² = 78%									
Test for overall effect: Z = 0.64 (P = 0.52)									
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	150	216.67	10	131.94	100	8	5.6%	18.06 [-133.06, 169.18]	
Subtotal (95% CI)			**30**			**28**	**39.1%**	**20.75 [-4.92, 46.42]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%									
Test for overall effect: Z = 1.58 (P = 0.11)									
Total (95% CI)			**69**			**58**	**100.0%**	**-2.40 [-41.04, 36.25]**	
Heterogeneity: Tau² = 984.22; Chi² = 11.56, df = 3 (P = 0.009); I² = 74%									
Test for overall effect: Z = 0.12 (P = 0.90)									
Test for subgroup differences: Chi² = 1.65, df = 1 (P = 0.20), I² = 39.3%									



Risk of bias legend

1.9 Fasting glucose [Mmol/l]

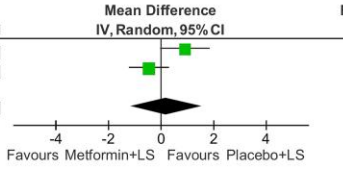
Study or Subgroup	Metformin + lifestyle Mean [Mmol/l]	SD [Mmol/l]	Total	Lifestyle +/- placebo Mean [Mmol/l]	SD [Mmol/l]	Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias
Amiri 2014	4.55	0.45	25	4.76	0.57	26	44.6%	-0.21 [-0.49, 0.07]	
Fux Otta 2010	4.73	0.62	14	4.94	0.6	15	20.6%	-0.21 [-0.65, 0.23]	
Gambineri 2006	5.05	0.5	20	4.94	0.56	20	34.7%	0.11 [-0.22, 0.44]	
Total (95% CI)			**59**			**61**	**100.0%**	**-0.10 [-0.31, 0.11]**	
Heterogeneity: Tau² = 0.01; Chi² = 2.39, df = 2 (P = 0.30); I² = 16%									
Test for overall effect: Z = 0.91 (P = 0.36)									



Risk of bias legend

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

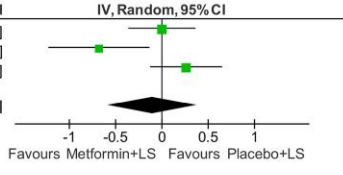
Study or Subgroup	Metformin + lifestyle Mean [Mmol/l]	SD [Mmol/l]	Total	Lifestyle +/- placebo Mean [Mmol/l]	SD [Mmol/l]	Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias
Amiri 2014	6.22	1.69	25	5.31	1.74	26	47.9%	0.91 [-0.03, 1.85]	
Fux Otta 2010	4.81	1.15	14	5.27	0.93	15	52.1%	-0.46 [-1.22, 0.30]	
Total (95% CI)			**39**			**41**	**100.0%**	**0.20 [-1.15, 1.54]**	
Heterogeneity: Tau² = 0.75; Chi² = 4.90, df = 1 (P = 0.03); I² = 80%									
Test for overall effect: Z = 0.29 (P = 0.77)									



Risk of bias legend

1.11 Total cholesterol [mmol/l]

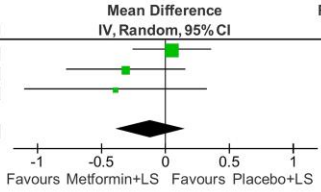
Study or Subgroup	Metformin + lifestyle Mean [mmol/l]	SD [mmol/l]	Total	Lifestyle +/- placebo Mean [mmol/l]	SD [mmol/l]	Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias
Amiri 2014	4.43	0.6	25	4.43	0.72	26	36.2%	0.00 [-0.36, 0.36]	
Fux Otta 2010	4.1	0.76	14	4.78	0.74	15	28.6%	-0.68 [-1.23, -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: Tau² = 0.13; Chi² = 7.62, df = 2 (P = 0.02); I² = 74%									
Test for overall effect: Z = 0.42 (P = 0.67)									



Risk of bias legend

1.12 LDL [Mmol/l]

Study or Subgroup	Metformin + lifestyle Mean [Mmol/l]	SD [Mmol/l]	Total	Lifestyle +/- placebo Mean [Mmol/l]	SD [Mmol/l]	Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias
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: Tau² = 0.01; Chi² = 2.32, df = 2 (P = 0.31); I² = 14%									
Test for overall effect: Z = 0.83 (P = 0.41)									



Risk of bias legend

Figure 3. Continued

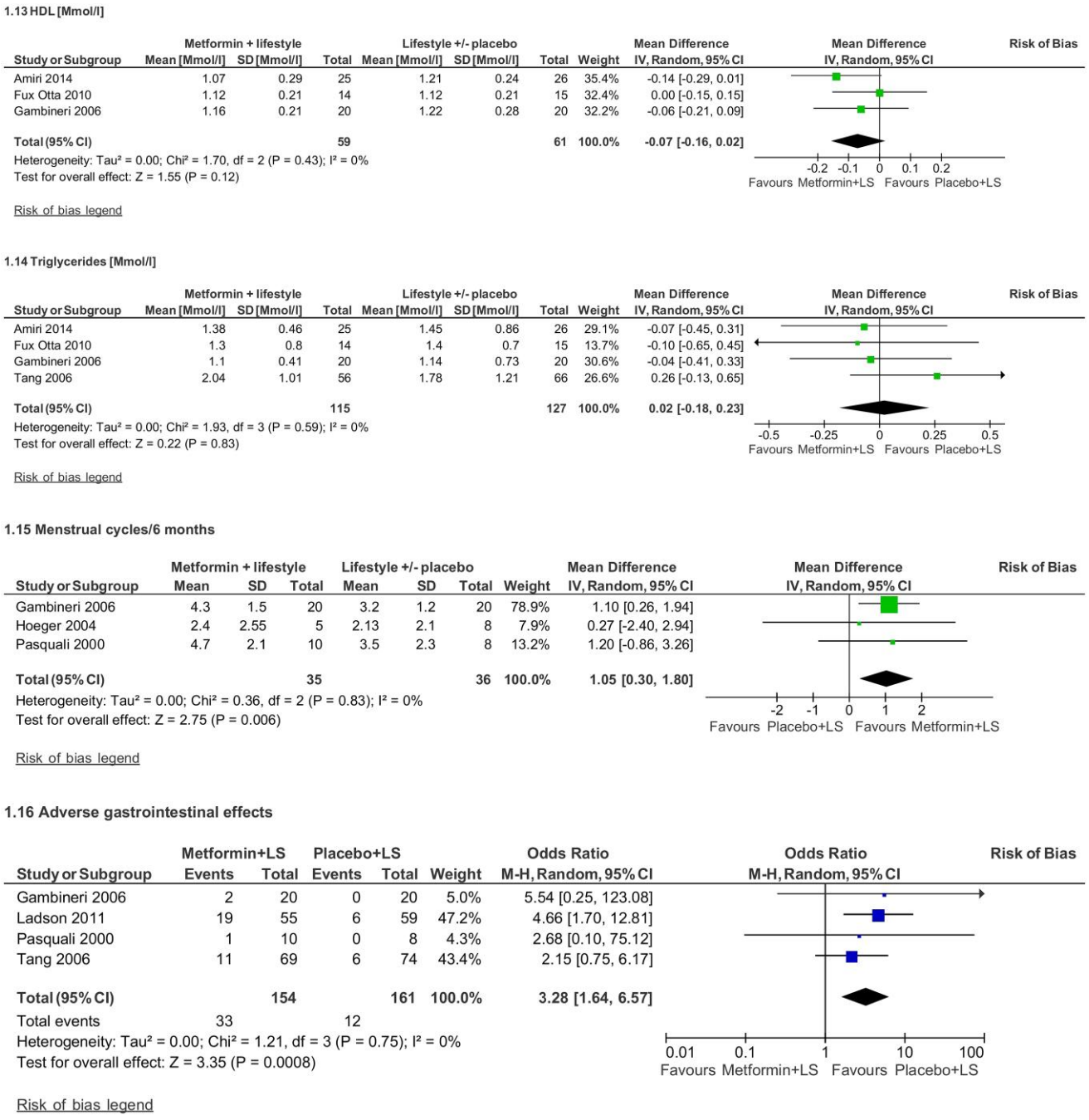


Figure 3. Continued

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

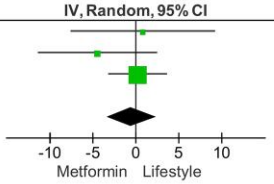
Insulin suppresses hepatic SHBG secretion and acts on the ovary to promote thecal cell androgen synthesis[58] with the

1 Metformin versus lifestyle

1.1 BMI [kg/m2]

Study or Subgroup	Metformin Mean [kg/m2]	Metformin SD [kg/m2]	Metformin Total	Lifestyle Mean [kg/m2]	Lifestyle SD [kg/m2]	Lifestyle Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias
Hoeger 2008	35.7	8.6	6	34.9	7	8	11.7%	0.80 [-7.62, 9.22]	
Hoeger 2004	36.15	5.29	6	40.63	7.98	8	17.2%	-4.48 [-11.44, 2.48]	
Esfahanian 2013	30.3	3.5	17	30.1	5.5	13	71.1%	0.20 [-3.22, 3.62]	
Total (95% CI)			**29**			**29**	**100.0%**	**-0.53 [-3.42, 2.35]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.51, df = 2 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.36 (P = 0.72)

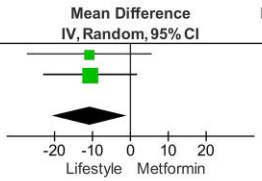


Risk of bias legend

1.2 SHBG [(nmol/l)]

Study or Subgroup	Metformin Mean [(nmol/l)]	Metformin SD [(nmol/l)]	Metformin Total	Lifestyle Mean [(nmol/l)]	Lifestyle SD [(nmol/l)]	Lifestyle Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias
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: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 2.12 (P = 0.03)

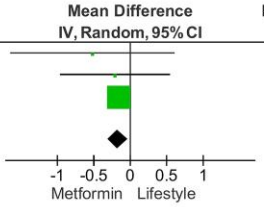


Risk of bias legend

1.3 Total testosterone [nmol/l]

Study or Subgroup	Metformin Mean [nmol/l]	Metformin SD [nmol/l]	Metformin Total	Lifestyle Mean [nmol/l]	Lifestyle SD [nmol/l]	Lifestyle Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias
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: Tau² = 0.00; Chi² = 0.40, df = 2 (P = 0.82); I² = 0%
Test for overall effect: Z = 2.35 (P = 0.02)

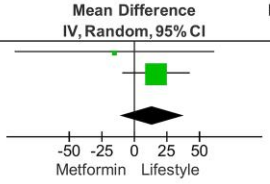


Risk of bias legend

1.4 Fasting insulin [pmol/l]

Study or Subgroup	Metformin Mean [pmol/l]	Metformin SD [pmol/l]	Metformin Total	Lifestyle Mean [pmol/l]	Lifestyle SD [pmol/l]	Lifestyle Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias
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: Tau² = 0.00; Chi² = 0.60, df = 1 (P = 0.44); I² = 0%
Test for overall effect: Z = 1.07 (P = 0.28)

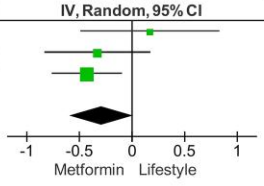


Risk of bias legend

1.5 Fasting glucose [mmol/l]

Study or Subgroup	Metformin Mean [mmol/l]	Metformin SD [mmol/l]	Metformin Total	Lifestyle Mean [mmol/l]	Lifestyle SD [mmol/l]	Lifestyle Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias
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: Tau² = 0.02; Chi² = 2.52, df = 2 (P = 0.28); I² = 21%
Test for overall effect: Z = 1.89 (P = 0.06)



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.

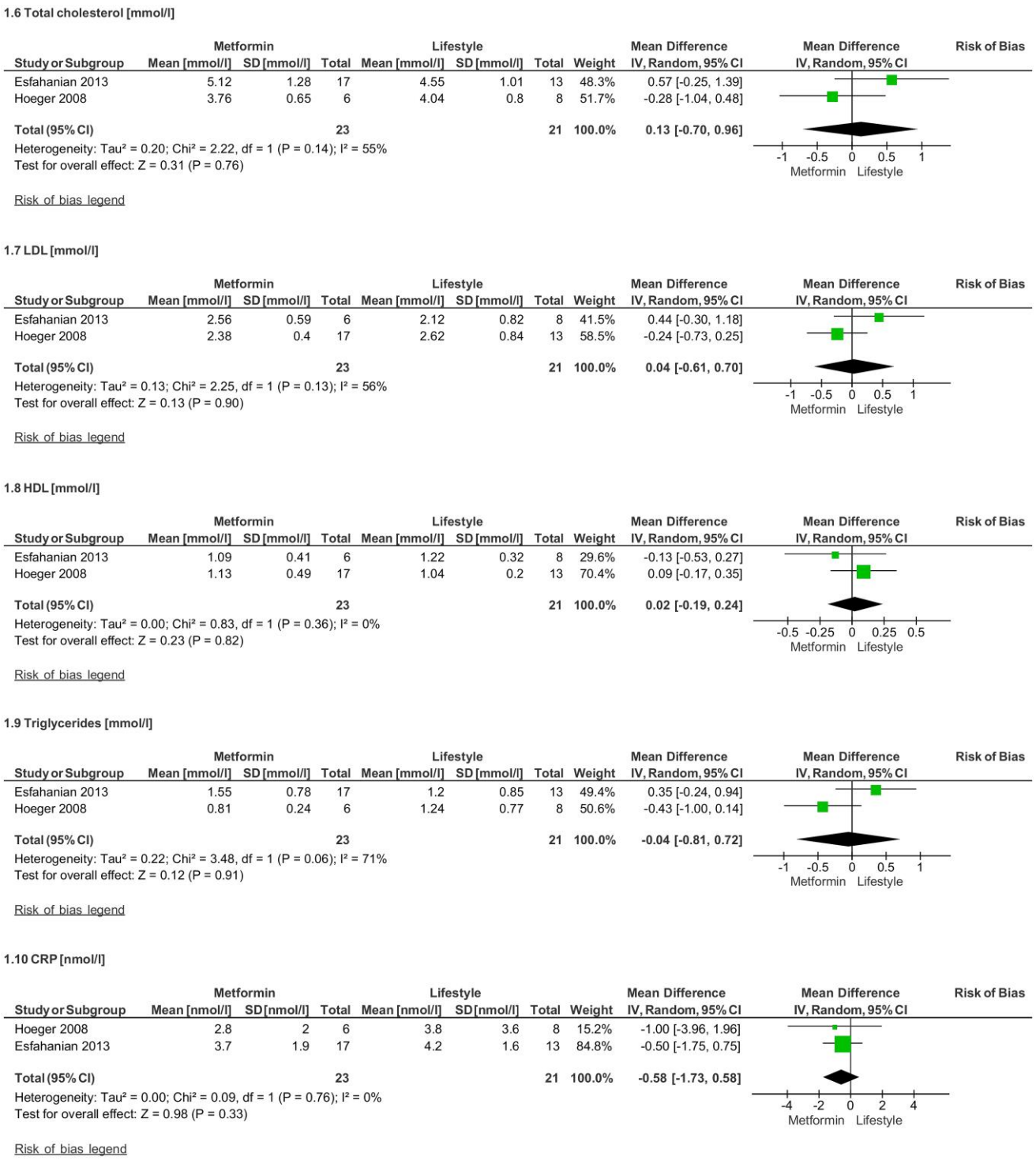


Figure 4. Continued

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/m^2.

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 guidelines[2] 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 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/m^2 for prevention of weight gain and management of weight and metabolic disorders. Metformin may be considered in adults with BMI < 25 kg/m^2 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

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Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

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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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