Appendix 8

STATENS BEREDNING FÖR MEDICINSK OCH SOCIAL UTVÄRDERING

Läkemedelsbehandling av polycystiskt ovarialsyndrom- hälsa och livskvalitet på kort och lång sikt, Pharmacological treatment of polycystic ovary syndrome - health and quality of life in the short and long term, report 394 (2025)

Appendix 8 Analyses and additional results

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1 Method

We have chosen to use SI units for the results. The SI units are pmol/l for fasting insulin and mmol/l for fasting glucose, LDL and triglycerides. Results reported in other units in studies were converted using the Unitslab webpage [1].

1.1 Meta-analyses

All outcomes included in meta-analyses are continuous. Results from meta-analyses are reported as mean differences between groups with 95% confidence intervals, except for Ferriman-Gallwey (FG) score. It was sometimes unclear whether studies used the modified FG-score or not. When these studies are included in the analysis the standardised mean difference with correction for small sample size bias (Hedge's g) were used [2]. Results reported as e.g. geometric mean or median are not included in the meta-analyses but reported narratively.

Meta-analyses were performed in RevMan Web [3]. For all analyses a random effects model was used and restricted maximum likelihood was used for estimating heterogeneity. Where meta-analyses included three or more studies the Hartung-Knapp-Sidik-Jonkman method was used for estimating confidence intervals. When only two studies were included the Wald-type method was used instead [4, 5].

Studies reporting mean at endpoint and studies reporting change in mean between endpoint and baseline are included in the same meta-analyses [6]. Where both numbers were reported change in mean was preferred, apart from analyses using standardised mean difference, where only endpoint data was included. For studies that reported results at more than one time point the latest time point was used, unless this was a substantial time after end of treatment.

Sensitivity analyses were performed by excluding studies with a high risk of bias, studies using the least squares method to calculate means, and crossover studies (appendix). None of these showed substantial differences from the original analyses. Analyses of studies where mean BMI at baseline was at least 30 were also performed.

In forest plots, symbols and colours are used to indicate the level of risk of bias, - equals high risk of bias, means moderate risk of bias, and + means low risk of bias.

1.2 Combined oral contraceptives

Meta-analyses comparing first to fourth generation, and third to fourth generation, were performed. Two studies compared the first and fourth generation (table 1). For the third generation compared to fourth generation five studies were included (table 1), but one of them did not contribute any data [7].

Table 1 Comparisons included in analyses.

Study Analysis	Intervention	Control

Podfigurna 2020 [8] *First vs fourth generation*	Chlormadinone acetate Ethinyl estradiol	Drospirenone Ethinyl estradiol
Yildizhan 2015 [9] *First vs fourth generation*	Chlormadinone acetate Ethinyl estradiol	Drospirenone Ethinyl estradiol
Amiri 2021 [10] *Third vs fourth generation*	Desogestrel Ethinyl estradiol	Drospirenone Ethinyl estradiol
Bhattacharya 2012 [11] *Third vs fourth generation*	Desogestrel Ethinyl estradiol	Drospirenone Ethinyl estradiol
Dasgupta 2023 [12] *Third vs fourth generation*	Desogestrel Ethinyl estradiol	Drospirenone Ethinyl estradiol
Kriplani 2010 [13] *Third vs fourth generation*	Desogestrel Ethinyl estradiol	Drospirenone Ethinyl estradiol

1.3 Antiandrogens

Studies where the only active difference between treatment groups was an antiandrogen were included (table 2) in the meta-analyses, referred to as antiandrogens+. The antiandrogens in the included studies were flutamide, finasteride, spironolactone and bicalutamide, and these were considered similar enough to be included in the same meta-analyses. For Tartagni 2000 [14] data were extracted from figure 1 using WebPlotDigitizer [15]. For hirsutism, results for all studies are also shown in a forest plot, but no combined result is calculated since there are significant differences between interventions.

Table 2 Comparisons included in analyses.

Study	Intervention	Control
Amiri 2014a [16]	Flutamide Lifestyle intervention	Placebo Lifestyle intervention
Amiri 2014b [16]	Flutamide Metformin Lifestyle intervention	Metformin Lifestyle intervention
Diri 2017 [17]	Finasteride Metformin	Metformin
Dumesic 2023 [18]	Flutamide	Placebo
Gambineri 2006a [19]	Flutamide Lifestyle intervention	Placebo Lifestyle intervention
Gambineri 2006b [19]	Flutamide Metformin Lifestyle intervention	Metformin Lifestyle intervention
Ganie 2013 [20]	Spironolactone Metformin Lifestyle intervention	Metformin Lifestyle intervention
Hagag 2014 [21]	Spironolactone Oral contraceptive	Oral contraceptive
Mazza 2014 [22]	Spironolactone Metformin Lifestyle intervention	Metformin Lifestyle intervention
Moretti 2018 [23]	Bicalutamide Oral contraceptive	Placebo Oral contraceptive
Tartagni 2000 [14]	Finasteride	Oral contraceptive

Study	Intervention	Control
	Oral contraceptive	
Vieira 2012 [24]	Spironolactone Oral contraceptive	Oral contraceptive

1.4 Metformin

Two sets of meta-analyses were conducted for metformin as intervention, metformin+ and metformin compared to lifestyle intervention.

1.4.1 Metformin+

This comparison includes studies where the only active difference between treatment groups was metformin. Both groups may also have had a lifestyle intervention (table 3). In addition to analyses of all studies subgroup analyses according to BMI were performed (BMI ≥25 and BMI <25). For results included in the subgroup analysis BMI ≥25 having a BMI of at least 25 was a criterion for inclusion, except for Cao 2023 where the inclusion criterion was BMI >24 (cut-off for overweight in an Asian population is 24 [25]). Some studies had higher cut-offs than 25, and for one the cut-off was above the 95th percentile [26]. For two studies there was no cut-off for inclusion but for one the average BMI at baseline was well above 25 [27] and for the other 89 percent had a BMI above 25 [28]. For the subgroup analyses BMI <25 (normal weight) was a criterion for inclusion. Where studies included participants with BMI both above and below 25 and reported them separately participants are included in appropriate subgroups. An O after the authors name marks participants in BMI ≥ 25 subgroups, and NO marks participants in subgroup BMI <25. NS means that results were not reported separately for subgroups.

Trolle 2007 and Trolle 2010 are considered publications of the same study, with a crossover design [29, 30]. In Trolle 2007 results for both phases are reported together. We consider the wash-out period between phases as adequate, and since Trolle 2007 report results for obese and non-obese participants separately, primarily these results are included. Results from Trolle 2010 are only included if they are not reported in Trolle 2007.

For Hoeger 2004 [31] data was extracted using WebPlotDigitizer [15] for four treatment groups, metformin and placebo without lifestyle intervention (Hoeger 2004-) and metformin and placebo with a lifestyle intervention (Hoeger 2004+).

Table 3 Comparisons included in analyses.

Study	Intervention	Control
Amiri 2014 [16]	Metformin Lifestyle intervention	Placebo Lifestyle intervention
Baillargeon 2004 [32]	Metformin	Placebo
Bodur 2018 [33]	Metformin	No treatment
Cao 2023 NO [34] [35]	Metformin	Placebo
Cao 2023 O [34] [35]	Metformin	Placebo
Chou 2009 [36]	Metformin	Placebo
Eisenhardt 2006 [37]	Metformin	Placebo

Fleming 2002 [38]	Metformin	Placebo
Fux Otta 2010 [39]	Metformin	Placebo
Gambineri 2006 [19]	Metformin Lifestyle intervention	Placebo Lifestyle intervention
Heidari 2019 [40]	Metformin	No treatment
Hoeger 2004- [31]	Metformin	Placebo
Hoeger 2004+ [31]	Metformin Lifestyle intervention	Placebo Lifestyle intervention
Hoeger 2008 [26]	Metformin	Placebo
Karimzadeh 2007 [27]	Metformin	Placebo
Ladson 2011a [41]	Metformin Lifestyle intervention	Placebo Lifestyle intervention
Lingaiah 2019 NO [42]	Metformin	Placebo
Lingaiah 2019 O [42]	Metformin	Placebo
Lord 2006 [28]	Metformin	Placebo
Maciel 2004 NO [43]	Metformin	Placebo
Maciel 2004 O [43]	Metformin	Placebo
Naka 2011 [44]	Metformin	No treatment
Ng 2001 [45]	Metformin	Placebo
Palomba 2007 [46]	Metformin	Placebo
Pasquali 2000 [47]	Metformin Lifestyle intervention	Placebo Lifestyle intervention
Romualdi 2010 [48]	Metformin	Placebo
Tang 2006 [49]	Metformin Lifestyle intervention	Placebo Lifestyle intervention
Telagareddy 2024 [50]	Metformin Lifestyle intervention	Lifestyle intervention
Tiwari 2018 [51]	Metformin Lifestyle intervention	Placebo Lifestyle intervention
Trolle 2007/2010 NS [29, 30]	Metformin	Placebo
Trolle 2007 NO [29, 30]	Metformin	Placebo
Trolle 2007 O [29, 30]	Metformin	Placebo
Zahra 2017 [52]	Metformin	Placebo

1.4.2 Metformin compared to lifestyle intervention

Three studies comparing metformin to a lifestyle intervention were included. For Dilimulati *et al* results were reported as least squares mean changes, which differs from the other included studies.

Table 4 Comparisons included in analyses.

Study	Intervention	Control
Dilimulati 2024 [53]	Metformin	Lifestyle intervention
Esfahanian 2013 [54]	Metformin	Lifestyle intervention
Hoeger 2008 [26]	Metformin	Lifestyle intervention

1.5 GLP-1 analogues

For GLP-1 analogues three sets of meta-analyses were performed, GLP-1 analogues compared to metformin, GLP-1 analogues compared to placebo and GLP-1+. Studies where the only active difference between treatment groups was the GLP-1 analogue were included in GLP-1+ (table 5). Studies used liraglutide, beinaglutide, or exenatide, and all of these were included in the same meta-analyses.

Table 5 Comparisons included in analyses.

Study Analyses	Intervention	Control
Elkind-Hirsch 2008 [55] GLP-1 vs metformin	Exenatide	Metformin
Elkind-Hirsch 2008 [55] GLP-1+	Exenatide Metformin	Metformin
Elkind-Hirsch 2022 [56] GLP-1 analogue vs placebo GLP-1+	Liraglutide Lifestyle intervention	Placebo Lifestyle intervention
Frössing 2018a, Frössing 2018b, Nylander 2017a, Nylander 2017b [57-60] GLP-1 analogue vs placebo GLP-1+	Liraglutide	Placebo
Ma 2021 [61] **Gan 2023 [62]** GLP-1+	Exenatide Metformin	Metformin
Tao 2021 [63] GLP-1+	Exenatide Metformin	Metformin
Tao 2021 [63] GLP-1 analogue vs metformin	Exenatide	Metformin
Wen 2023 [35] GLP-1+	Beinaglutide Metformin	Metformin
Xing 2022 [64] GLP-1+	Liraglutide Metformin	Metformin

1.6 Long term analyses

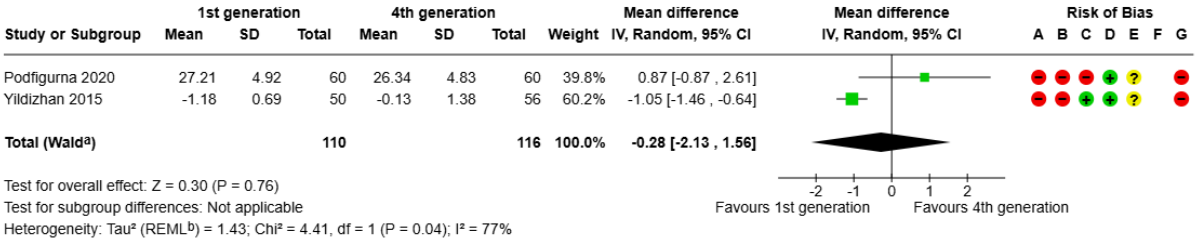
Three studies reported follow-up data for at least 12 months for the comparison antiandrogens+ [17, 19, 24]. For the comparison metformin+ two studies reported follow-up data for at least 12 months [19, 46].

2 Analyses regarding combined oral contraceptives

2.1 Meta-analyses for different kinds of combined oral contraceptives

2.1.1 First generation compared to fourth generation

BMI (kg/m^2)



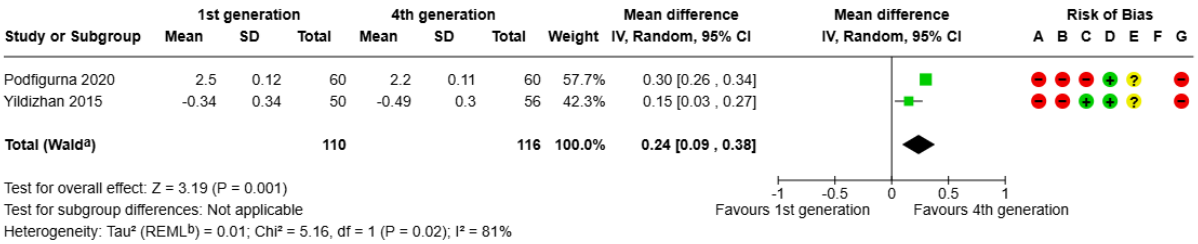
Study or Subgroup	1st generation Mean	SD	Total	4th generation Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Podfigurna 2020	27.21	4.92	60	26.34	4.83	60	39.8%	0.87 [-0.87 , 2.61]
Yildizhan 2015	-1.18	0.69	50	-0.13	1.38	56	60.2%	-1.05 [-1.46 , -0.64]
Total (Wald[a])			**110**			**116**	**100.0%**	**-0.28 [-2.13 , 1.56]**

Test for overall effect: Z = 0.30 (P = 0.76)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 1.43; Chi² = 4.41, df = 1 (P = 0.04); I² = 77%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

HOMA-IR



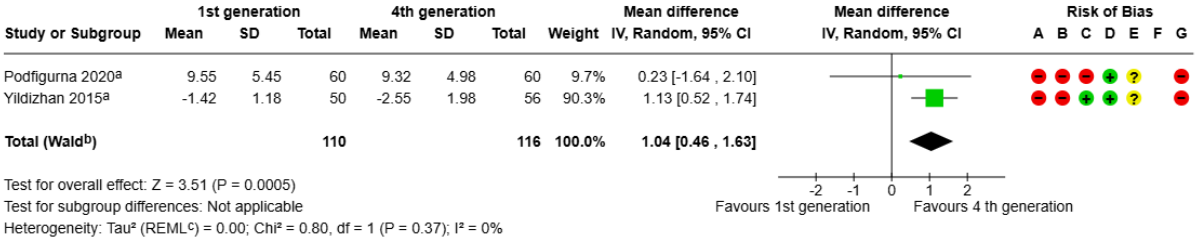
Study or Subgroup	1st generation Mean	SD	Total	4th generation Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Podfigurna 2020	2.5	0.12	60	2.2	0.11	60	57.7%	0.30 [0.26 , 0.34]
Yildizhan 2015	-0.34	0.34	50	-0.49	0.3	56	42.3%	0.15 [0.03 , 0.27]
Total (Wald[a])			**110**			**116**	**100.0%**	**0.24 [0.09 , 0.38]**

Test for overall effect: Z = 3.19 (P = 0.001)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.01; Chi² = 5.16, df = 1 (P = 0.02); I² = 81%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Hirsutism



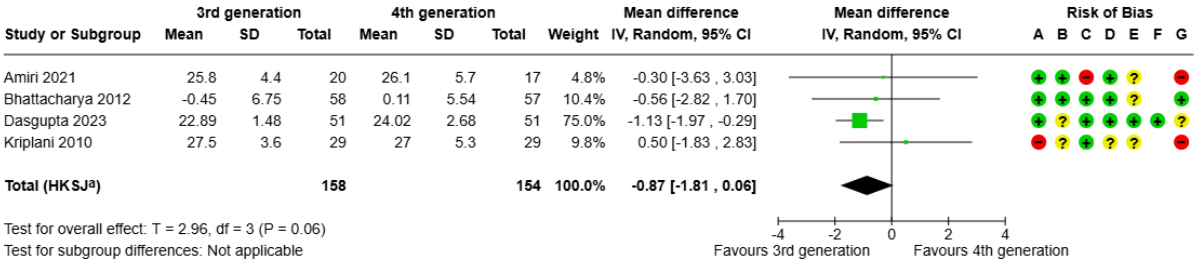
Test for overall effect: Z = 3.51 (P = 0.0005)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[c]) = 0.00; Chi² = 0.80, df = 1 (P = 0.37); I² = 0%

Footnotes
[a]modified FG-score
[b]CI calculated by Wald-type method.
[c]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

2.1.2 Third generation compared to fourth generation

BMI (kg/m²)

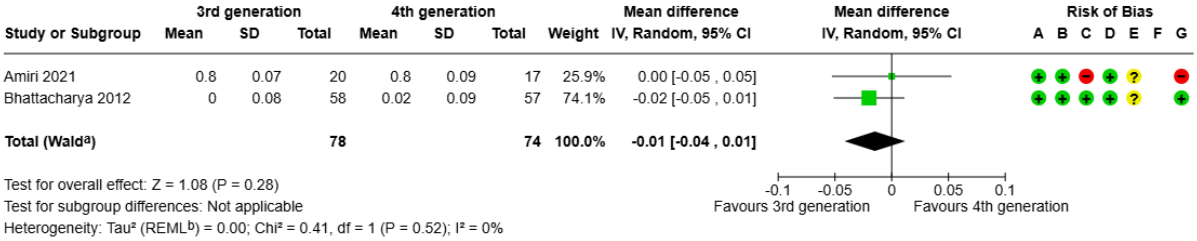


Test for overall effect: T = 2.96, df = 3 (P = 0.06)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 1.88, df = 3 (P = 0.60); I² = 0%

Footnotes
[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

WHR

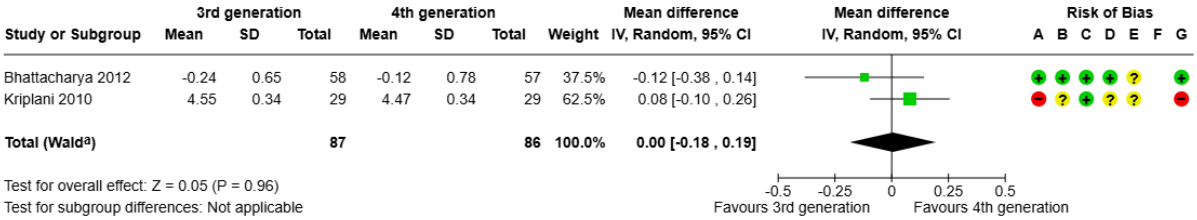


Test for overall effect: Z = 1.08 (P = 0.28)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Fasting glucose (mmol/l)

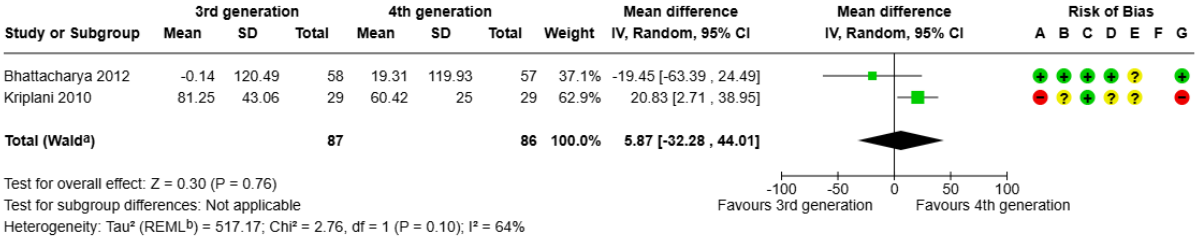


Test for overall effect: Z = 0.05 (P = 0.96)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.01; Chi² = 1.54, df = 1 (P = 0.21); I² = 35%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Fasting insulin (pmol/l)

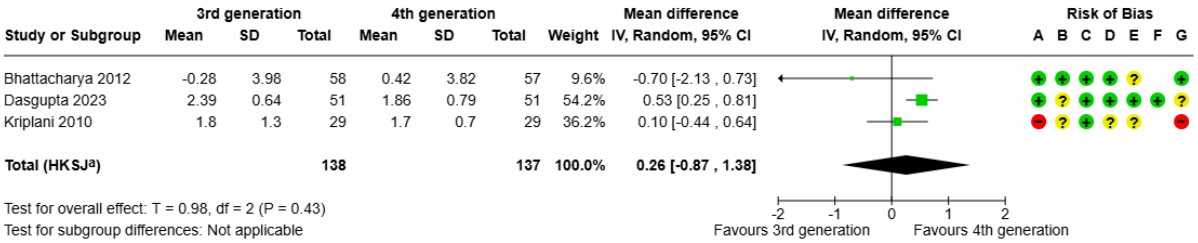


Test for overall effect: Z = 0.30 (P = 0.76)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 517.17; Chi² = 2.76, df = 1 (P = 0.10); I² = 64%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

HOMA-IR

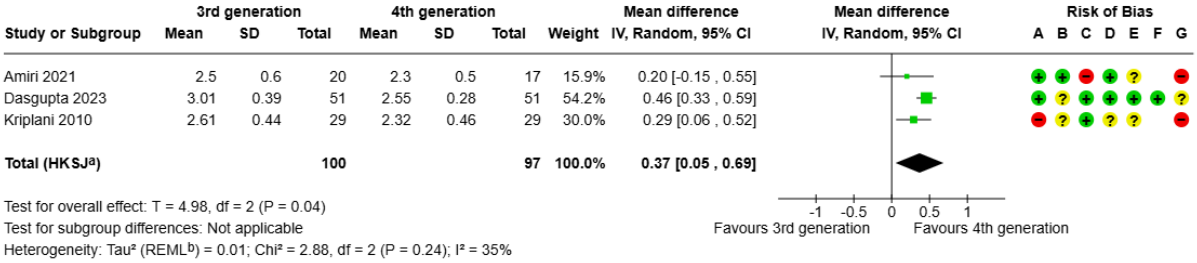


Test for overall effect: T = 0.98, df = 2 (P = 0.43)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.09; Chi² = 4.32, df = 2 (P = 0.12); I² = 52%

Footnotes
[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

LDL

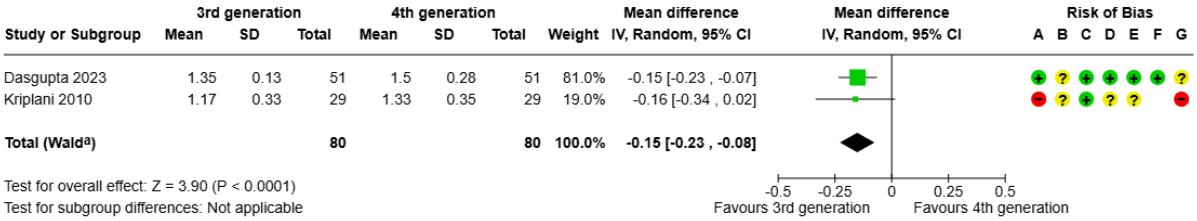


Test for overall effect: T = 4.98, df = 2 (P = 0.04)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.01; Chi² = 2.88, df = 2 (P = 0.24); I² = 35%

Footnotes
[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Triglycerides (mmol/l)



Test for overall effect: Z = 3.90 (P < 0.0001)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%

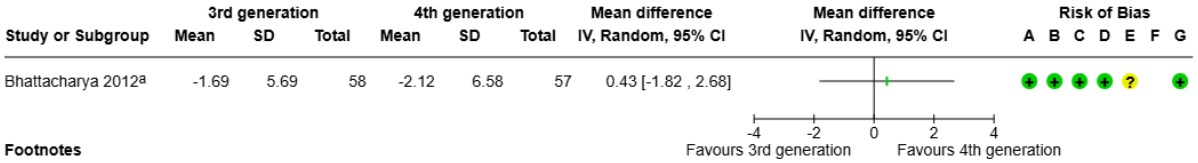
Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Table 6 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Intervention	Control	Result	RoB
Amiri 2021 [10]	3rd generation n=20 Median: 1.3 IQR: 0.8 to 1.4	4th generation n=17 Median: 1.1 IQR: 0.8 to 1.3	Favours 4th generation.	High

Hirsutism



Footnotes
[a]modified Ferriman-Gallwey score

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Table 7 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Intervention	Control	Result	RoB
Kriplani 2010 [13]	3rd generation n=29	4th generation n=29	"In the study group, hirsutism score as evidenced by the extent of hair growth was reduced significantly from a baseline value of 12.6±4.5 (mean±S.D.) to 8±4.3 (36.5%) at the end of 6 months of treatment (p=.04) and remained decreased at 8.4±3.8 (mean±S.D.) at 6 months post-treatment. There was no change in hirsutism score in the control group throughout the study period."	High

2.2 Summary of findings for combined oral contraceptives

Table 8 *First generation combined oral contraceptives compared to fourth generation.*

Outcome	Meta-analysis (MA): Number of participants (Number of studies) References Narrative analysis (NA): Number of participants (Number of studies) References	Effect Mean difference (95% CI)	Certainty of evidence (GRADE)	Downrating (GRADE)
BMI	MA: 226 (2) [8, 9] NA: No studies	No difference -0.28 (-2.13 to 1.56)	⊕OOO	-2 risk of bias[a] -2 imprecision[b]
HOMA-IR	MA: 226 (2) [8, 9] NA: No studies	Favours fourth generation 0.24 (0.09 to 0.38)	⊕OOO	-2 risk of bias[a] -1 imprecision[c]

Hirsutism	MA: 226 (2) [8, 9] NA: No studies	Favours fourth generation 1.04 (0.46 to 1.63)	⊕OOO	-2 risk of bias[a] -1 imprecision[c]i

a) only studies with a high risk of bias
b) few participants and wide confidence interval
c) few participants

Table 9 Third generation combined oral contraceptives vs fourth generation.

Outcome	Meta-analysis (MA): Number of participants (Number of studies) References Narrative analysis (NA): Number of participants (Number of studies) References	Effect Mean difference (95% CI)	Certainty of evidence (GRADE)	Downrating (GRADE)
BMI	MA: 312 (4) [10-13] NA: No studies	No difference -0.87 (-1.81 to 0.06)	⊕OOO	-1 risk of bias[a] -2 imprecision[b]
WHR	MA: 152 (2) [10, 11] NA: No studies	No difference -0.01 (-0.04 to 0.01)	⊕OOO	-1 risk of bias[a] -2 imprecision[c]
Glukos	MA: 173 (2) [11, 13] NA: No studies	No difference 0.00 (-0.18 to 0.19)	⊕OOO	-2 risk of bias[d] -2 imprecision[e]
Insulin	MA: 173 (2) [11, 13] NA: No studies	No difference 5.87 (-32.28 to 44.01)	⊕OOO	-2 risk of bias[d] -2 imprecision[c]
HOMA-IR	MA: 275 (3) [11-13] NA: No studies	No difference 0.26 (-0.87 to 1.38)	⊕OOO	-1 risk of bias[f] -2 imprecision[b]
LDL	MA: 197 (3) [12, 13] NA: No studies	Favours fourth generation 0.37 (0.05 to 0.69)	⊕OOO	-2 risk of bias[d] -1 imprecision[e]
TG	MA: 160 (2) [12, 13] NA: 37 (1) [10]	Favours third generation -0.15 (-0.23 to -0.08)	⊕OOO	-1 risk of bias[a] -2 imprecision[e]
Hirsutism	MA: 115 (1) [11] NA: 58 (1) [13]	No difference 0.43 (-1.82 to 2.68)	⊕OOO	-2 imprecision[c] -1 indirectness[g]

a) half of the included studies has a high risk of bias, however the largest weight in the summary estimate is from studies with low or moderate risk of bias
b) the confidence interval includes a clinically significant effect for one or both treatment groups, but the point estimate shows no effect
c) few participants and wide confidence interval
d) half or more of the studies have a high risk of bias
e) few participants
f) a study with a high risk of bias is included but most studies have a low or moderate risk of bias

g) result is based on a single study

Table 10 *Adverse events combined oral contraceptive pills.*

Study (Reference)	No. of participants	Gastrointestinal adverse event n (%)	Other adverse events n (%)
Dasgupta 2023 [12]	3rd generation 51 4th generation 51	3rd generation Nausea: 22 (43), Bloating: 51 (100) 4th generation Nausea: 12 (24), Bloating: 51 (100)	3rd generation Feeling of weight gain: 7 (14), Hair loss: 7 (14), Tiredness/sleepiness: 6 (12), Break through bleeding: 4 (8), Amenorrhea: 9 (18) 4th generation Feeling of weight gain: 5 (10), Hair loss: 7 (14), Tiredness/sleepiness: 8 (16), Break through bleeding: 7 (14), Amenorrhea: 2 (4)

3 Analyses regarding antiandrogens

3.1 Meta-analyses for antiandrogens+

BMI (kg/m^2)

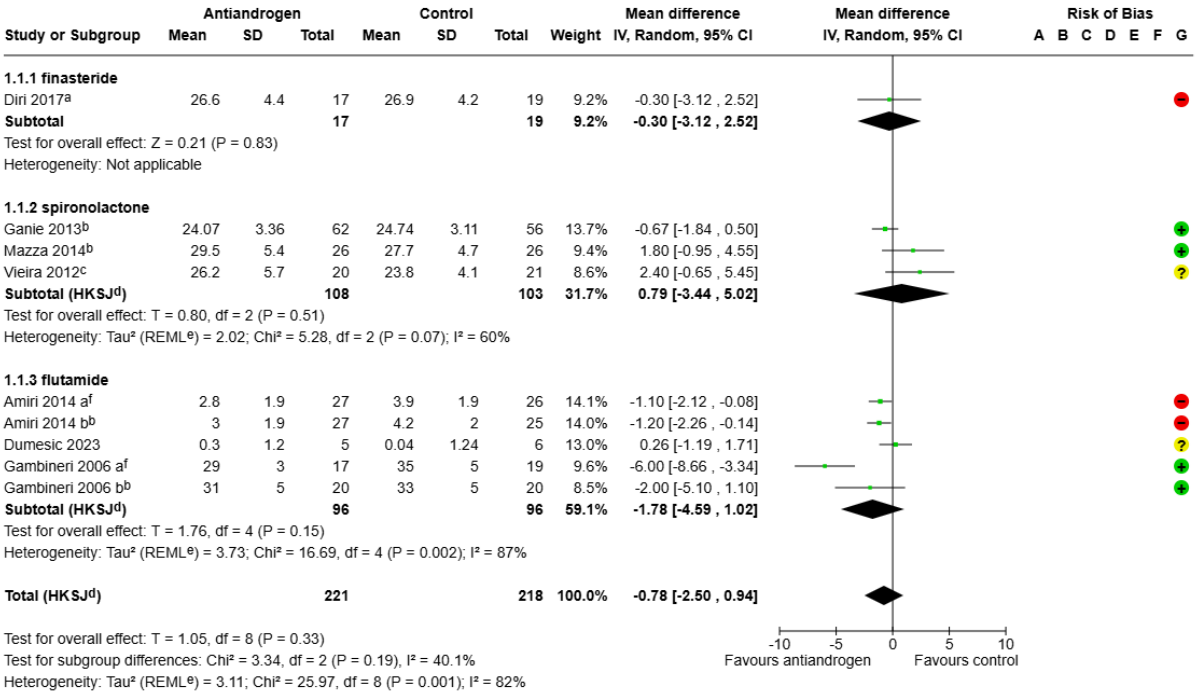
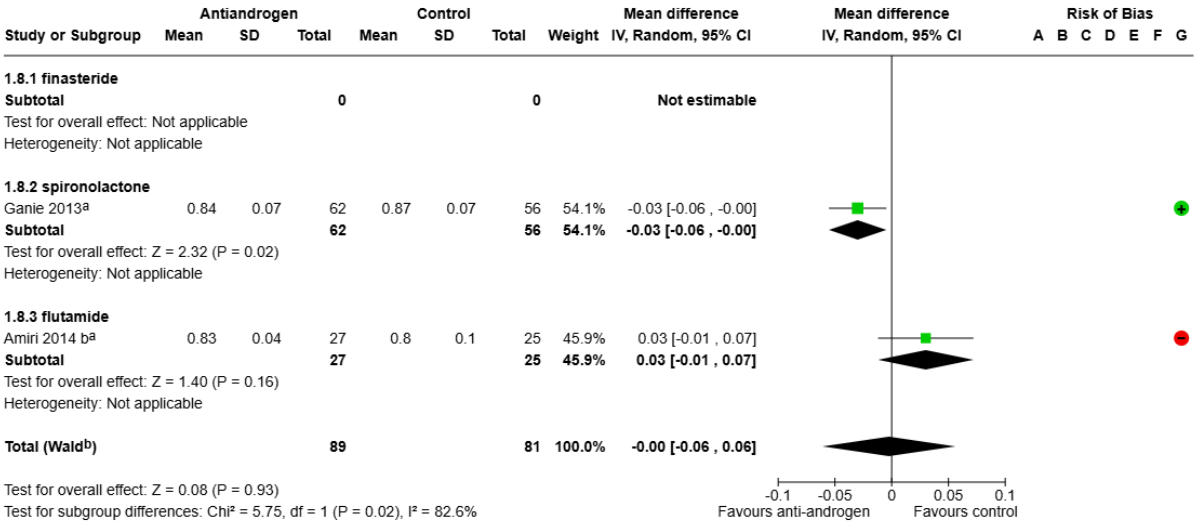


Table 11 Studies not included in meta-analysis (included in narrative analysis).

Study (Reference)	Intervention	Control	Result	Risk of bias
Moretti 2018 [23]	Bicalutamide + oral contraceptive n=28 Geometric mean: 26.7 SD: 6.8	Oral contraceptive n=24 Geometric mean: 24.5 SD: 7.4	Favours control	Moderate

WHR



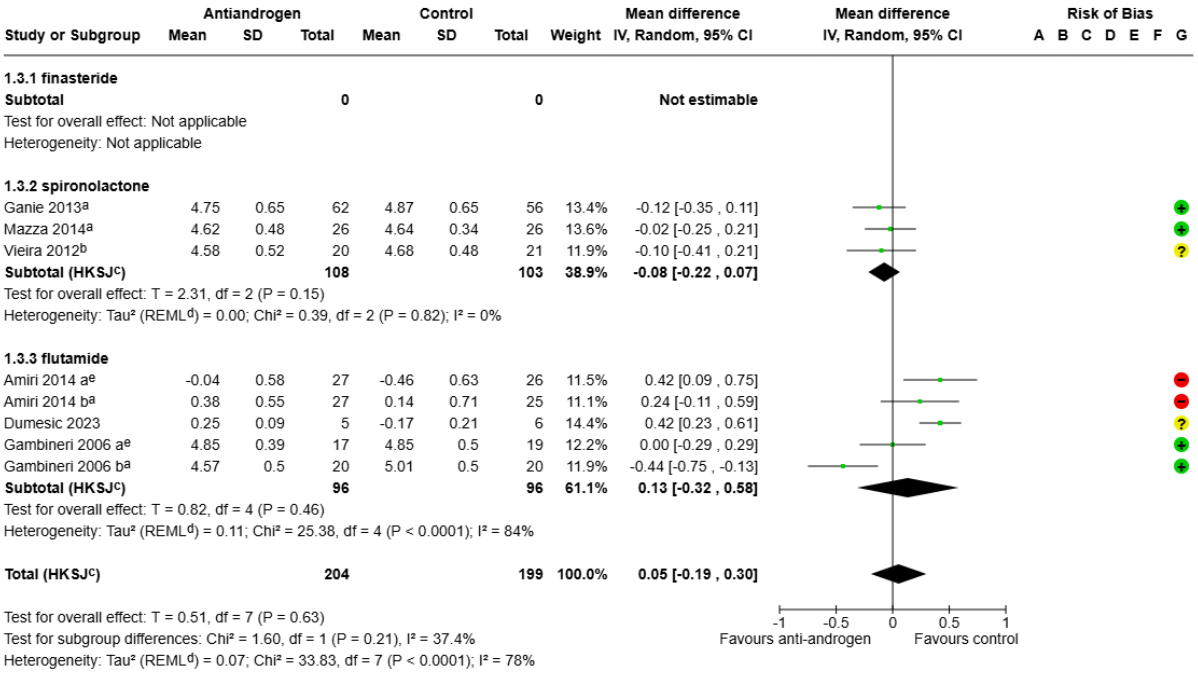
Footnotes

[a]with metformin and lifestyle intervention for both groups
[b]CI calculated by Wald-type method.
[c]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Fasting glucose (mmol/l)



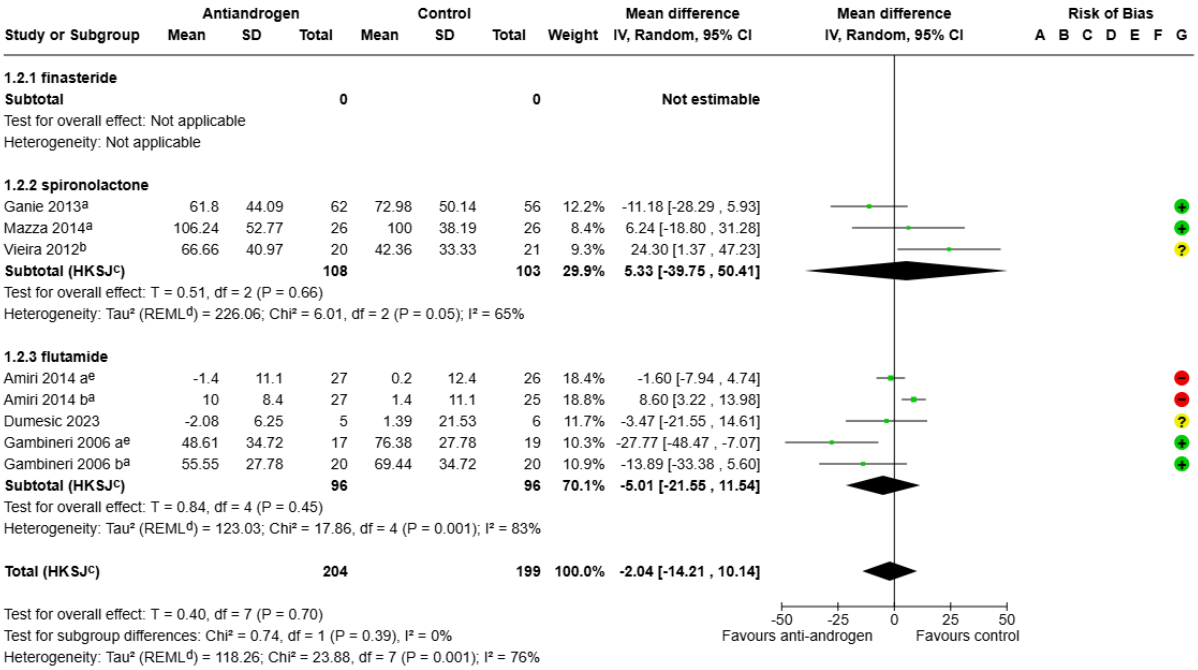
Footnotes

[a]with metformin and lifestyle intervention for both groups
[b]with oral contraceptives for both groups
[c]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[d]Tau² calculated by Restricted Maximum-Likelihood method.
[e]with lifestyle intervention for both groups

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Fasting insulin (pmol/l)



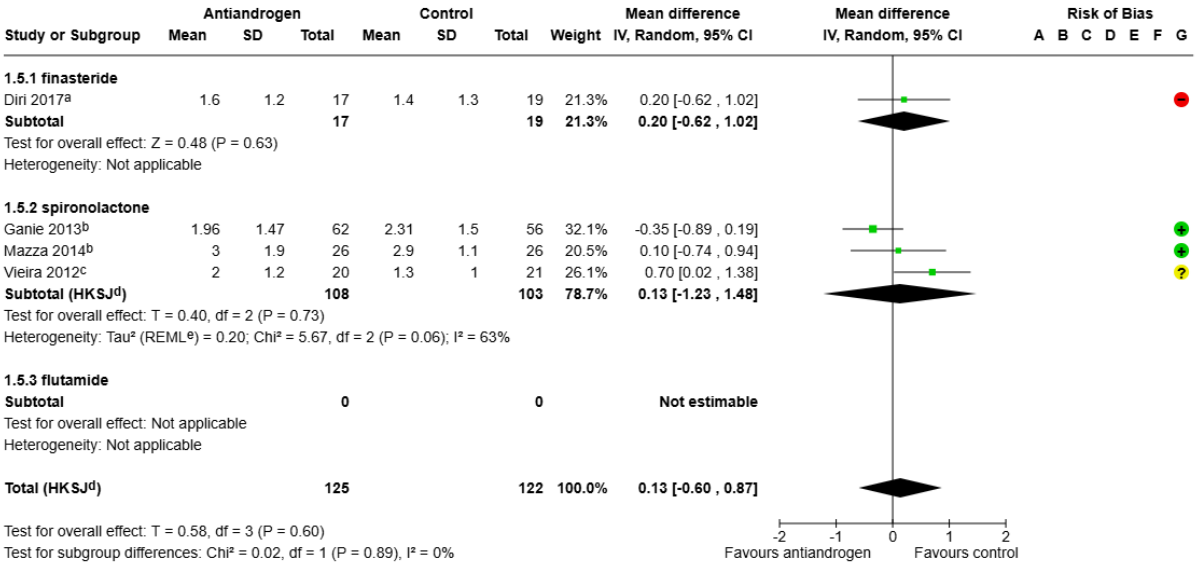
Footnotes

[a]with metformin and lifestyle intervention for both groups
[b]with oral contraceptives for both groups
[c]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[d]Tau² calculated by Restricted Maximum-Likelihood method.
[e]with lifestyle intervention for both groups

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

HOMA-IR



Footnotes

[a]with metformin for both groups
[b]with metformin and lifestyle intervention for both groups
[c]with oral contraceptives for both groups
[d]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[e]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

LDL (mmol/l)

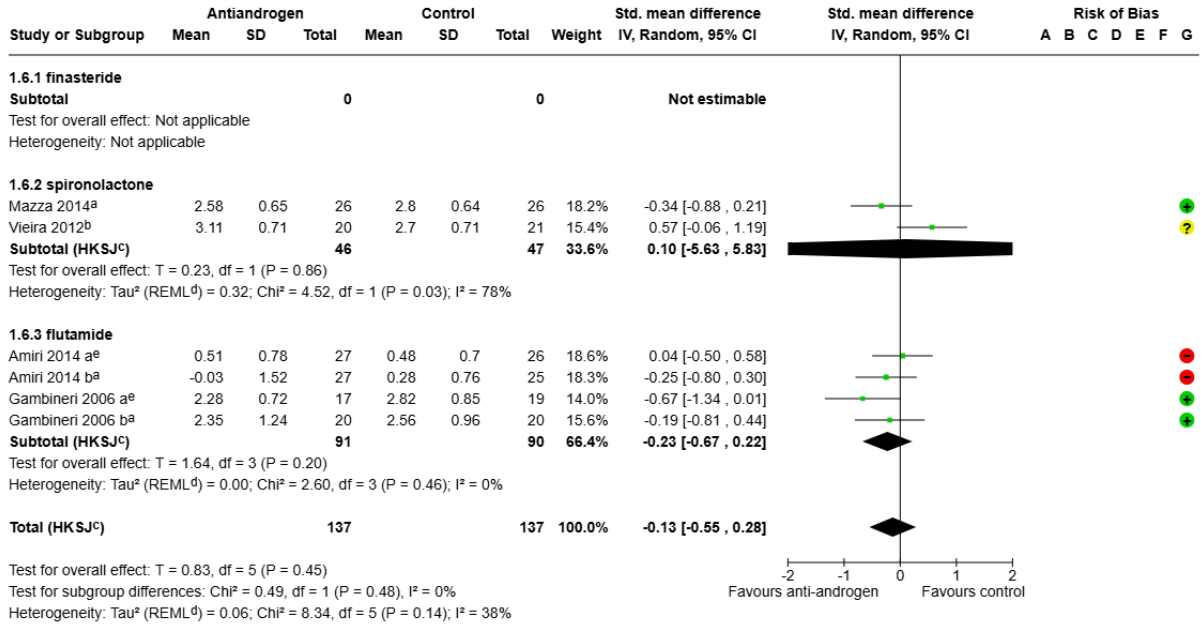
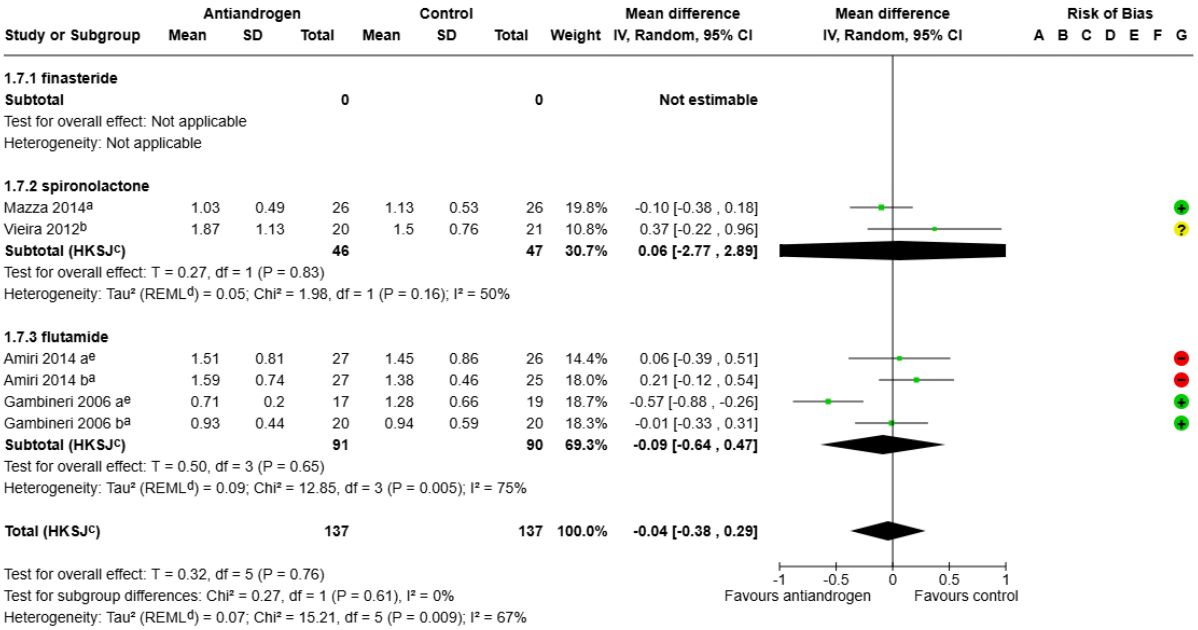


Table 12 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Intervention	Control	Result	Risk of bias
Hagag 2014 [21]	Spironolactone + oral contraceptive n=72	Oral contraceptive n= 25	"mild elevation (+20% vs. baseline) of the LDL-C levels was reported in all groups"	Moderate
Moretti 2018 [23]	Bicalutamide + oral contraceptive n=28 Geometric mean: 2.89 SD: 0.64	Oral contraceptive n=24 Geometric mean: 2.52 SD: 0.93	Favours control	Moderate

Triglycerides (mmol/l)



Footnotes

[a]with metformin and lifestyle intervention for both groups
[b]with oral contraceptives for both groups
[c]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[d]Tau² calculated by Restricted Maximum-Likelihood method.
[e]with lifestyle intervention for both groups

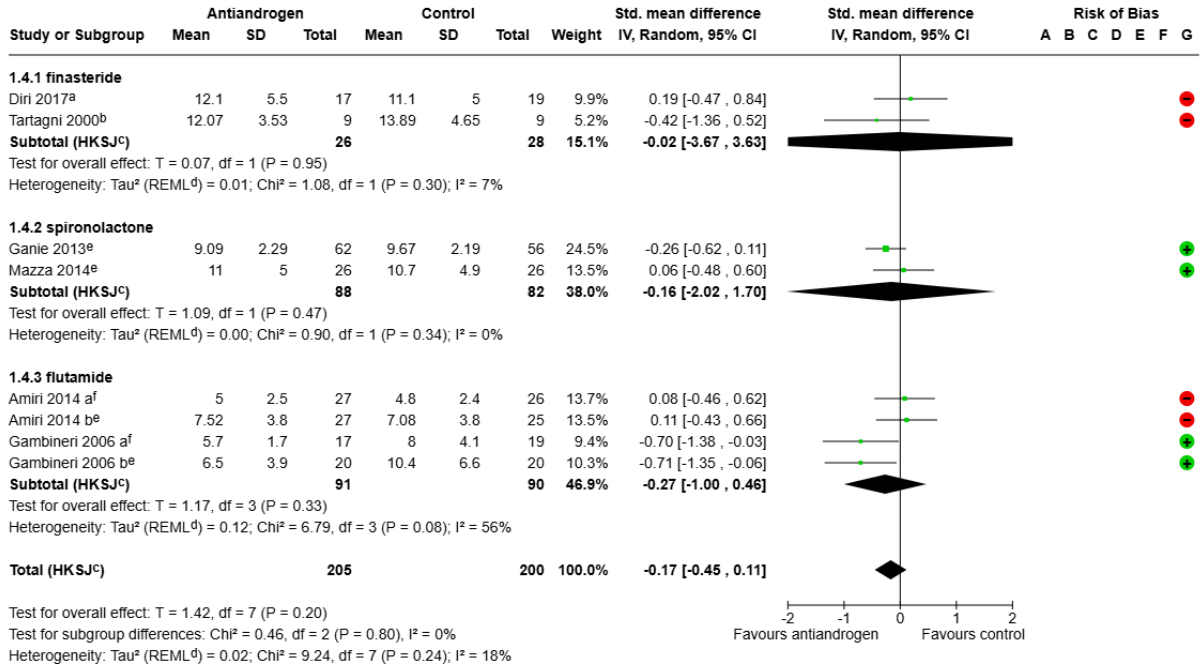
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Table 13 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Intervention	Control	Result	Risk of bias
Hagag 2014 [21]	Spironolactone + oral contraceptive n=72 Percent change: 32 SE: 8.8	Oral contraceptive n=25 Percent change: 35 SE: 5.9	No difference	Moderate
Moretti 2018 [23]	Bicalutamide + oral contraceptive n=28 Geometric mean: 1.51 SD: 0.62	Oral contraceptive n=24 Geometric mean: 1.02 SD: 0.31	Favours control	Moderate

Hirsutism



Footnotes

[a]with metformin for both groups
[b]with oral contraceptives for both groups
[c]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[d]Tau² calculated by Restricted Maximum-Likelihood method.
[e]with metformin and lifestyle intervention for both groups
[f]with lifestyle intervention for both groups

Risk of bias legend

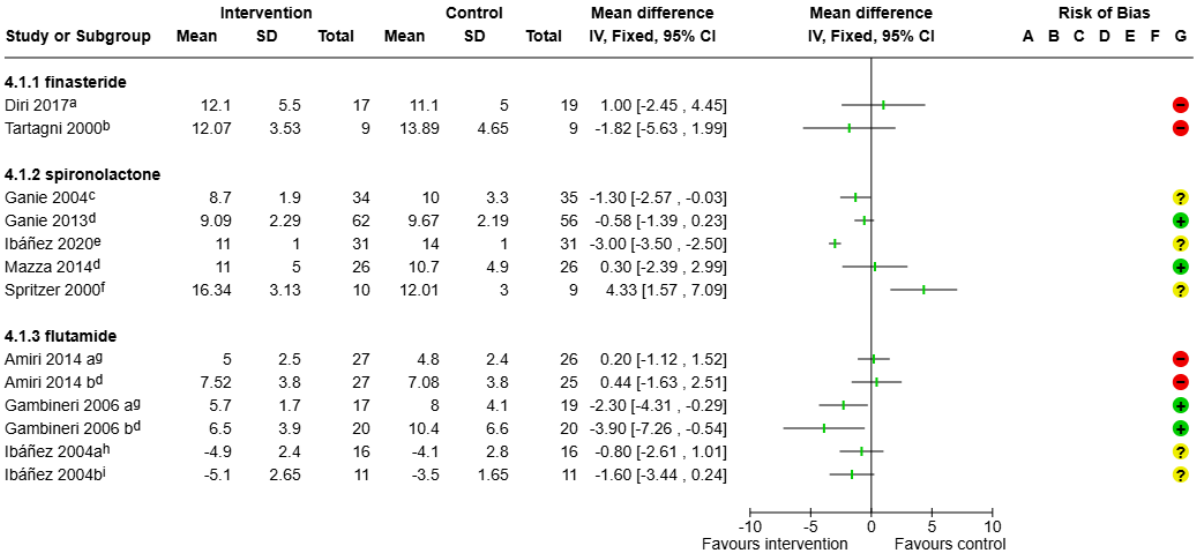
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Table 14 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Intervention	Control	Result	Risk of bias
Hagag 2014 [21]	Spironolactone + oral contraceptive n=72 Percent change: 57 SE: 2.4	Oral contraceptive n=25 Percent change: 38 SE: 3.2	Favours AA	Moderate
Moretti 2018 [23]	Bicalutamide + oral contraceptive n=28 Geometric mean: 9.7 SD: 3.2	Oral contraceptive n=24 Geometric mean: 9.8 SD: 4	No difference	Moderate

3.2 Antiandrogens individual studies

Hirsutism



Footnotes

[a]with metformin for both groups
[b]with oral contraceptives for both groups
[c]antiandrogen + lifestyle intervention vs metformin + liffestyle intervention
[d]with metformin and lifestyle intervention for both groups
[e]antiandrogen + pioglitazone + metformin vs oral contraceptives
[f]antiandrogen vs oral contraceptives
[g]with lifestyle intervention for both groups
[h]antiandrogen + metformin vs oral contraceptives
[i]antiandrogen + metformin + oral contraceptives vs oral contraceptives

Risk of bias legend

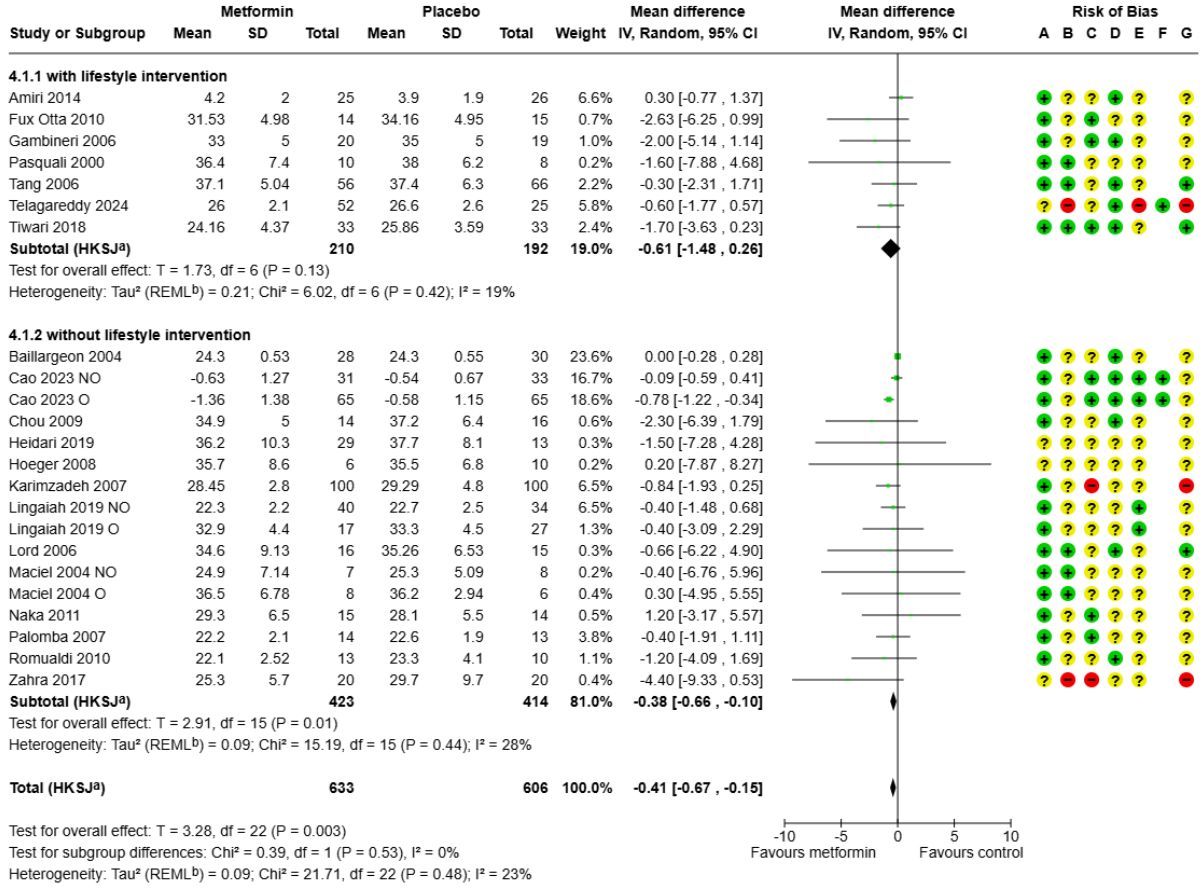
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

4 Analyses regarding metformin

4.1 Meta-analyses for metformin with or without lifestyle intervention compared to placebo with or without lifestyle intervention

4.1.1 All studies

BMI (kg/m²)



Footnotes

[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.

[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Table 14 Studies not included in meta-analysis (included in narrative analysis).

Study (Reference)	Metformin	Placebo	Result	RoB
Eisenhardt 2006 [37]	n=22 Median: 31.1 IQR: 22.9 to 34.2	n=23 Median: 32.4 IQR: 26.7 to 37.1	Favours metformin	Moderate
Fleming 2002 [38]	n=26 mean: 34.6	n=39 mean: 35.6	Favours metformin	High
Ng 2001 [45]	n=7 Median: 23.0 Range: 18.9 to 32.4	n=8 Median: 23.1 Range: 18.8 to 29.1	Favours metformin	Moderate

WHR

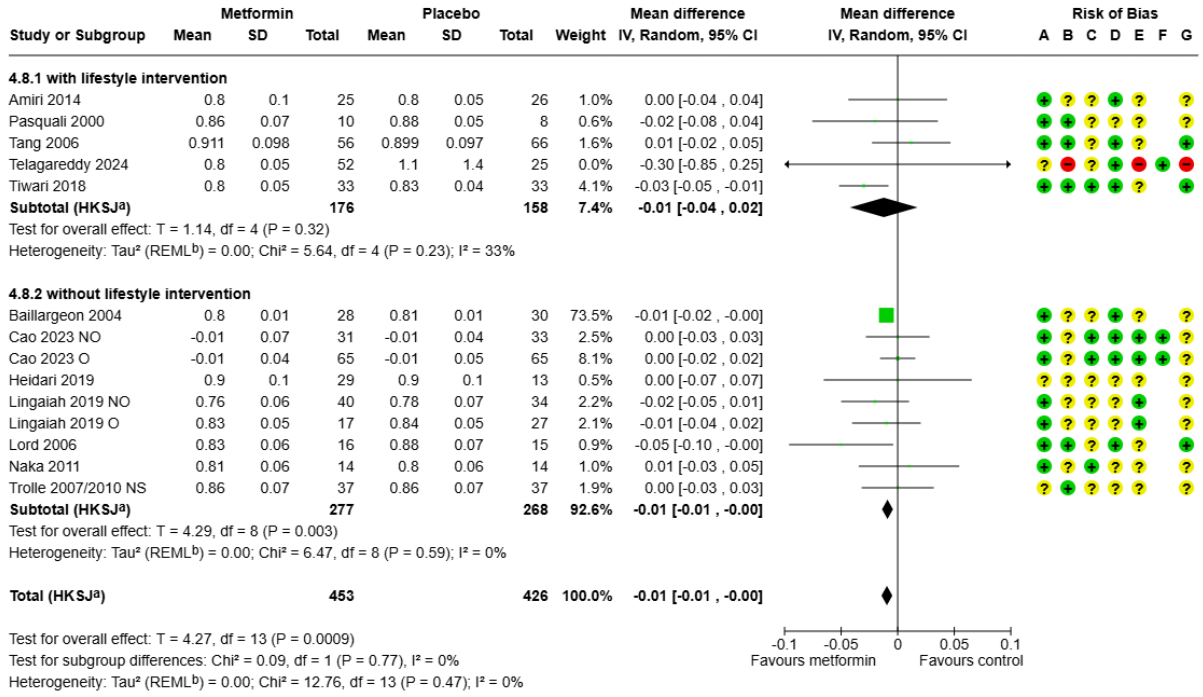


Table 15 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Metformin	Placebo	Result	RoB
Fleming 2002 [38]	n=26 Mean: 0.88	n=39 Mean: 0.88	No difference	High
Fux Otta 2010 [39]	n=14 Median: 0.85 IQR: 0.78 till 0.92	n=15 Median: 0.92 IQR: 0.84 till 1	Favours metformin	Moderate

Fasting glucose (mmol/l)

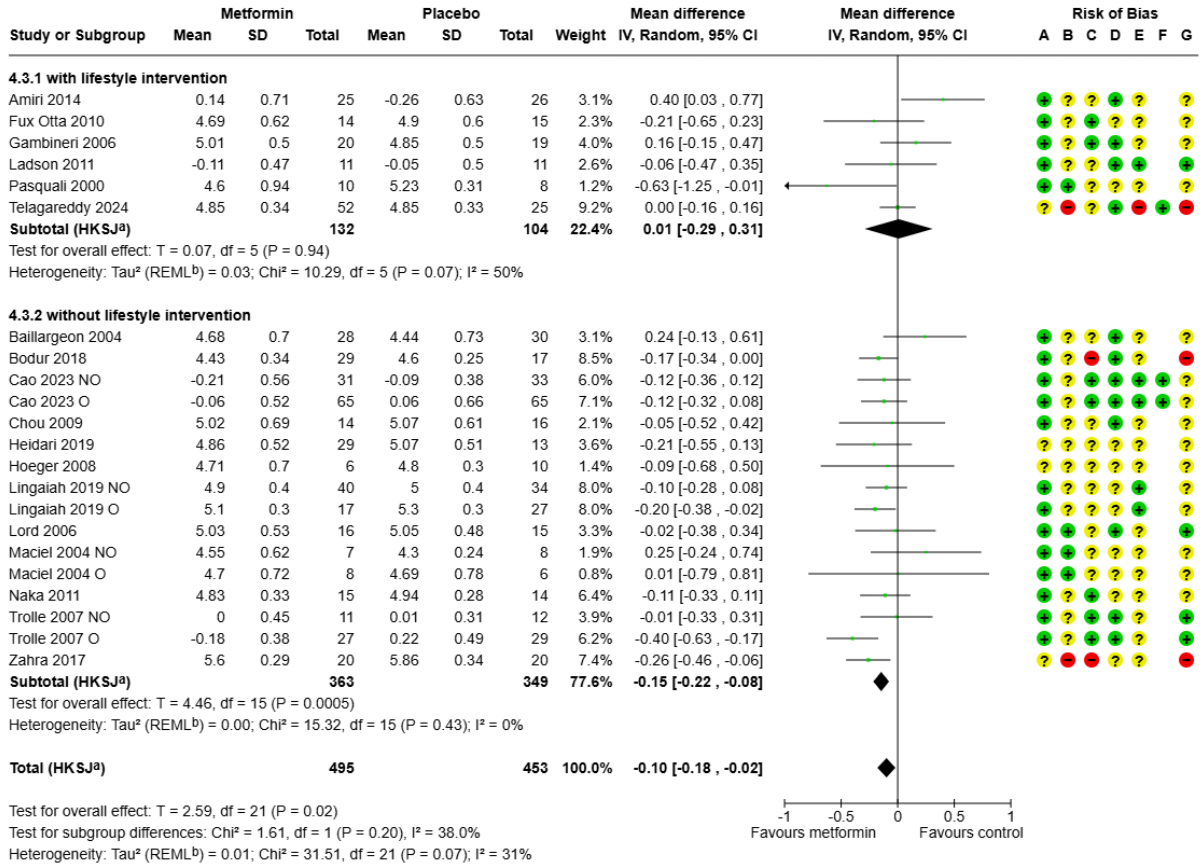


Table 16 Studies not included in meta-analysis (included in narrative analysis).

Study (Reference)	Metformin	Placebo	Result	RoB
Eisenhardt 2006 [37]	n=22 Median: 4.77 IQR = 4.11 till 5.61	n=23 Median: 4.61 IQR: 4.00 till 5.22	Favours placebo	Moderate
Fleming 2002 [38]	n=26 Mean: 5.0[1]	n=39 Mean: 5.0[1]	No difference	High
Ng 2001 [45]	n=7 Median: 5.1 Range: 4.6 to 5.6	n=8 Median: 4.9 Range: 4.4 to 5.7	Favours placebo	Moderate

[1] Reported as nmol/l, however given the order of magnitude this seems unlikely.

Fasting insulin (pmol/l)

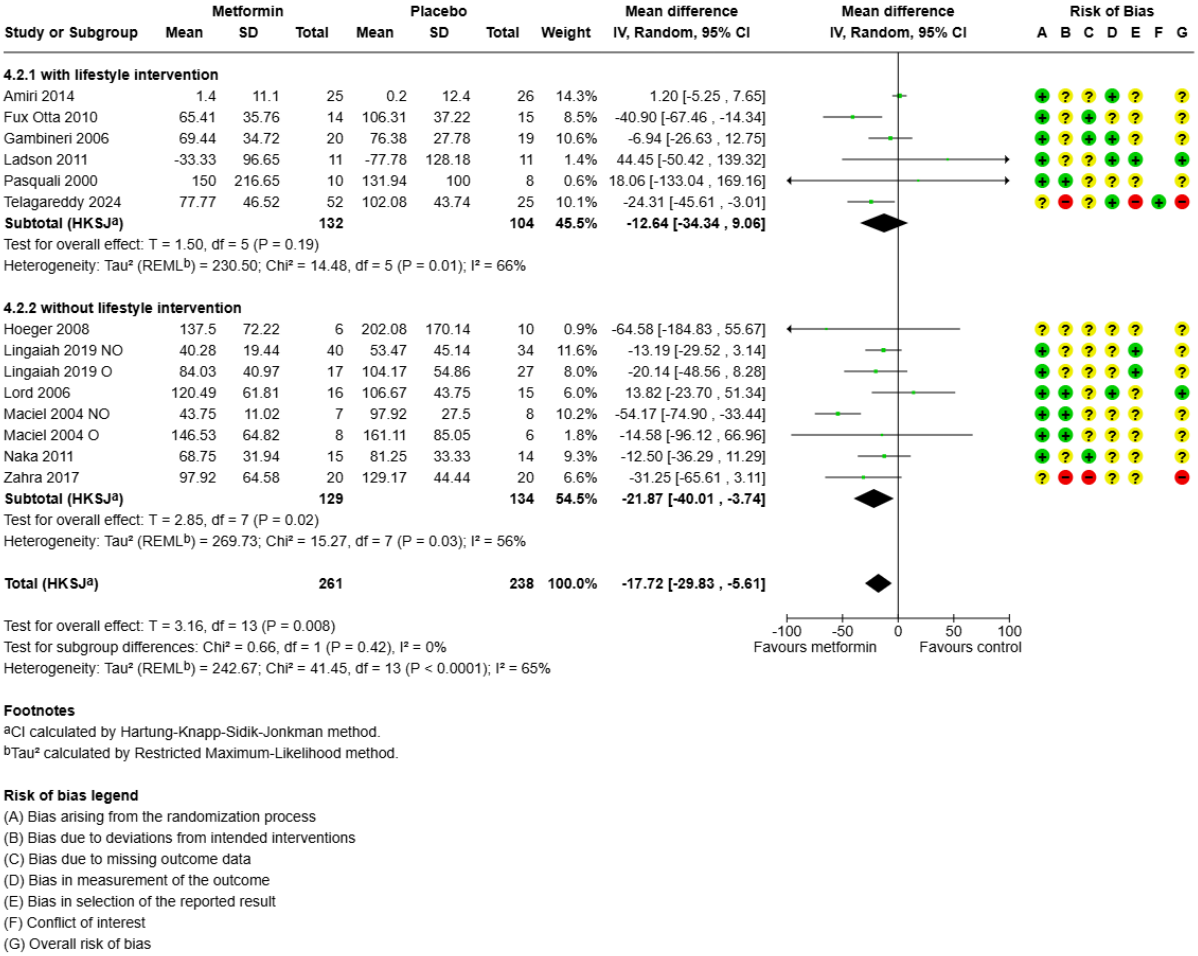


Table 17 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Metformin	Placebo	Result	RoB
Chou 2003 [36]	n = 14 Median: 275.69 IQR: 206.25 to 340.97	n=16 Median: 222.22 IQR: 173.61 to 252.78	Favours placebo	Moderate
Eisenhardt 2006 [37]	n=22 Median: 138.89 IQR: 111.11 to 180.56	n=23 Median: 152.78 IQR: 111.11 to 166.67	Favours metformin	Moderate
Fleming 2002 [38]	n=26 Mean: 113.89	n=39 Mean: 121.53	Favours metformin	High
Ng 2001 [45]	n=7 Median: 50.69 Range: 19.44 to 118.06	n=8 Median: 56.94 Range: 27.08 to 62.50	Favours metformin	Moderate
Tang 2006 [49]	n=56 Median: 72.7	n=66 Median = 81.8	Favours metformin	Low
Trolle 2007 O [29, 30]	n= 25 Median: -14.51	n= 23 Median: 5.35	Favours metformin	Low

	Range 5-95 percentile: -127.64 to 58.68	Range 5-95 percentile: -53.96 to 90.00		
Trolle 2007 NO [29, 30]	n=11 Median: 2.64 Range 5-95 percentile: -72.85 to 165.97	n=12 -0.97 Range 5 – 95 percentile: -20.83 to 69.58	Favours placebo	Low

HOMA-IR

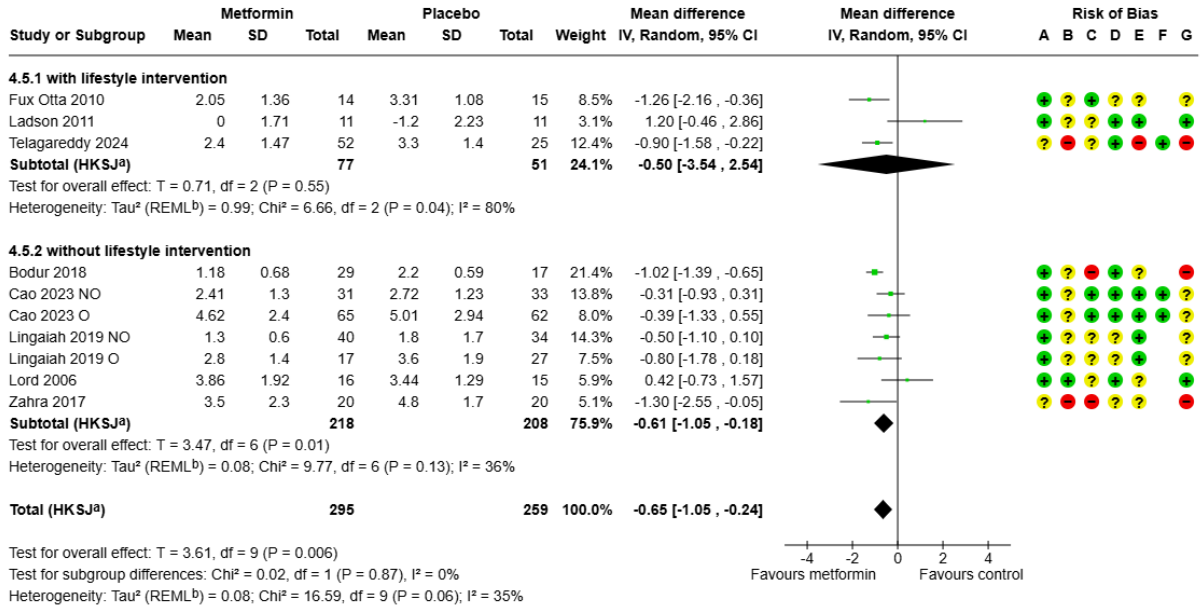


Table 18 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Metformin	Placebo	Result	RoB
Eisenhardt 2006 [37]	n=22 Median: 3.96 IQR: 2.93 till 5.68	n=23 Median: 4.02 IQR: 2.97 till 5.87	Favours metformin	Moderate
Trolle 2007 O [29, 30]	n=23 Median: -0.66 Range 5 -95 percentile: -5.96 to 1.54	n=21 Median: 0.38 Range 5-95 percentile: -2.10 to 3.62	Favours metformin	Low
Trolle 2007 NO [29, 30]	n=10 Median: 0.16 Range 5–95 percentile: -2.48 to 4.27	n=11 Median: 0 Range 5–95 percentile: -0.63 to 2.17	Favours metformin	Low

LDL (mmol/l)

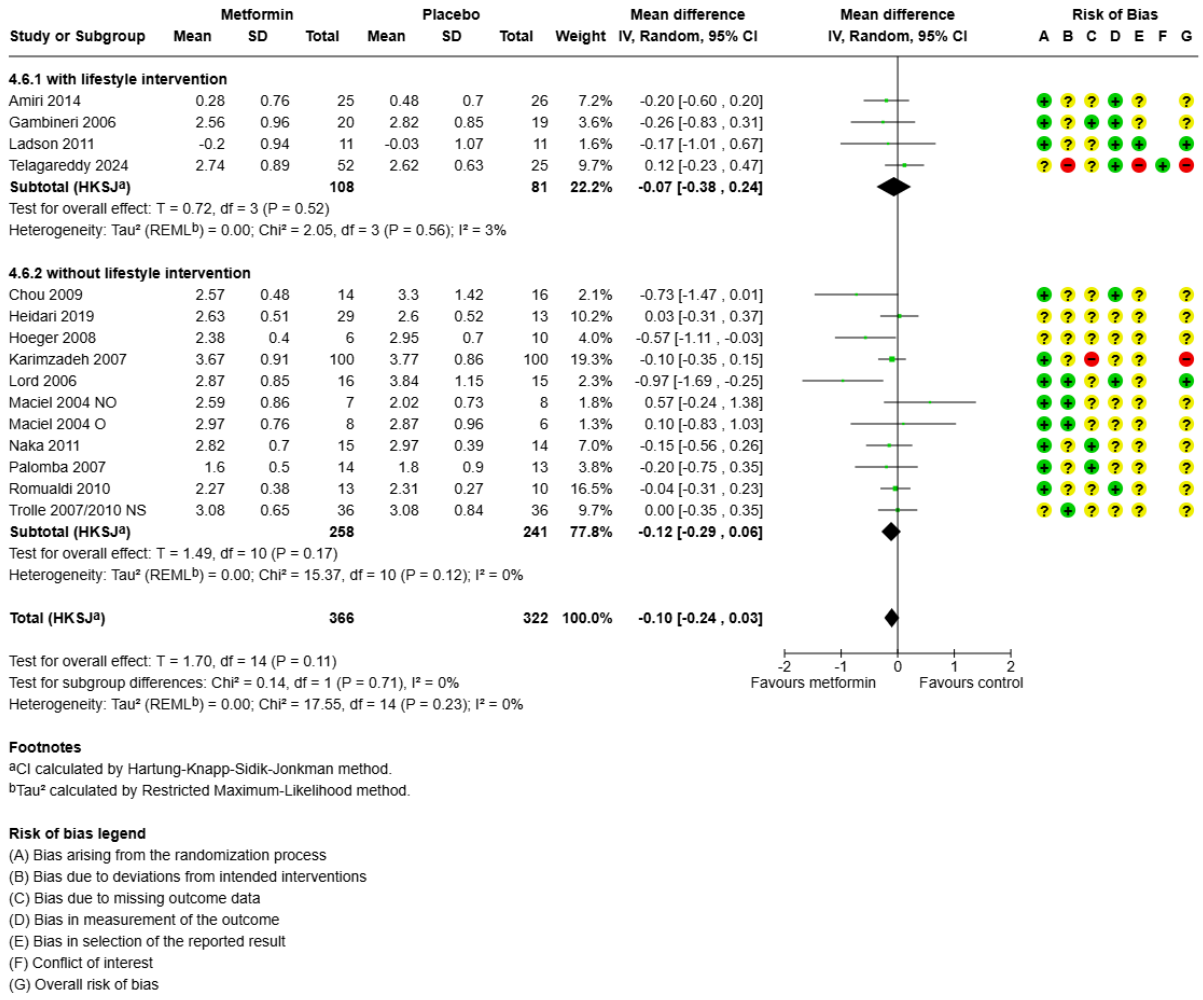


Table 19 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Metformin	Placebo	Result	RoB
Fleming 2002 [38]	n=26 Mean: 2.81	n=39 Mean: 3.27	Favours metformin	High
Ng 2001 [45]	n=7 Median: 2.5 Range: 1.8 to 4.3	n=8 Median: 3.4 Range: 1.9 till 6.2	Favours metformin	Moderate

Triglycerides (mmol/l)

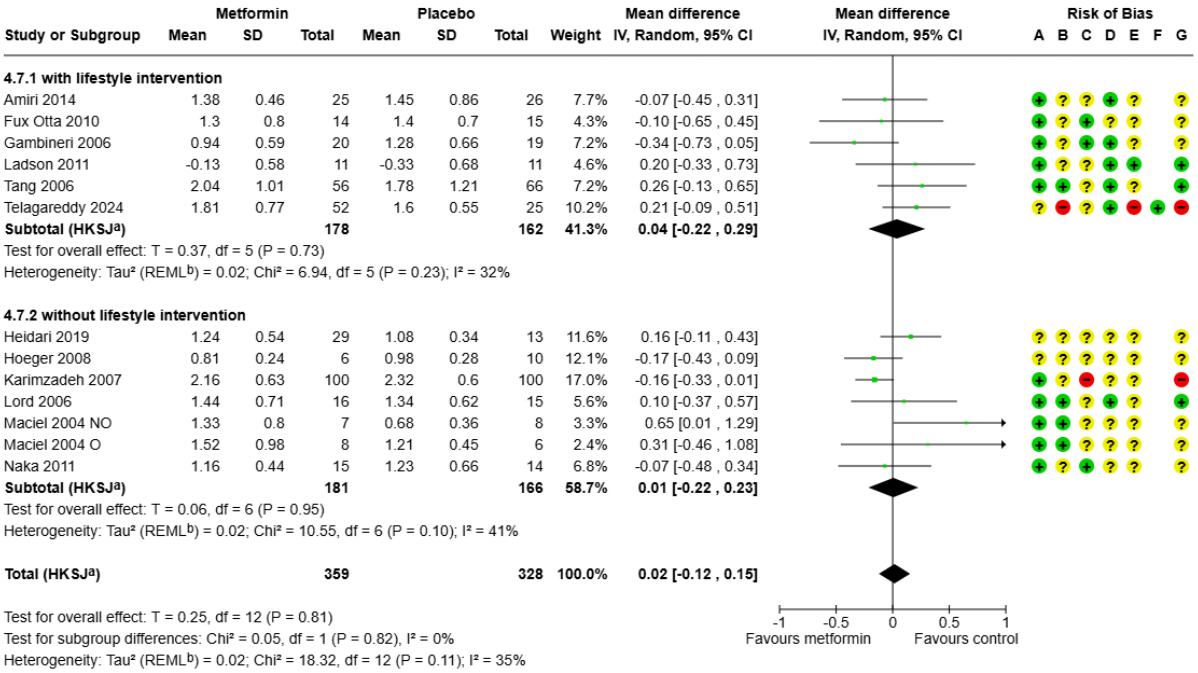


Table 20 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Metformin	Placebo	Result	RoB
Chou 2003 [36]	n=14 Median: 1.27 IQR: 0.77 to 1.90	n=16 Median: 1.44 IQR: 1.10 to 1.89	Favours metformin	Moderate
Fleming 2002 [38]	n=26 Mean: 1.63	n=39 Mean: 1.44	Favours placebo	High
Ng 2001 [45]	n=7 Median: 1.0 Range: 0.4 to 1.5	n=8 Median: 1.1 Range: 0.4 to 2.2	Favours metformin	Moderate

Hirsutism

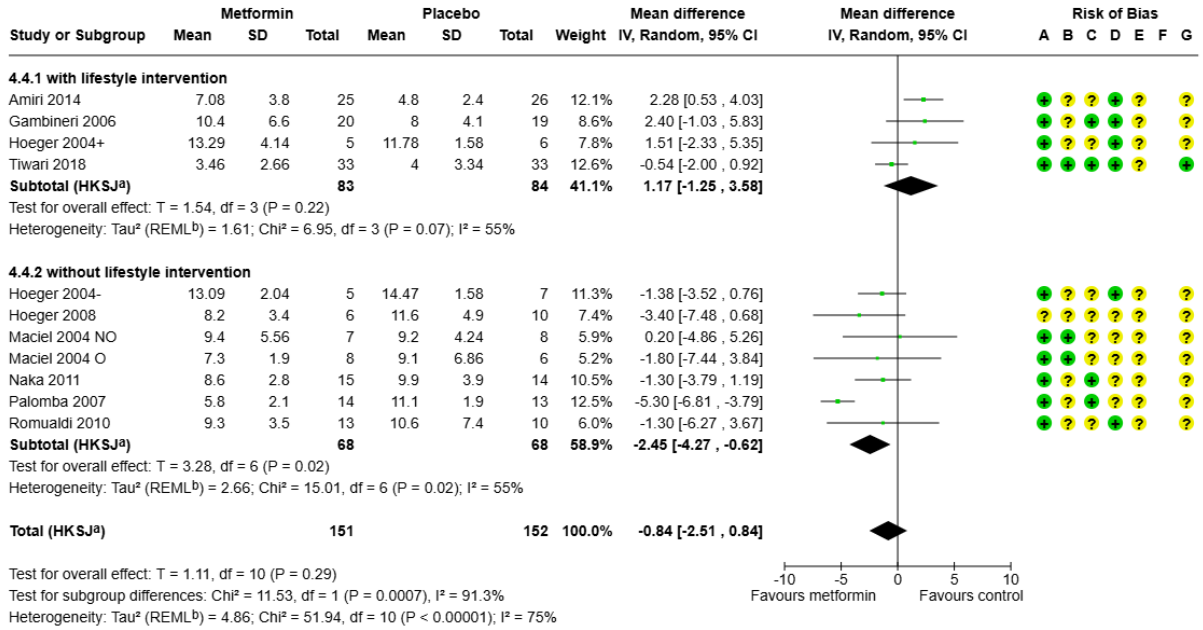


Table 21 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Metformin	Placebo	Result	RoB
Eisenhardt 2006 [37]	n=22 Median: 9.2 IQR: 7.9 to 11.8	n=23 Median: 8.8 IQR: 7.5 to 11.0	Favours placebo	Moderate

4.1.2 BMI ≥25

BMI (kg/m^2)

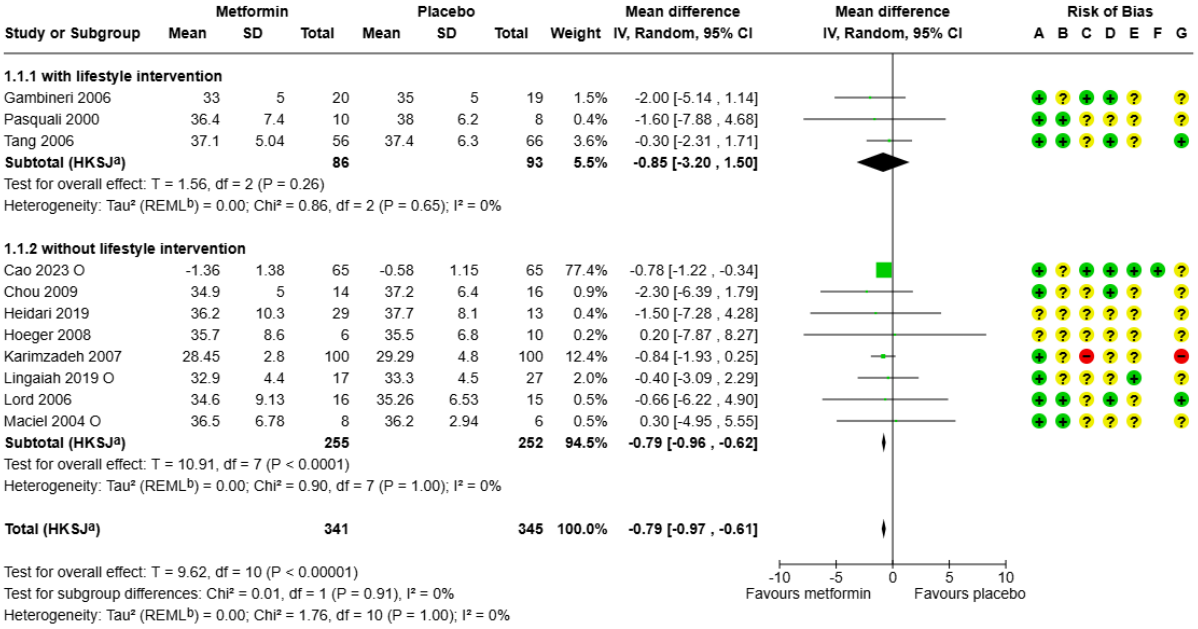


Table 22 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Metformin	Placebo	Result	RoB
Eisenhardt 2006 [37]	n=22 Median: 31.1 IQR: 22.9 to 34.2	n=23 Median: 32.4 IQR: 26.7 to 37.1	Favours metformin	Moderate
Fleming 2002 [38]	n=26 mean: 34.6	n=39 mean: 35.6	Favours metformin	High

WHR

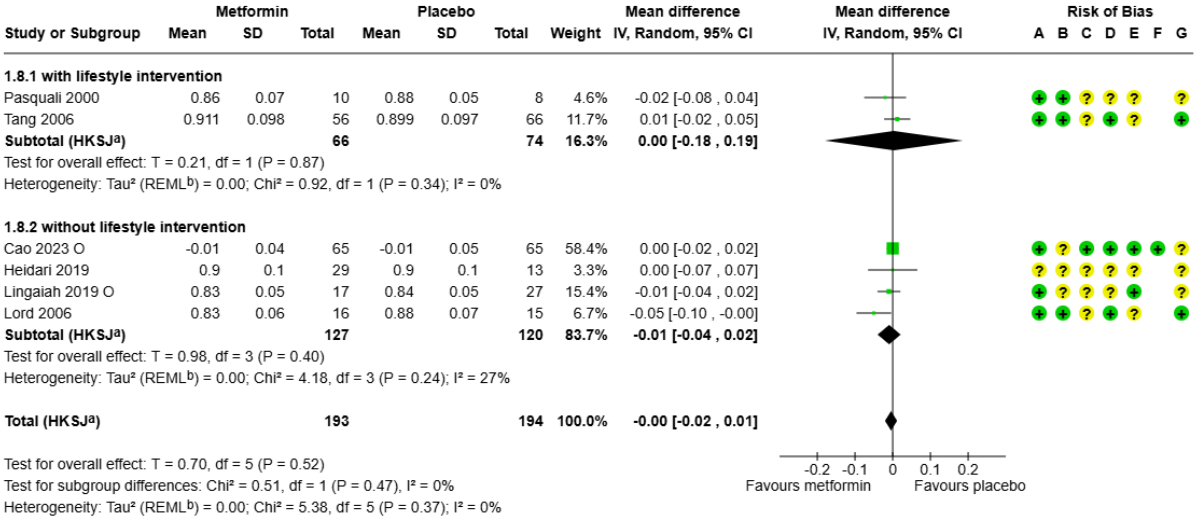


Table 23 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Metformin	Placebo	Result	RoB
Fleming 2002 [38]	n=26 Mean: 0.88	n=39 Mean: 0.88	No difference	High

Fasting glucose (mmol/l)

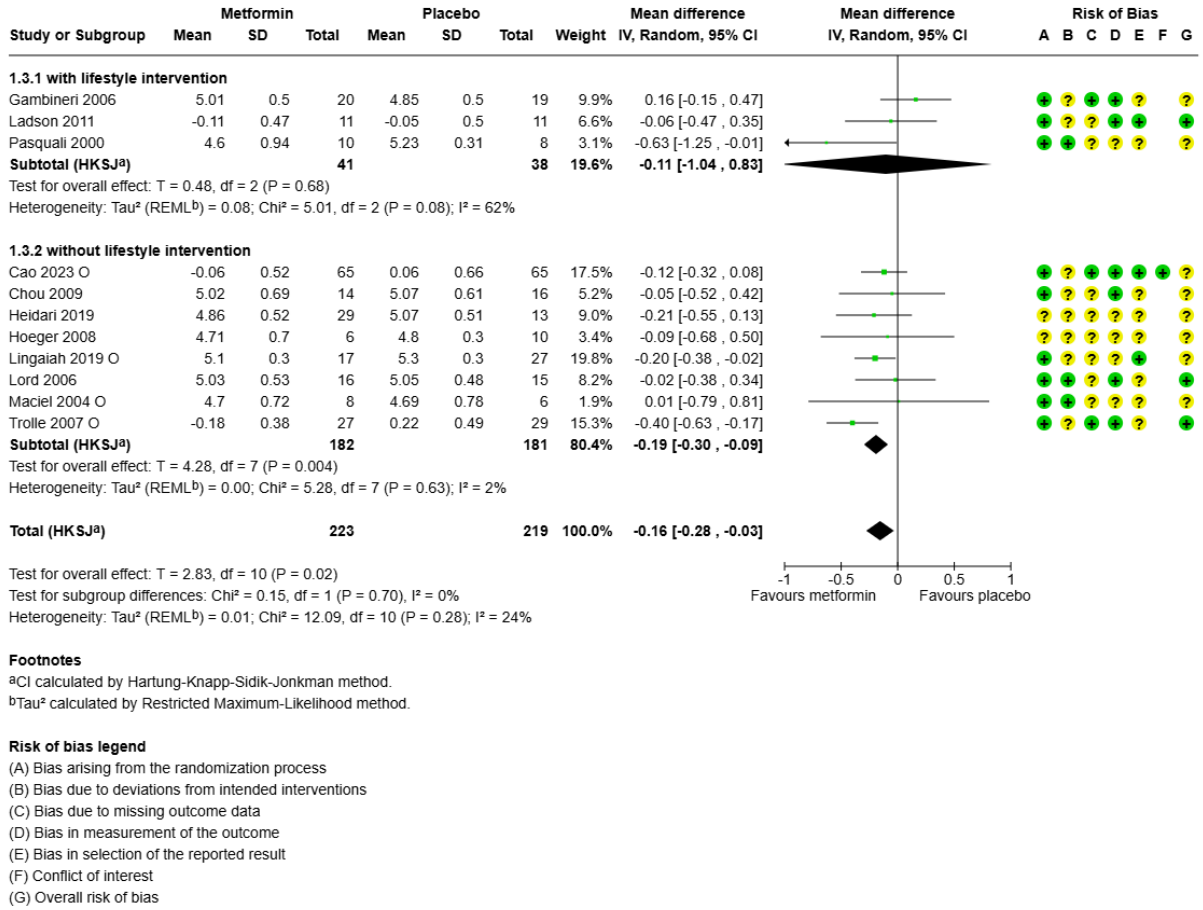


Table 24 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Metformin	Placebo	Result	RoB
Eisenhardt 2006 [37]	n=22 Median: 4.77 IQR = 4.11 till 5.61	n=23 Median: 4.61 IQR: 4.00 till 5.22	Favours placebo	Moderate
Fleming 2002 [38]	n=26 Mean: 5.0[2]	n=39 Mean: 5.0[2]	No difference	High
Tang 2006 [49]	n= 56 Mean: 4.83	n=66 Mean: 4.88	Favours metformin	Low

[2] Reported as nmol/l, however given the order of magnitude this seems unlikely.

Fasting insulin (pmol/l)

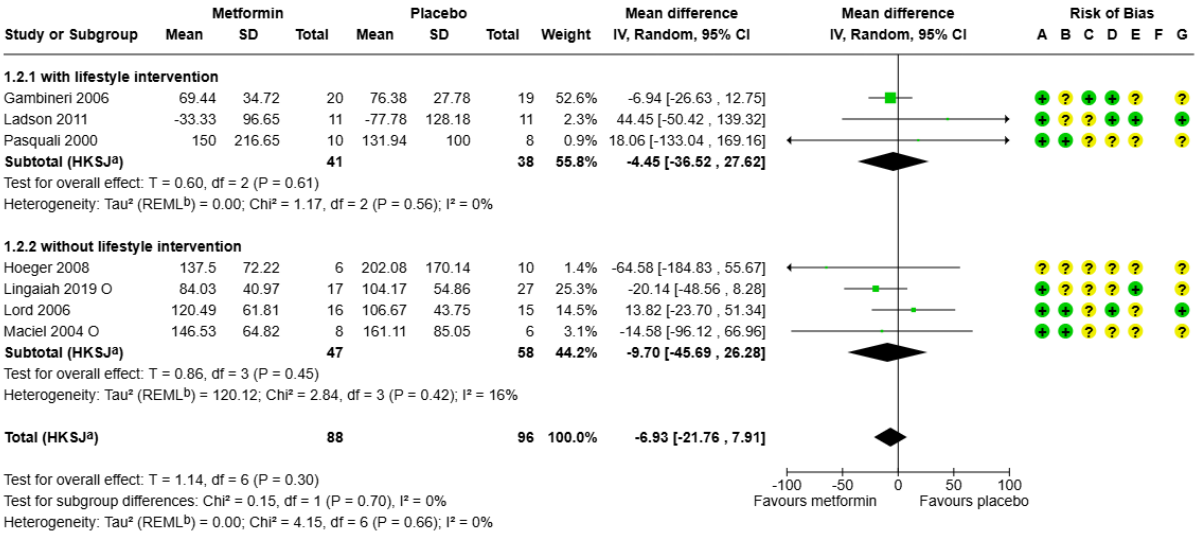


Table 25 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Metformin	Placebo	Result	RoB
Chou 2003 [36]	n=14 Median: 275.69 IQR: 206.25 to 340.97	n=16 Median: 222.22 IQR: 173.61 to 252.78	Favours placebo	Moderate
Eisenhardt 2006 [37]	n=22 Median: 138.89 IQR: 111.11 to 180.56	n=23 Median: 152.78 IQR: 111.11 to 166.67	Favours metformin	Moderate
Fleming 2002 [38]	n=26 Mean: 113.89	n=39 Mean: 121.53	Favours metformin	High
Tang 2006 [49]	n=56 Mean: 72.7	n=66 Mean = 81.8	Favours metformin	Low
Trolle 2007 O[29, 30]	n= 25 Median: -14.51 Range 5-95 percentile: -127.64 to 58.68	n= 23 Median: 5.35 Range 5-95 percentile: -53.96 to 90.00	Favours metformin	Low

HOMA-IR

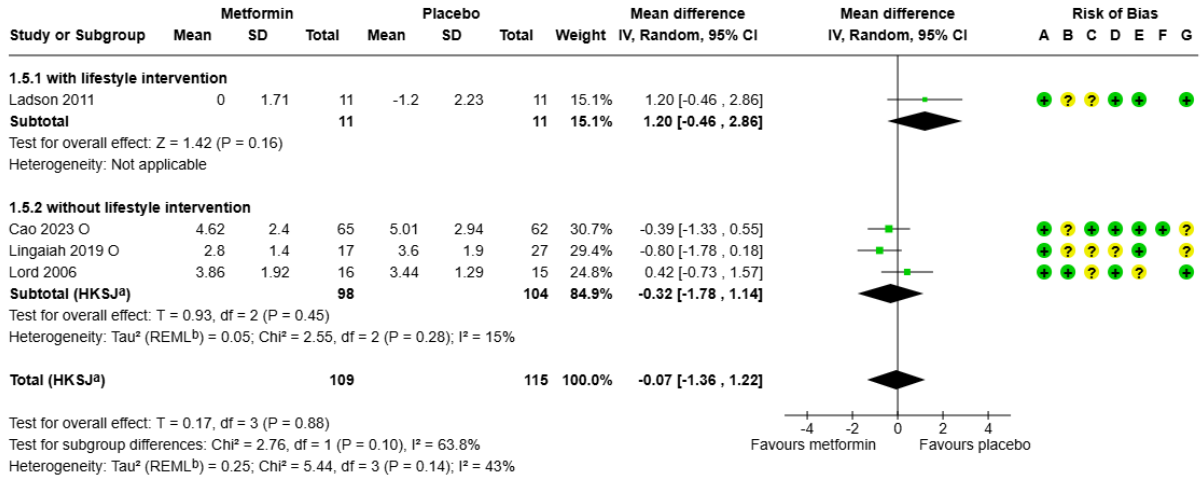


Table 26 Studies not included in meta-analysis (included in narrative analysis).

Study (Reference)	Metformin	Placebo	Result	RoB
Eisenhardt 2006 [37]	n=22 Median: 3.96 IQR: 2.93 till 5.68	n=23 Median: 4.02 IQR: 2.97 till 5.87	Favours metformin	Moderate
Trolle 2007 O [29, 30]	n=23 Median: -0.66 Range 5 -95 percentile: -5.96 to 1.54	n=21 Median: 0.38 Range 5-95 percentile: -2.10 to 3.62	Favours metformin	Low

LDL (mmol/l)

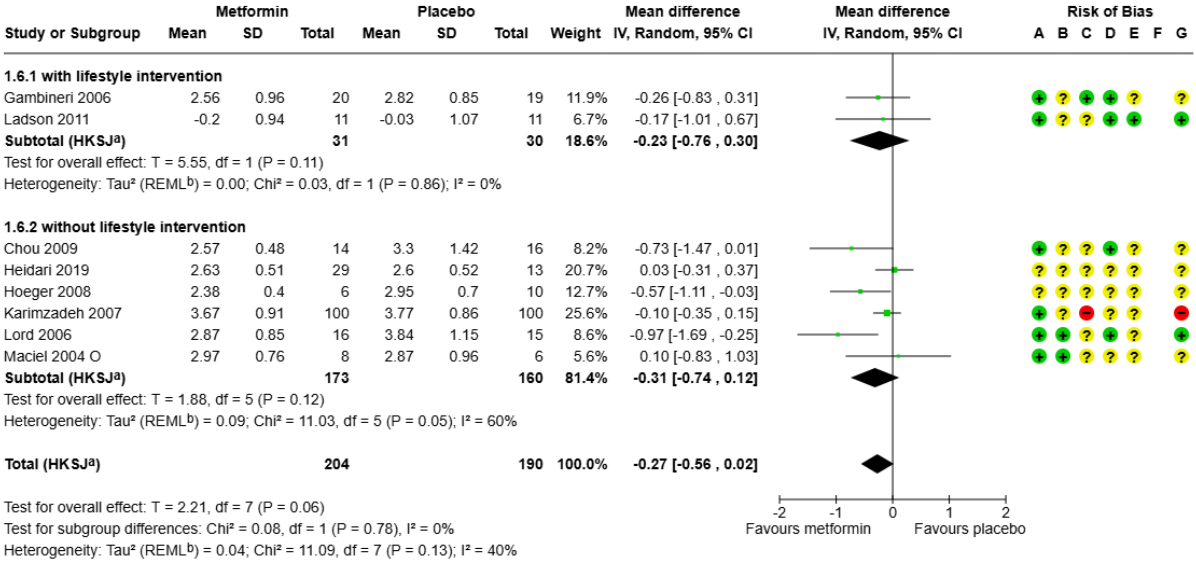
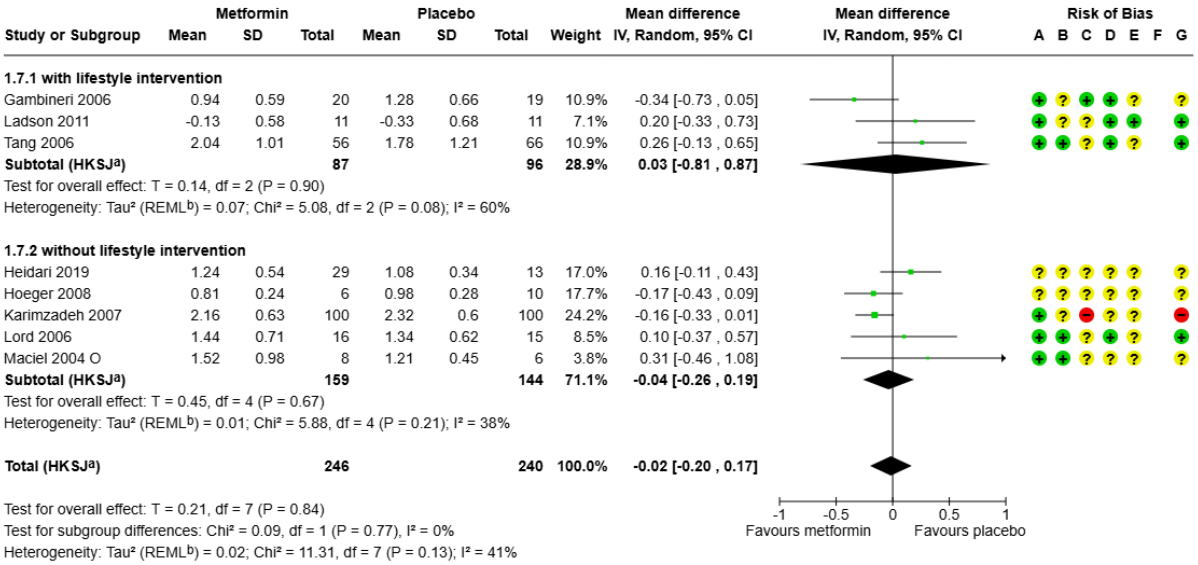


Table 27 Studies not included in meta-analysis (included in narrative analysis).

Study (Reference)	Metformin	Placebo	Result	RoB
Fleming 2002 [38]	n=26 Mean: 2.81	n=39 Mean: 3.27	Favours metformin	High

Triglycerides (mmol/l)



Footnotes

[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.

[b]Tau² calculated by Restricted Maximum-Likelihood method.

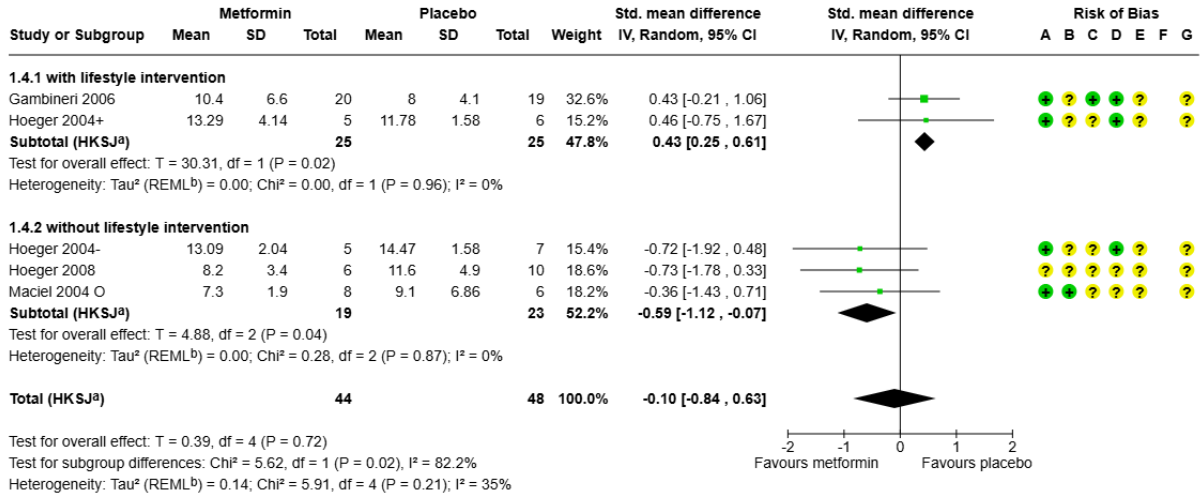
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Table 28 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Metformin	Placebo	Result	RoB
Chou 2003 [36]	n=14 Median: 1.27 IQR: 0.77 to 1.90	n=16 Median: 1.44 IQR: 1.10 to 1.89	Favours metformin	Moderate
Fleming 2002 [38]	n=26 Mean: 1.63	n=39 Mean: 1.44	Favours placebo	High

Hirsutism



Footnotes

[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend

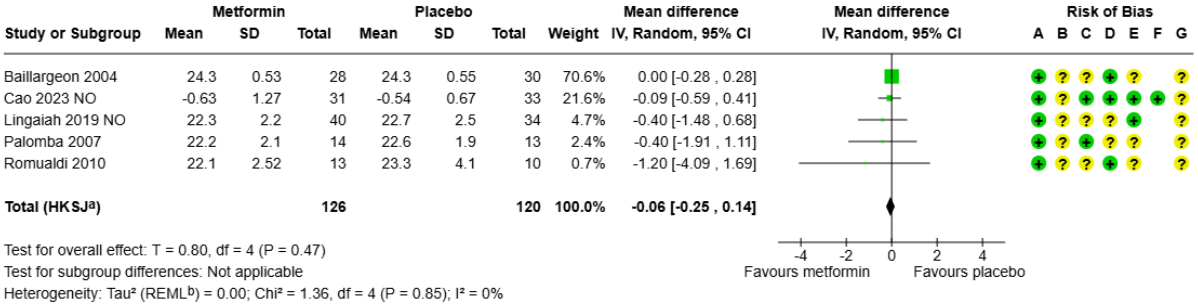
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Table 29 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Metformin	Placebo	Result	RoB
Eisenhardt 2006 [37]	n=22 Median: 9.2 IQR: 7.9 to 11.8	n=23 Median: 8.8 IQR: 7.5 to 11.0	Favours placebo	Moderate

4.1.3 BMI <25

BMI (kg/m²)



Test for overall effect: T = 0.80, df = 4 (P = 0.47)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 1.36, df = 4 (P = 0.85); I² = 0%

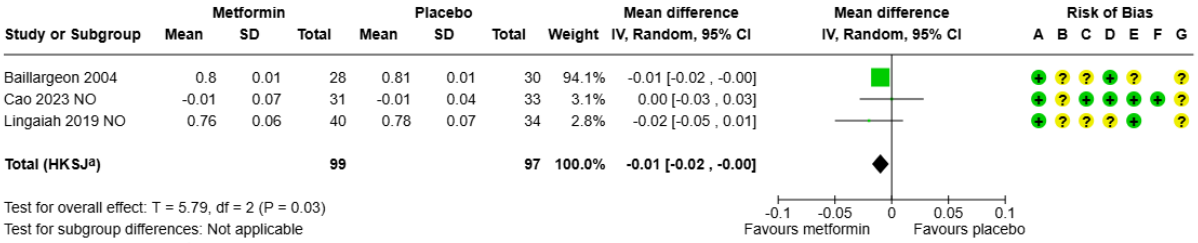
Footnotes
[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Table 30 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Metformin	Placebo	Result	RoB
Ng 2001 [45]	n=7 Median: 23.0 Range: 18.9 to 32.4	n=8 Median: 23.1 Range: 18.8 to 29.1	Favours metformin	Moderate

WHR

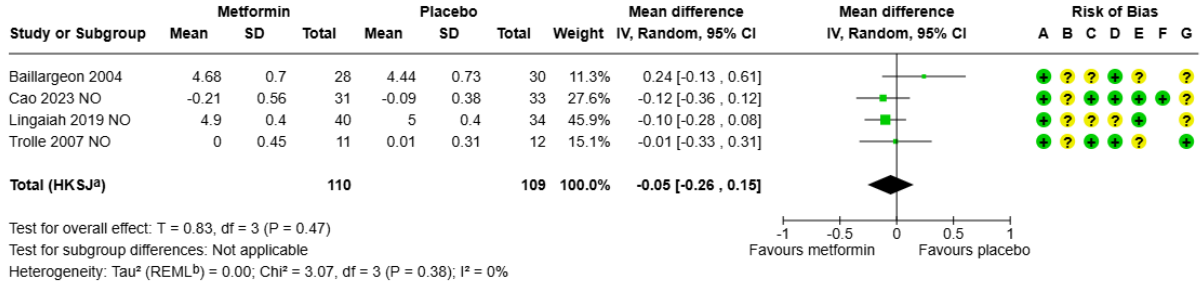


Test for overall effect: T = 5.79, df = 2 (P = 0.03)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 0.91, df = 2 (P = 0.63); I² = 0%

Footnotes
[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Fasting glucose (mmol/l)



Test for overall effect: T = 0.83, df = 3 (P = 0.47)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 3.07, df = 3 (P = 0.38); I² = 0%

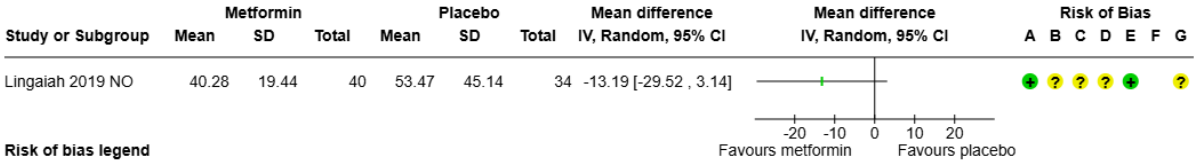
Footnotes
[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Table 31 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Metformin	Placebo	Result	RoB
Ng 2001 [45]	n=7 Median: 5.1 Range: 4.6 to 5.6	n=8 Median: 4.9 Range: 4.4 to 5.7	Favours placebo	Moderate

Fasting insulin (pmol/l)



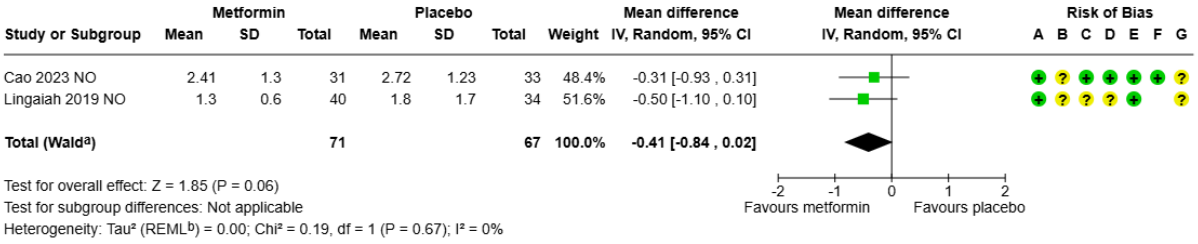
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Table 32 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Metformin	Placebo	Result	RoB
Ng 2001 [45]	n=7 Median: 50.69 Range: 19.44 to 118.06	n=8 Median: 56.94 Range: 27.08 to 62.50	Favours metformin	Moderate
Trolle 2007 NO [29, 30]	n=11 Median: 2.64	n=12 -0.97	Favours placebo	Low

	Range 5-95 percentile: -72.85 to 165.97	Range 5 – 95 percentile: -20.83 to 69.58		

HOMA-IR



Test for overall effect: Z = 1.85 (P = 0.06)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 0.19, df = 1 (P = 0.67); I² = 0%

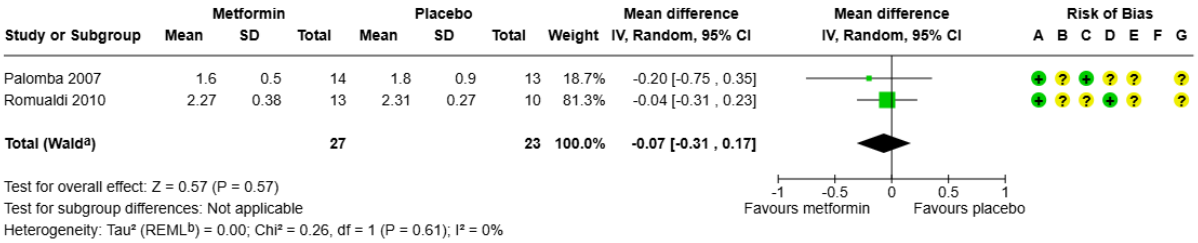
Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Table 33 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Metformin	Placebo	Result	RoB
Trolle 2007 NO [29, 30]	n=10 Median: 0.16 Range 5–95 percentile: -2.48 to 4.27	n=11 Median: 0 Range 5–95 percentile: -0.63 to 2.17	Favours metformin	Low

LDL (mmol/l)



Test for overall effect: Z = 0.57 (P = 0.57)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Table 34 *Studies not included in meta-analysis (included in narrative analysis).*

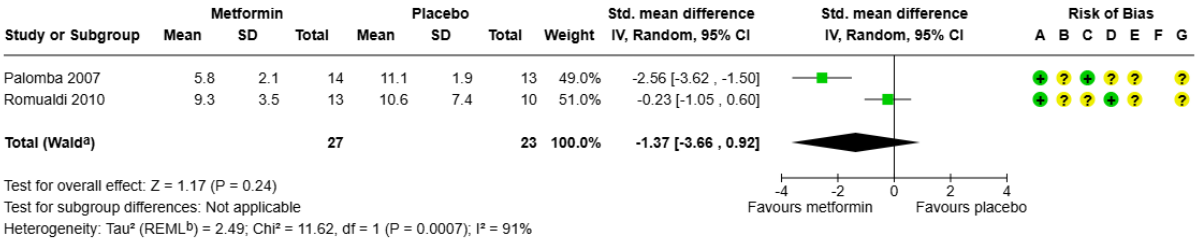
Study (Reference)	Metformin	Placebo	Result	RoB
Ng 2001 [45]	n=7 Median: 2.5 Range: 1.8 to 4.3	n=8 Median: 3.4 Range: 1.9 till 6.2	Favours metformin	Moderate

Triglycerides (mmol/l)

Table 35 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Metformin	Placebo	Result	
Ng 2001 [45]	n=7 Median: 1.0 Range: 0.4 to 1.5	n=8 Median: 1.1 Range: 0.4 to 2.2	Favours metformin	Moderate

Hirsutism



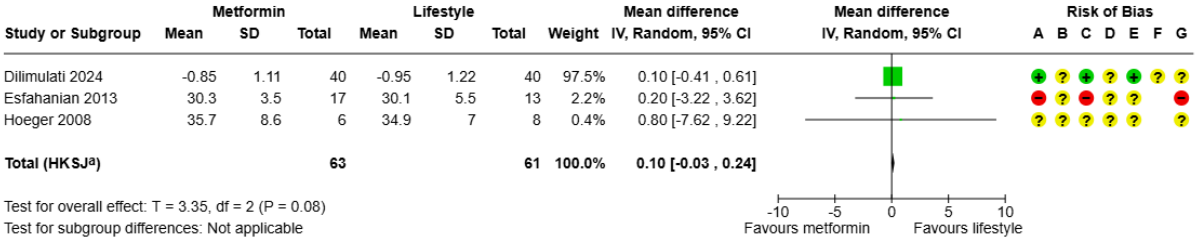
Test for overall effect: Z = 1.17 (P = 0.24)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 2.49; Chi² = 11.62, df = 1 (P = 0.0007); I² = 91%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

4.2 Meta-analyses for metformin compared to lifestyle intervention

BMI (kg/m²)

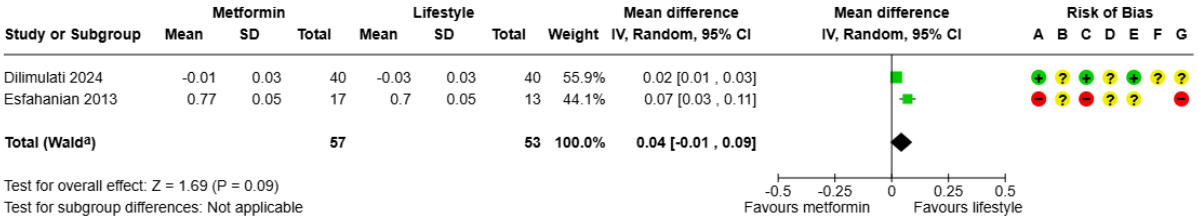


Test for overall effect: T = 3.35, df = 2 (P = 0.08)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 0.03, df = 2 (P = 0.99); I² = 0%

Footnotes
[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

WHR



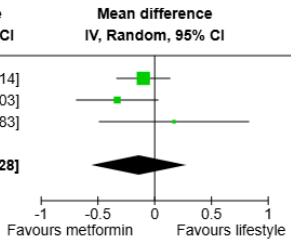
Test for overall effect: Z = 1.69 (P = 0.09)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 6.50, df = 1 (P = 0.01); I² = 85%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Fasting glucose (mmol/l)

Study or Subgroup	Metformin Mean	SD	Total	Lifestyle Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Dilimulati 2024	-0.28	0.65	40	-0.18	0.41	40	64.1%	-0.10 [-0.34 , 0.14]	+ ? + ? + ? ?
Esfahanian 2013	4.74	0.38	17	5.07	0.58	13	27.6%	-0.33 [-0.69 , 0.03]	- ? - ? ? -
Hoeger 2008	4.71	0.7	6	4.54	0.51	8	8.3%	0.17 [-0.49 , 0.83]	? ? ? ? ? ?
Total (HKSJ[a])			**63**			**61**	**100.0%**	**-0.14 [-0.56 , 0.28]**	



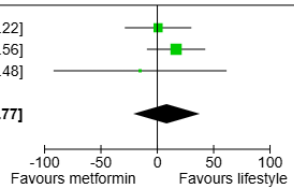
Test for overall effect: T = 1.45, df = 2 (P = 0.28)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 2.00, df = 2 (P = 0.37); I² = 0%

Footnotes
[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Fasting insulin (pmol/l)

Study or Subgroup	Metformin Mean	SD	Total	Lifestyle Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Dilimulati 2024	-23.4	72.7	40	-24.1	61.56	40	40.9%	0.70 [-28.82 , 30.22]	+ ? + ? + ? ?
Esfahanian 2013	79.86	43.06	17	63.19	29.17	13	53.1%	16.67 [-9.22 , 42.56]	- ? - ? ? -
Hoeger 2008	137.5	72.22	6	152.78	72.92	8	6.0%	-15.28 [-92.04 , 61.48]	? ? ? ? ? ?
Total (HKSJ[a])			**63**			**61**	**100.0%**	**8.22 [-21.34 , 37.77]**	

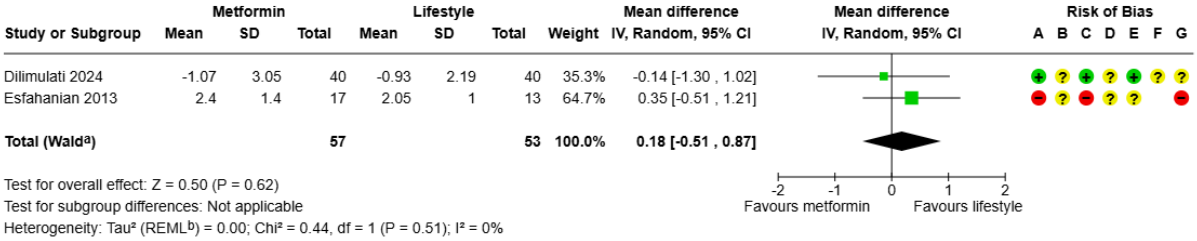


Test for overall effect: T = 1.20, df = 2 (P = 0.35)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 1.02, df = 2 (P = 0.60); I² = 0%

Footnotes
[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

HOMA-IR

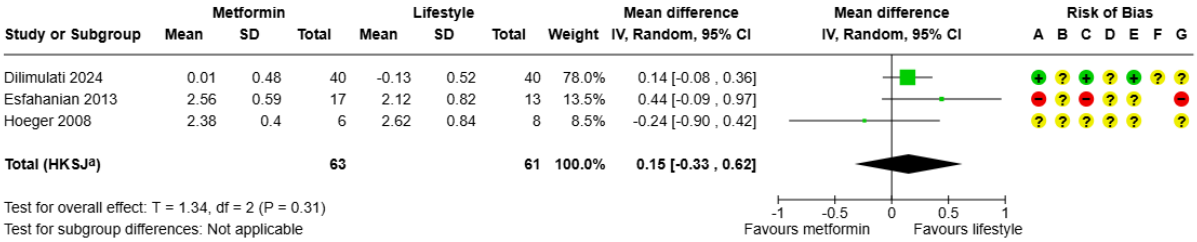


Test for overall effect: Z = 0.50 (P = 0.62)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 0.44, df = 1 (P = 0.51); I² = 0%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

LDL (mmol/l)

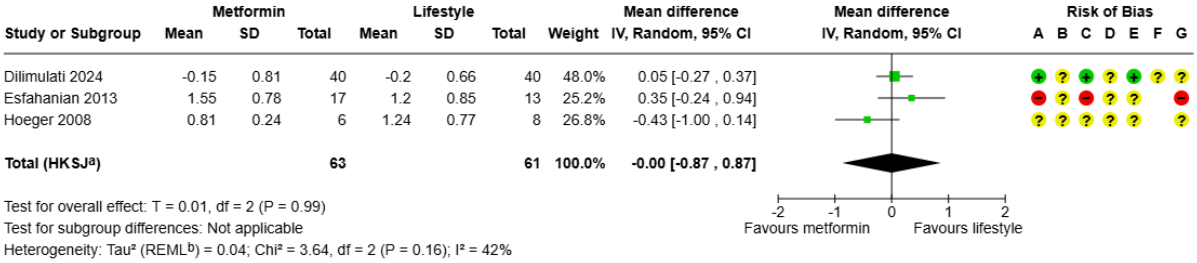


Test for overall effect: T = 1.34, df = 2 (P = 0.31)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 2.50, df = 2 (P = 0.29); I² = 0%

Footnotes
[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Triglycerides (mmol/l)

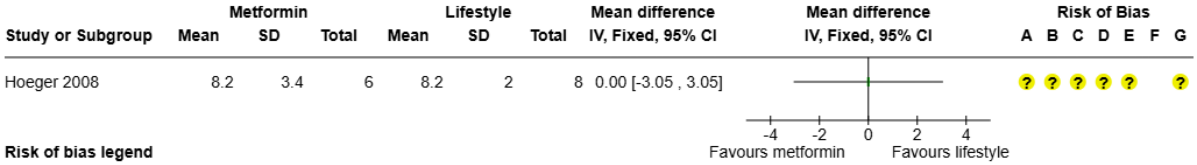


Test for overall effect: T = 0.01, df = 2 (P = 0.99)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.04; Chi² = 3.64, df = 2 (P = 0.16); I² = 42%

Footnotes
[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Hirsutism



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended intervention
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

4.2.1 Summary of findings for metformin compared to lifestyle intervention

Table 36 *Metformin compared to lifestyle intervention.*

Outcome	Meta-analysis (MA): Number of participants (Number of studies) References Narrative analysis (NA): Number of participants (Number of studies) References	Effect Mean difference (95% CI)	Certainty of evidence (GRADE)	Downrating (GRADE)
BMI	MA: 124 (3) [26, 53, 54] NA: No studies	No difference 0.10 (-0.03 to 0.24)	⊕OOO	-1 risk of bias[a] -2 imprecision[b]
WHR	MA: 110 (2) [53, 54] NA: No studies	No difference 0.04 (-0.01 to 0.09)	⊕OOO	-2 risk of bias[c] -2 imprecision[b]
Glucose	MA: 124 (3)	No difference	⊕OOO	-1 risk of bias[a]

	[26, 53, 54] **NA**: No studies	-0.14 (-0.56 to 0.28)		-2 imprecision[d]
Insulin	**MA**: 124 (3) [26, 53, 54] **NA**: No studies	No difference 8.22 (-21.34 to 37.77)	⊕OOO	-1 risk of bias[a] -2 imprecision[d]
HOMA-IR	**MA**: 110 (2) [53, 54] **NA**: No studies	No difference 0.18 (-0.51 to 0.87)	⊕OOO	-2 risk of bias[c] -2 imprecision[d]
LDL	**MA**: 124 (3) [26, 53, 54] **NA**: No studies	No difference 0.15 (-0.33 to 0.62)	⊕OOO	-1 risk of bias[a] -2 imprecision[d]
Triglycerides	**MA**: 124 (3) [26, 53, 54] **NA**: No studies	No difference -0.00 (-0.87 to 0.87)	⊕OOO	-1 risk of bias[a] -2 imprecision[d]
Hirsutism	**MA**: 14 (1) [26] **NA**: No studies	No difference 0.00 (-3.05 to 3.05)	⊕OOO	-1 risk of bias[e] -1 indirectness[f] -2 imprecision[d]

a) Includes studies with a moderate risk of bias and a high risk of bias
b) few participants
c) One study with a high risk of bias and one with moderate
d) few participants with wide confidence intervals
e) one study with moderate risk of bias
f) result is based on a single study

4.3 Synthesis without meta-analysis (SWiM) for metformin and menstrual frequency

Table 37 SWIM metformin and menstrual frequency

Author Year Country Reference	Number of participants, population, length of study	Outcome	Result	RoB
Metformin vs Placebo, outcome menstrual frequency and regularity.				
Amiri 2014 [16]	N=50, adult, 6 mo	Restored menses	No difference	Moderate
Baillargeon 2004, Venezuela [32]	N=58, non-obese adults, 6 Mo	Frequencies of menstrual bleedings	Favours metformin	Moderate
Bridger 2006, Canada [65]	N=21, Adolescents, 3 Mo	Restored menses	Favours metformin	Low
Chou 2003, Brazil [36]	N=30, Obese adults, 3 mo	Pattern menstrual cycles	Favours metformin	Moderate

Eisenhardt 2006, Germany [37]	N=38, Obese adults, 3 mo	Menstrual disturbance	Favours metformin	Moderate
Fux Otta 2010, Argentina [39]	N=29, adults, 4 mo	Menstrual cycling	Favours metformin	Moderate
Gambineri 2006, Italy [19]	N=40, obese adults, 6 mo	Menstrual pattern	Favours metformin	Low
Hoeger 2004, USA [31]	N=13, obese adults, 6 mo	Menstrual events	Favours metformin	Moderate
Hoeger 2008, USA [26]	N=16, Obese adolescents, 6 mo	Menstrual cycles/24 weeks	Favours metformin	Moderate
Karimzadeh 2007, Iran [27]	N=200, obese adults, 3 mo	Participants with oligomenorrhea	Favours metformin	High
Ladson 2011a [41]	N=38, adults, 6 mo	Menstrual bleeding episodes	Favours metformin	High
Maciel 2004, Brazil [43]	N= 29, Obese and non-obese adults, 6 mo	Menstrual index	Favours metformin	Moderate
Romualdi 2010 Italy [48]	N=23, non-obese adults, 6 mo	Menstrual abnormalities	Favours metformin	Moderate
Tang 2006, UK [49]	N=143, obese adults, 6 mo	Menstrual events/6 mo	Favours metformin	Low
Tiwari 2018, India [51]	N=66, adults, 6 mo	Clinical symptoms of oligomenorrhoea, polymenorrhoea and secondary amenorrhoea	Favours metformin	Low
Trolle 2007, Denmark [29, 30]	N=50, adults, 6 mo	Menstrual bleeding	Favours metformin	Low
Zahra 2017, Pakistan [52]	N=40, adults, 3 mo	Menstrual cycle frequency, Menstrual duration, and menstrual amount of blood flow	No difference	High
Result	N=884 Length of study 6 mo=11 studies 3 mo=5 studies 4 mo=1 study		Favours metformin-15 Favours placebo=0 No difference=2	Low= 5 studies Moderate= 9 studies High = 3 studies
Metformin vs lifestyle/diet outcome menses				

Dilimulati 2024 [53]	N=80, Adults, 3 mo	Menstrual cycle/year	No difference	Moderate
Esfahanian 2013, Iran [54]	N= 30, obese adults, 3 mo	Improvement of cycle disorder	Favours placebo	High
Hoeger 2004, USA [31]	N=11, obese adults, 6 mo	Menstrual events	Favours metformin	Moderate
Hoeger 2008, USA [26]	N=14, Obese adolescents, 6 mo	Menstrual cycles	Favours metformin	Moderate
Result	N=135 Length of study: 6 mo=2 studies 3 mo=2 studies	Pos= effect for metformin	Favours metformin=2 Favours placebo=1 No difference=1	Low= 0 studies Moderate= 3 studies High = 1 study

4.4 Summary of studies added in updated literature search for metformin

Table 38 Studies added to analyses of metformin compared to placebo and/or lifestyle interventions.

Author Year Country Reference	Population	Intervention vs control Additive treatment No. of participants (analysed) Length of treatment	Outcomes	Risk of bias
Wen 2022 Cao 2023 China [34, 35]	Rotterdam 18–40 years BMI ≥18.5 kg/m^2 Insulin resistens= HOMA-IR ≥2.14	I: Metformin 500 mg x 3 C: Placebo Addition: sham acupuncture in both groups I: 95–97 (depending on variable) C: 95–98 (depending on variable) 4 months	BMI, WHR fasting glucose, fasting insulin, HOMA-IR Adverse events	Moderate
Dilimulati 2024 China [53]	Rotterdam 18–45 years HOMA-IR score ≥1.8 (insulin resistance according to Asian standard)	I: Metformin 1000 mg/day K: WeChat, digital lifestyle intervention (diet, exercise, sleep, mental health) I: 40 C: 40 3 months	BMI, WHR fasting glucose, fasting insulin, HOMA-IR LDL, triglycerides, menstrual cycles, Adverse events, depression, anxiety	Moderate
Telagareddy 2024 India [50]	Rotterdam 18–40 years BMI ≥23 kg/m^2	I: Metformin 500 mg x 3 C: Lifestyle intervention Addition: lifestyle intervention also for group I	BMI, WHR fasting glucose, fasting insulin, HOMA-IR LDL, triglycerides	Hög

		I: 52 C: 25 6 months		

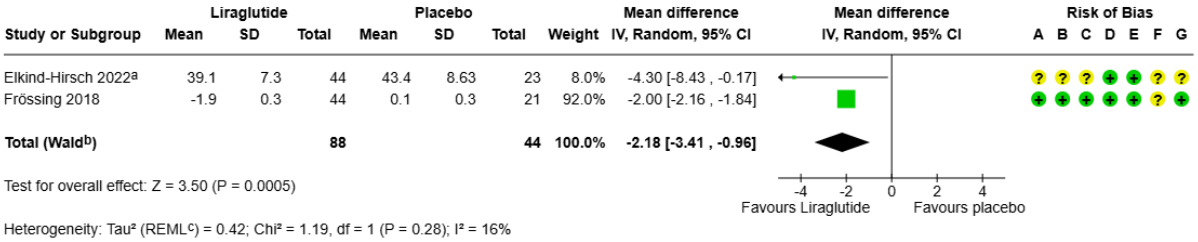
BMI = body mass index; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; LDL = low density lipoprotein cholesterol, TG =triglycerides; Rotterdam = Rotterdam diagnostic criteria for PCOS; WHR = waist hip ratio

5 Analyses regarding GLP-1 analogues

5.1 Meta-analyses for GLP-1 analogues compared to placebo or other drugs

Liraglutide compared to placebo

BMI (kg/m²)

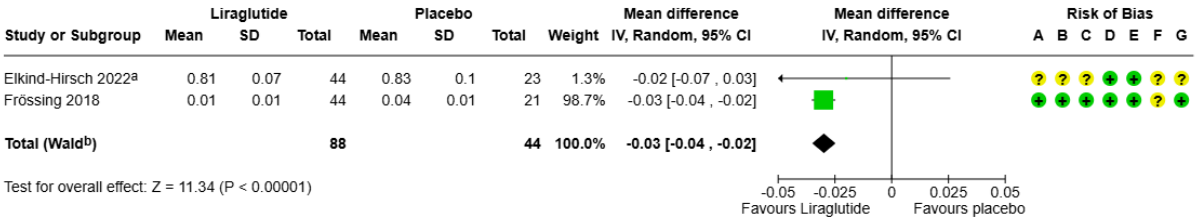


Heterogeneity: Tau² (REML[c]) = 0.42; Chi² = 1.19, df = 1 (P = 0.28); I² = 16%

Footnotes
[a]with lifestyle intervention for both groups
[b]CI calculated by Wald-type method.
[c]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Risk of bias arising from the randomization process
(B) Risk of bias due to deviations from the intended interventions
(C) Missing outcome data
(D) Risk of bias in measurement of the outcome
(E) Risk of bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

WHR

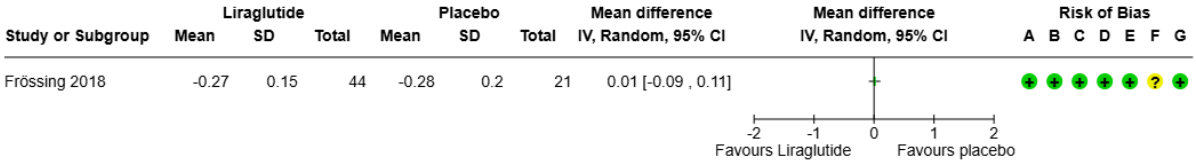


Heterogeneity: Tau² (REML[c]) = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%

Footnotes
[a]with lifestyle intervention for both groups
[b]CI calculated by Wald-type method.
[c]Tau² calculated by Restricted Maximum-Likelihood method.

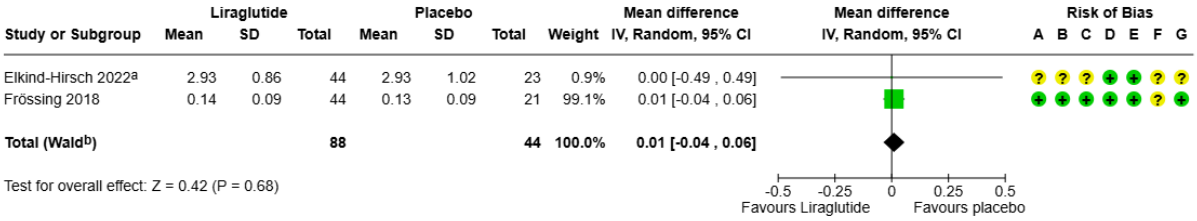
Risk of bias legend
(A) Risk of bias arising from the randomization process
(B) Risk of bias due to deviations from the intended interventions
(C) Missing outcome data
(D) Risk of bias in measurement of the outcome
(E) Risk of bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

HOMA-IR



Risk of bias legend
(A) Risk of bias arising from the randomization process
(B) Risk of bias due to deviations from the intended interventions
(C) Missing outcome data
(D) Risk of bias in measurement of the outcome
(E) Risk of bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

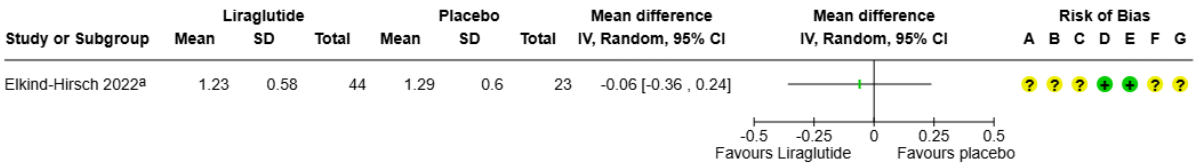
LDL (mmol/l)



Footnotes
[a]with lifestyle intervention for both groups
[b]CI calculated by Wald-type method.
[c]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Risk of bias arising from the randomization process
(B) Risk of bias due to deviations from the intended interventions
(C) Missing outcome data
(D) Risk of bias in measurement of the outcome
(E) Risk of bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Triglycerides (mmol/l)



Footnotes
[a]with lifestyle intervention for both groups

Risk of bias legend
(A) Risk of bias arising from the randomization process
(B) Risk of bias due to deviations from the intended interventions
(C) Missing outcome data
(D) Risk of bias in measurement of the outcome
(E) Risk of bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Hirsutism

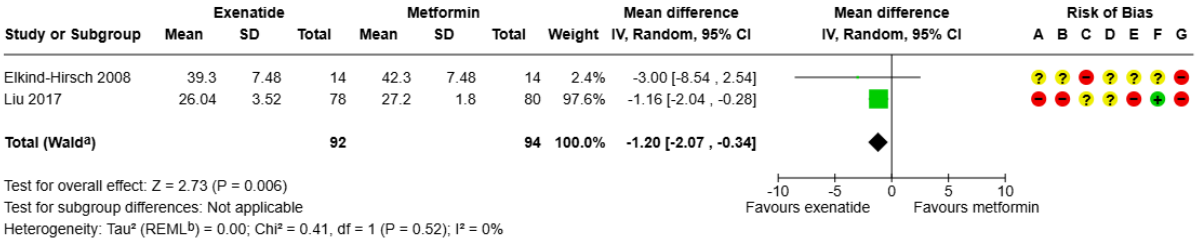
Table 39 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Intervention	Control	Result	RoB

Frössing 2018 [59]	Liraglutide n=48	Placebo n=24	”We observed no effect on Ferriman-Gallway score in either group.”	Low

Exenatide compared to metformin

BMI (kg/m²)



Test for overall effect: Z = 2.73 (P = 0.006)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%

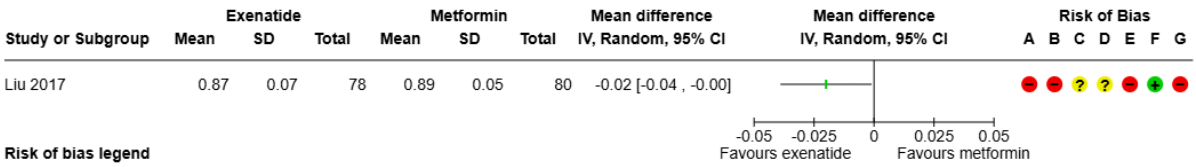
Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Risk of bias arising from the randomization process
(B) Risk of bias due to deviations from the intended interventions
(C) Missing outcome data
(D) Risk of bias in measurement of the outcome
(E) Risk of bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Table 40 *Studies not included in meta-analysis (included in narrative analysis).*

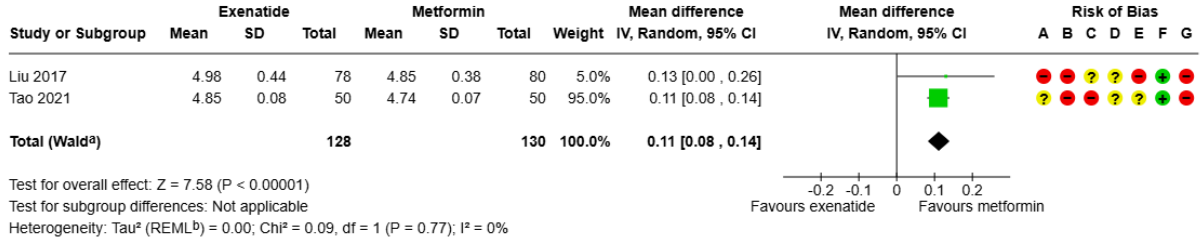
Study (Reference)	Exenatide	Metformin	Result	RoB
Tao 2021 [63]	n=50 Median: 28.46 IQR: 25.69 to 31.37	n=50 Median: 28.19 IQR: 25.91 to 30.86	Favours metformin	High

WHR



Risk of bias legend
(A) Risk of bias arising from the randomization process
(B) Risk of bias due to deviations from the intended interventions
(C) Missing outcome data
(D) Risk of bias in measurement of the outcome
(E) Risk of bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Fasting glucose (mmol/l)

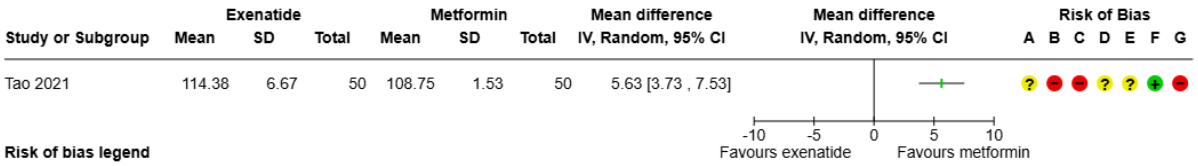


Test for overall effect: Z = 7.58 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 0.09, df = 1 (P = 0.77); I² = 0%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

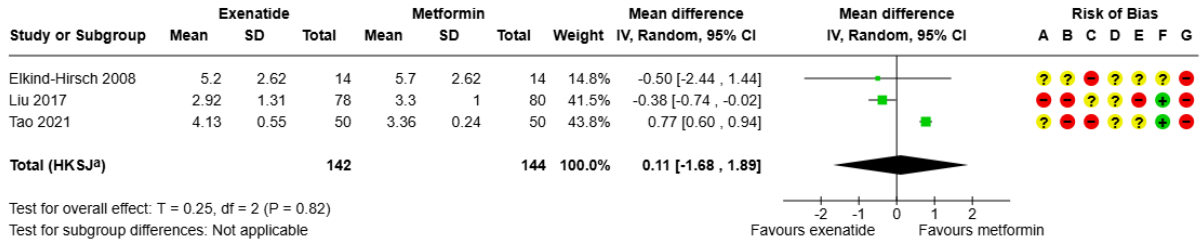
Risk of bias legend
(A) Risk of bias arising from the randomization process
(B) Risk of bias due to deviations from the intended interventions
(C) Missing outcome data
(D) Risk of bias in measurement of the outcome
(E) Risk of bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Fasting insulin (pmol/l)



Risk of bias legend
(A) Risk of bias arising from the randomization process
(B) Risk of bias due to deviations from the intended interventions
(C) Missing outcome data
(D) Risk of bias in measurement of the outcome
(E) Risk of bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

HOMA-IR

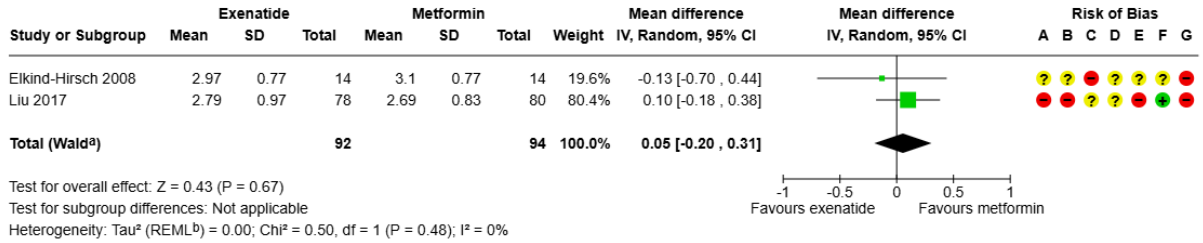


Test for overall effect: T = 0.25, df = 2 (P = 0.82)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.49; Chi² = 32.88, df = 2 (P < 0.00001); I² = 92%

Footnotes
[a]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Risk of bias arising from the randomization process
(B) Risk of bias due to deviations from the intended interventions
(C) Missing outcome data
(D) Risk of bias in measurement of the outcome
(E) Risk of bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

LDL (mmol/l)



Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0%

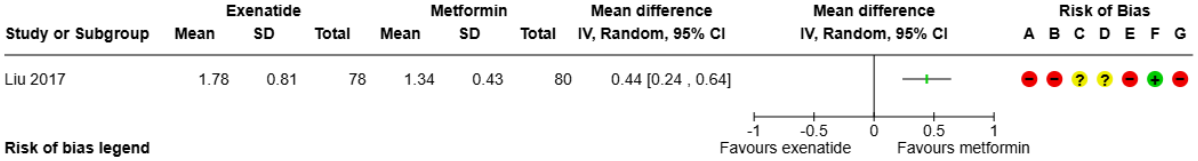
Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Risk of bias arising from the randomization process
(B) Risk of bias due to deviations from the intended interventions
(C) Missing outcome data
(D) Risk of bias in measurement of the outcome
(E) Risk of bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Table 41 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Exenatide	Metformin	Result	RoB
Tao 2021 [63]	n=50 Median: 2.71 IQR: 2.33 to 3.03	n=50 Median: 2.52 IQR: 2.21 to 2.59	Favours metformin	High

Triglycerides (mmol/l)



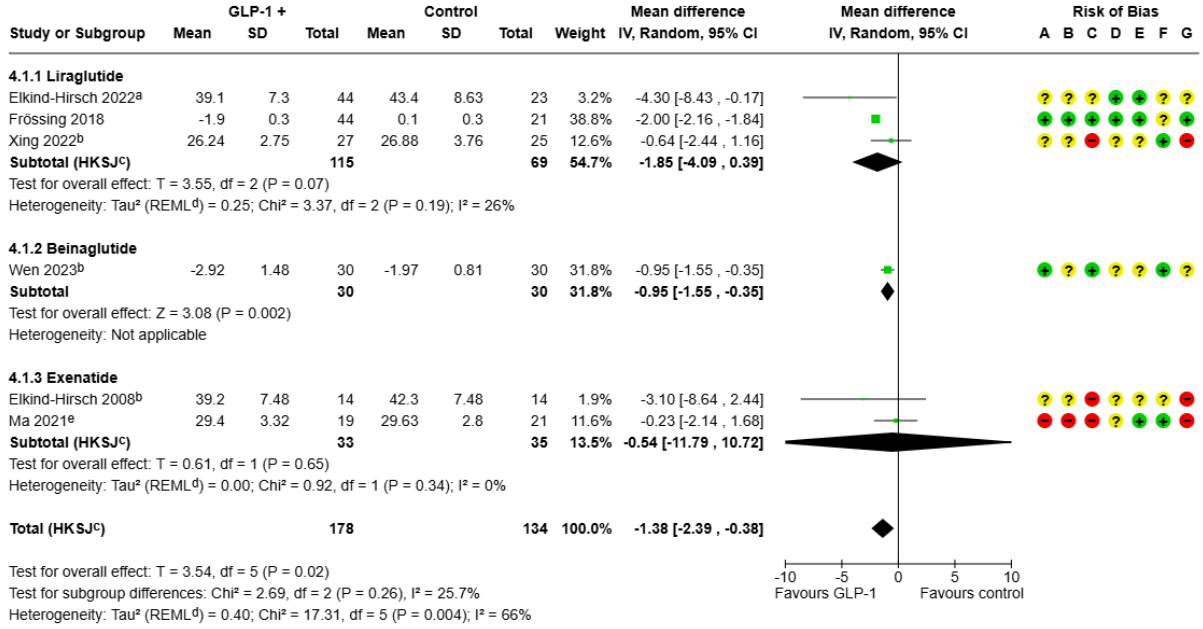
Risk of bias legend
(A) Risk of bias arising from the randomization process
(B) Risk of bias due to deviations from the intended interventions
(C) Missing outcome data
(D) Risk of bias in measurement of the outcome
(E) Risk of bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Table 42 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Exenatide	Metformin	Result	RoB
Tao 2021 [63]	n=50 Median: 1.26 IQR: 0.93 to 1.52	n=50 Median: 1.38 IQR: 1.26 to 1.44	Favours exenatide	High

GLP-1 +

BMI (kg/m²)



Footnotes

[a]with lifestyle intervention for both groups
[b]with metformin for both groups
[c]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[d]Tau² calculated by Restricted Maximum-Likelihood method.
[e]with metformin and CPA/EE for both groups

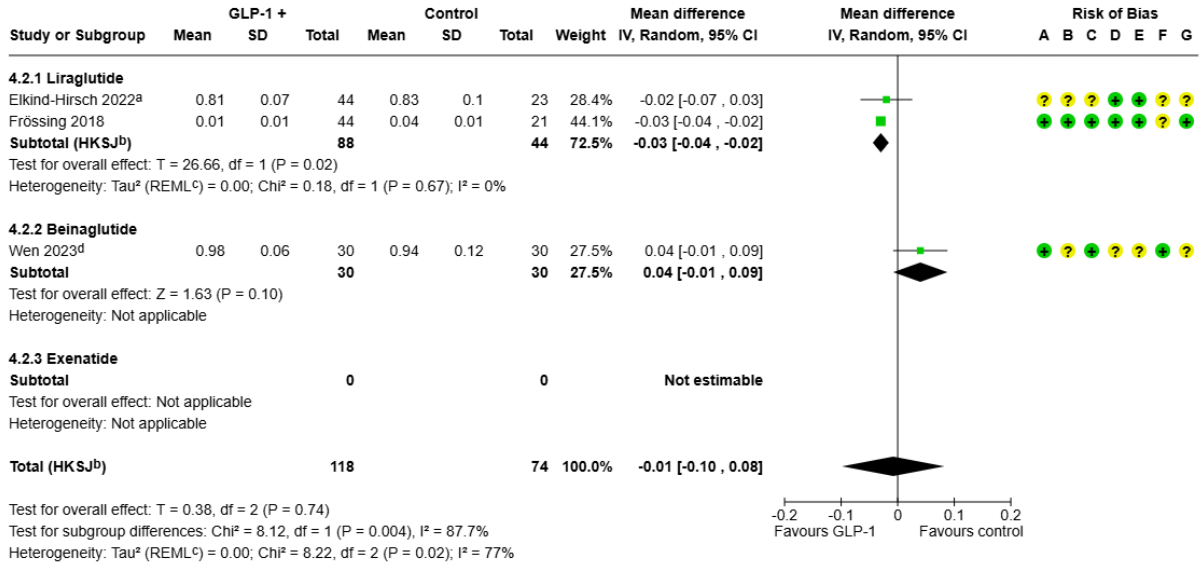
Risk of bias legend

(A) Risk of bias arising from the randomization process
(B) Risk of bias due to deviations from the intended interventions
(C) Missing outcome data
(D) Risk of bias in measurement of the outcome
(E) Risk of bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Table 43 *Studies not included in meta-analysis (included in narrative analysis).*

Study Reference	Intervention	Control	Result	RoB
Tao 2021 [63]	Exenatide + metformin n=50 Mean: 29.17 SD: 4.80	Metformin n=50 Median: 28.46 IQR: 25.69, 31.37	Can not be compared	High

WHR



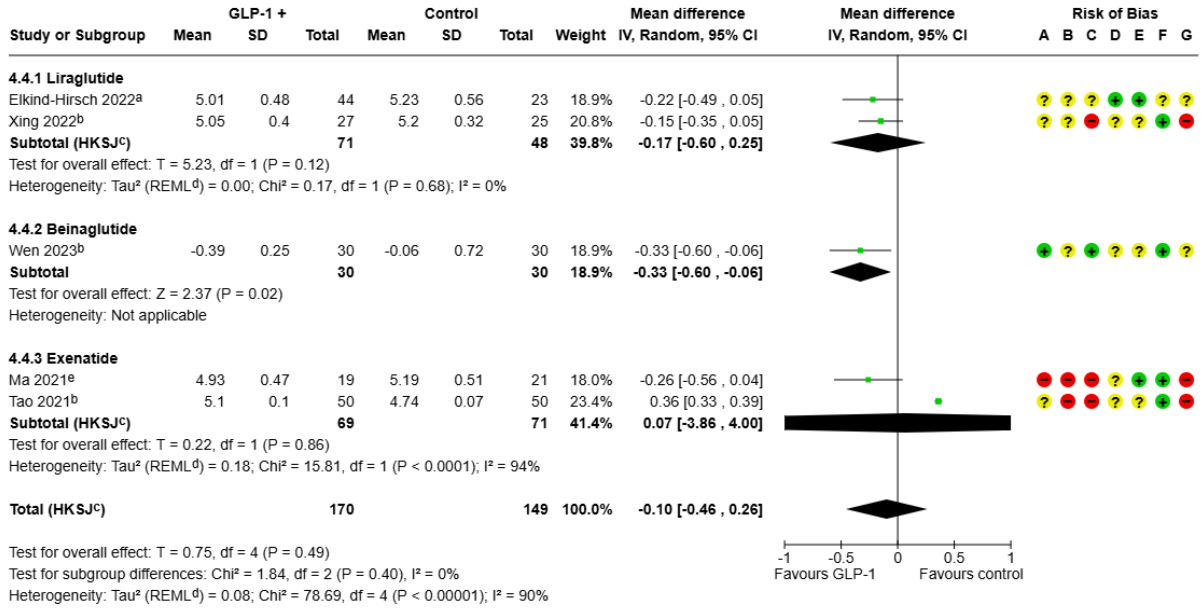
Footnotes
[a]with lifestyle intervention for both groups
[b]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[c]Tau² calculated by Restricted Maximum-Likelihood method.
[d]with metformin for both groups

Risk of bias legend
(A) Risk of bias arising from the randomization process
(B) Risk of bias due to deviations from the intended interventions
(C) Missing outcome data
(D) Risk of bias in measurement of the outcome
(E) Risk of bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Table 44 *Studies not included in meta-analysis (included in narrative analysis).*

Study Reference	Intervention	Control	Result	RoB
Wen 2023 [66]	Beinaglutide + metformin n=30 Median: -0.01 IQR: 0.04	Metformin n=30 Median: -0.02 IQR: 0.03	Favours control	Moderate

Fasting glucose (mmol/l)



Footnotes

[a]with lifestyle intervention for both groups
[b]with metformin for both groups
[c]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[d]Tau² calculated by Restricted Maximum-Likelihood method.
[e]with metformin and CPA/EE for both groups

Risk of bias legend

(A) Risk of bias arising from the randomization process
(B) Risk of bias due to deviations from the intended interventions
(C) Missing outcome data
(D) Risk of bias in measurement of the outcome
(E) Risk of bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Fasting insulin (pmol/l)

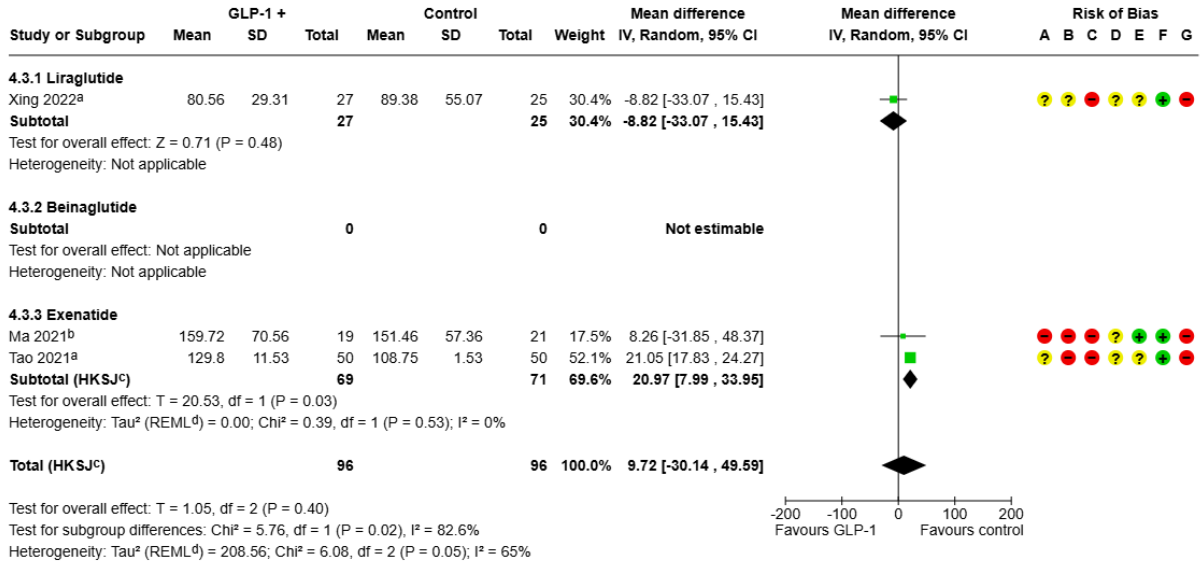


Table 45 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Intervention	Control	Result	RoB
Wen 2023 [66]	Beinaglutide + metformin n=30 Median: -14,03 IQR: 28,68	Metformin n= 30 Median: -12,92 IQR: 36,74	Favours GLP-1	Moderate

HOMA-IR

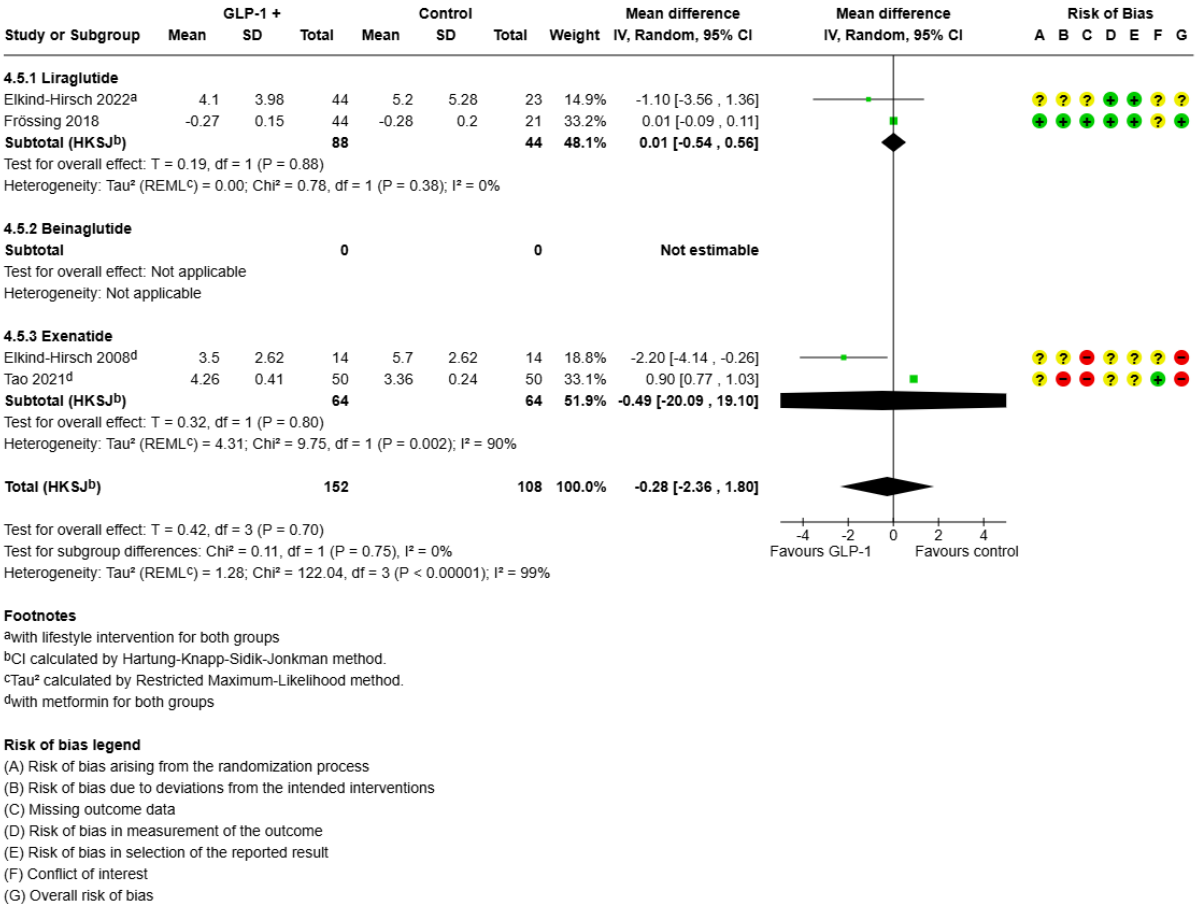
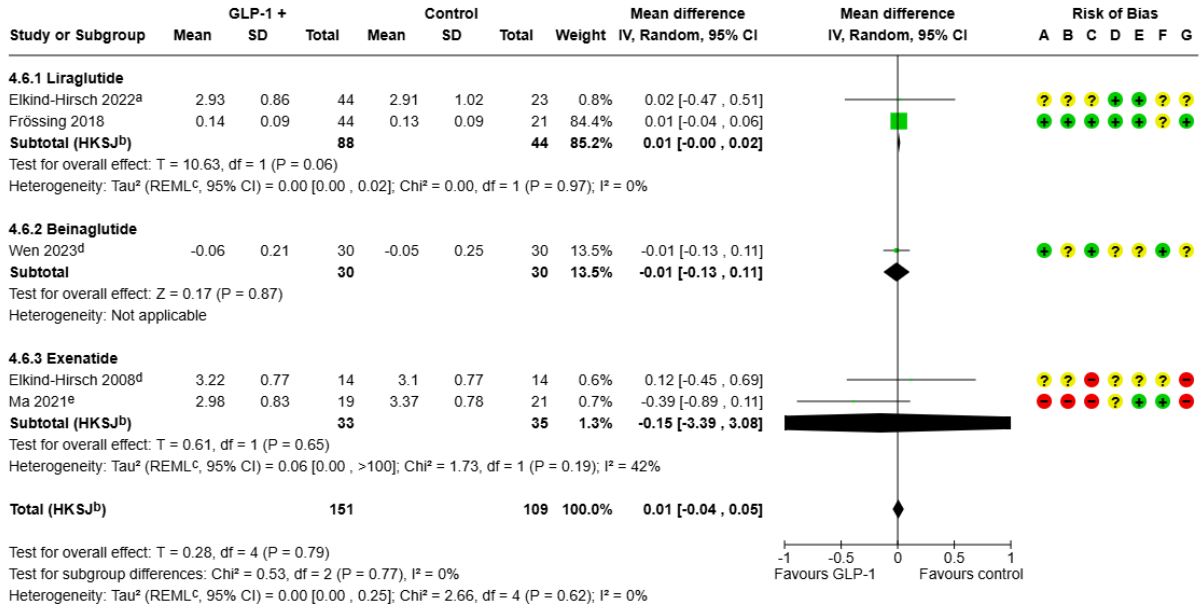


Table 46 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Intervention	Control	Result	RoB
Ma 2021 Gan 2023 [61, 62]	Exenatide + metformin + CPA/EE n=19 Median: 4.70 IQR: 4.20 to 6.21	Metformin + CPA/EE n=21 Median: 4.80 IQR: 3.47 to 6.39	Favours GLP-1	High
Wen 2023 [66]	Beinaglutide + metformin n=30 Median: -0.94 IQR: 0.62	Metformin n=30 Median: -0.27 IQR: 0.86	Favours GLP-1	Moderate

LDL (mmol/l)



Footnotes

[a]with lifestyle intervention for both groups
[b]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[c]Tau² calculated by Restricted Maximum-Likelihood method.
[d]with metformin for both groups
[e]with metformin and CPA/EE for both groups

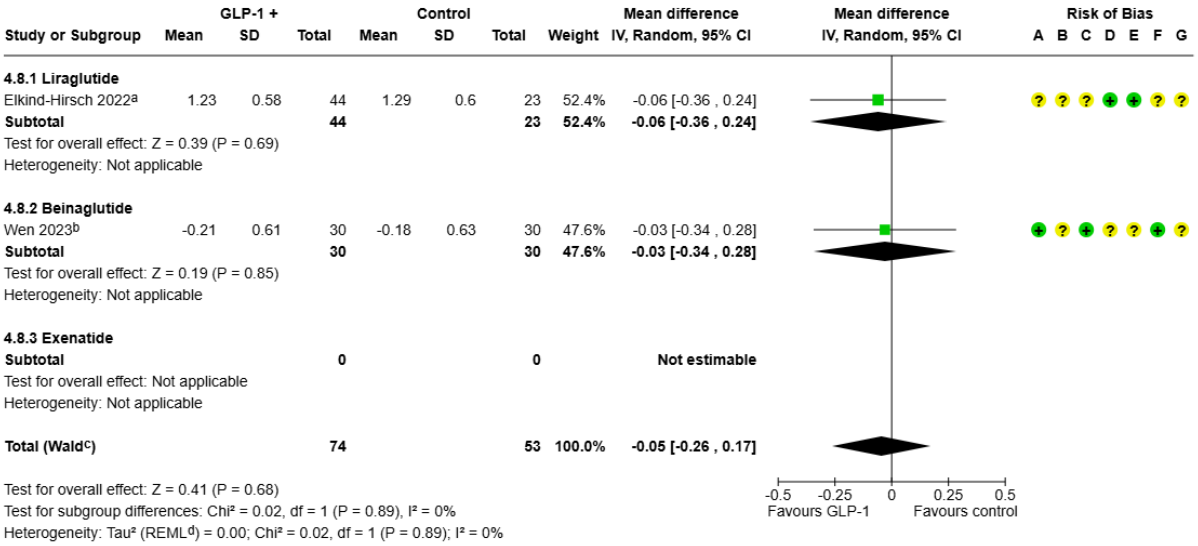
Risk of bias legend

(A) Risk of bias arising from the randomization process
(B) Risk of bias due to deviations from the intended interventions
(C) Missing outcome data
(D) Risk of bias in measurement of the outcome
(E) Risk of bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Table 47 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	GLP-1	Control	Result	RoB
Tao 2021 [63]	Exenatide + metformin n=50 Median: 2.81 IQR: 2.51, 3.21	Metformin n=50 Median: 2.71 IQR: 2.33, 3.03	Favours control	High

Triglycerides (mmol/l)



Footnotes
[a]with lifestyle intervention for both groups
[b]with metformin for both groups
[c]CI calculated by Wald-type method.
[d]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend
(A) Risk of bias arising from the randomization process
(B) Risk of bias due to deviations from the intended interventions
(C) Missing outcome data
(D) Risk of bias in measurement of the outcome
(E) Risk of bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Table 48 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Intervention	Control	Result	RoB
Ma 2021 Gan 2023 [61] [62]	Exenatide + metformin + CPA/EE n=19 Median: 2.0 IQR: 1.59 to 3.20	Metformin n=21 Median: 2.46 IQR: 1.56 to 3.61	Favours GLP-1	High
Tao 2021 [63]	Exenatide + metformin n=50 Median: 1.19 IQR: 1.04, 1.80	Metformin n=50 Median: 1.26 IQR: 0.93, 1.52	Favours GLP-1	High

Hirsutism

Table 49 *Studies not included in meta-analysis (included in narrative analysis).*

Study (Reference)	Intervention	Control	Result	RoB

Frössing 2018b [59]	Liraglutide n=48	Placebo n=24	” We observed no effect on Ferriman-Gallway score in either group.”	Low

5.2 Synthesis without meta-analysis (SWiM) for GLP-1 analogues and menstrual frequency

Table 50 SWIM GLP-1-analogues and menstrual frequency.

Author Year Country Reference	Number of participants, age, population, length of study, GLP-1 variant	Outcome	Result	RoB
SWIM GLP-1 vs Metformin, outcome menstrual frequency and regularity				
Elkind-Hirsch 2008 USA [55]	N=40 (originally N=60 3, arms, analysed 14 participants/arm completed) 18-40 years Overweight/obese oligoovulatory Nondiabetic 24 weeks Exenatide	Menstrual frequency	Favours GLP-1	High
Liu 2017, Li 2022, Zheng 2017 China [67-69]	N=176 (analysed 80 vs 78 participants) BMI ≥24 (Overweight/obese) Nondiabetic 12 weeks Exenatide	Menstrual frequency ratio (MFR) ratio of actual menses to expected menses during the weeks of observation	Favours GLP-1	High
Results	N analysed= 186 Length of study: 6 mo (24 weeks) = 1 3 mo= 1		Favours GLP-1 =2 Favours metformin=0	
GLP-1 vs placebo or where GLP-1 is the only add-on				
GLP-1 vs Placebo				
Elkind-Hirsch 2022 USA [56]	N= 82 (liraglutide N 55 vs placebo N 27, analysed N44 vs N23) 18-45 years Obesity (BMI >30) Non diabetic Liraglutide 32 weeks (8 mo)	Menstrual frequency	Favours GLP-1	Moderate

Frössing 2018a, Frössing 2018b, Nylander 2017a, Nylander 2017b Denmark [57-60]	N= 72 (liraglutide N=48 placebo N=24, analysed N=44 vs N=21) ≥18 y BMI ≥25 Insulin resistant 26 weeks (6,5 mo) Liraglutide	Bleeding ratio (number of menstrual bleedings divided by study period (months))	Favours GLP-1	Low
Result	N analysed= 132 Length of study: 8 mo (32 weeks) = 1 6,5 mo (26 weeks) = 1		Favours GLP-1 =2 Favours placebo=0	
GLP-1 and metformin vs metformin				
Xing 2022 China [64]	N=60 (analysed met N=25, Met+ LIRA N=27) Rotterdam typ B (hyperandrogenism + ovulatory dysfunction) 18-40 years BMI ≥24 (overweight) Liraglutide and metformin vs metformin 12 weeks	Regular menstrual cycles (%,n)	Favours GLP-1 and metformin	High
Elkind-Hirsch 2008 USA [55]	N=40 (originally N=60 3, arms, analysed 14 participants/arm completed) 18-40 years Overweight oligoovulatory Non diabetic 24 weeks Exenatide	Menstrual frequency	Favours GLP-1 and metformin	High
Result	N analysed= 80 Length of study: 6 mo (24 weeks) = 1 3 mo (12 weeks) = 1		Favours GLP-1 =2 Favours control=0	
GLP-1 and calorie-restricted diet vs calorie-restricted diet				
Zhang 2023 China [70]	N= 68 (dulaglutide+ diet N=35, diet N=33) 18-45 yr BMI ≥24 Dulaglutide and calorie-restricted diet vs calorie-restricted diet Until a 7% weight loss goal or 6 months	Menstrual Cycles (no./yr)	Favours control	High

Result	N= 68 Length of study: 6 mo or 7% weight loss= 1		Favours GLP-1= 0 Favours control=1	
Result total	N= 250 Length of study: 6 mo= 2 3 mo (12 weeks) = 1 8 mo (32 weeks) = 1 6,5 mo (26 weeks) = 1		Favours GLP-1= 4 Favours control=1	
GLP-1 vs contraceptive pills				
Liao 2023 China [71]	N=70 (analysed N=60) 18-50 y BMI ≥24 (overweight) 12 weeks Liraglutide + metformin vs cyproterone acetate/ethinylestradiol (CPA/EE) + Metformin Liraglutide	Regular menstruation, n (%), Amenorrhea, n (%), Oligomenorrhoea, n (%)	Favours CPA/EE+met	High

5.3 Adverse events GLP-1 analogues

Table 51 Adverse events GLP-1 analogues

Study (Reference)	No. of participants (analysed)	Gastrointestinal adverse events n (%)	Other adverse events n (%)
Ma 2021 Gan 2023 [61, 62]	**Exenatide** 19 **Metformin** 21	**Exenatide** Nausea: 11 (44), Diarrhea: 9 (36), Bloating: 6 (24), Vomiting: 2 (8), Stomachache: 0 (0), Constipation: 2 (8) **Metformin** Nausea: 10 (40), Diarrhea: 11 (44), Bloating: 2 (8), Vomiting: 3 (12), Stomachache: 2 (8), Constipation: 1 (4)	**Exenatide** Headache: 2 (8), Fatigue: 3 (12), Dizzy: 1 (4), Urticaria: 1 (4), Injection site pain: 2 (8), Injection site itchy: 12 (48), Subcutaneous induration: 11 (44) **Metformin** Headache: 1 (4), Fatigue: 2 (8), Dizzy: 1 (4), Urticaria: 0, Injection site pain: 0, Injection site pain: 0, Subcutaneous induration: 0
Zhang 2023 [70]	**Dulaglutide + diet** 35 **Diet** 33	**Dulaglutide + diet** Adverse events-related (type GI) discontinuation: 2 (6), Patients with ≥1 GI TEAE: 13 (37), Nausea: 8 (23), Vomiting: 7 (20), Diarrhea: 0, Constipation: 4 (11), Loss of appetite: 4 (11), Abdominal distension: 2 (6), Abdominal pain: 1 (3), Eructation: 1 (3), Sensations of hunger: 0	**Dulaglutide + diet** Hypoglycemia: 0, Dizziness: 3 (8), Injection site reaction: 0, Upper respiratory tract infection: 0, Headache: 1 (3), Nasopharyngitis: 0 **Diet**

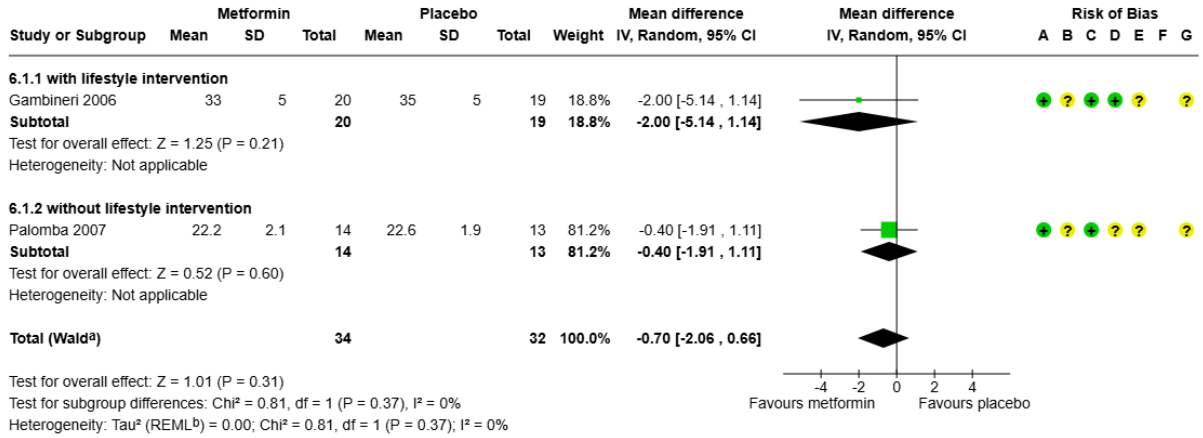
		Diet Adverse events-related (type GI) discontinuation: 0, Patients with ≥1 GI TEAE: 0, Nausea: 0, Vomiting: 0, Diarrhea: 0, Constipation: 0, Loss of appetite: 0, Abdominal distension: 0, Abdominal pain: 0, Eructation: 0, Sensations of hunger: 3 (9)	Hypoglycemia: 0, Dizziness: 1 (3), Injection site reaction: 0, Upper respiratory tract infection: 0, Headache: 0, Nasopharyngitis: 0
Elkind-Hirsch 2022 [56]	**Liraglutide** 44 **Placebo** 23	**Liraglutide** Nausea; 14 (25.5), Vomiting: 5(9), Diarrhea: 4 (7.3), Constipation: 3 (5.5), Heartburn: 2(3.6), Reflux: 2(3.6), Indigestion: 2 (3.6) **Placebo** Nausea: 3 (11), Vomiting: 0, Diarrhea: 0, Constipation: 1 (3.7), Heartburn: 1(3.7), Reflux: 0, Indigestion: 0	**Liraglutide** Injection site reaction: 3 (5.5), Prolonged menstrual bleeding: 3 (5.5), no menstrual cycles: 0, COVID 19: 0 **Placebo** Injection site reaction: 0, Prolonged menstrual bleeding: 1 (3.7), no menstrual cycles: 1 (3.7), COVID 19: 1 (3.7)
Frössing 2018a, Frössing 2018b, Nylander 2017a, Nylander 2017b Denmark [57-60]	**Liraglutide** 44 **Placebo** 21	**Liraglutide** Nausea: 37 (78.7), Vomiting: 5 (10.6), Ructus/heartburn: 8 (17.0), Diarrhea: 5 (10.6), Constipation: 12 (25.5), Gastroenteritis. 5 (10.6), Epigastrial pain: 8 (17.0), Gallstone related pain: 3 (6.4), Cholecystectomy: 2 (4.3) **Placebo** Nausea: 3 (13.0), Vomiting: 0, Ructus/heartburn: 0, Diarrhea: 1 (4.4), Constipation: 0, Gastroenteritis: 2 (8.7), Epigastrial pain: 0, Gallstone related pain: 1 (4.4), Cholecystectomy: 0	**Liraglutide** Hypotension: 1 (2.1), Tachycardia: 1 (2.1), Syncope: 1 (2.1), Dizziness: 4 (8.5), Headache: 0, Upper respiratory tract infection: 7 (14.9), Urinary tract infection: 2 (4.3), Hair loss: 1 (2.1), Rash at injection site: 3 (6.4), Joint pain: 1 (2.1) **Placebo** Hypotension: 0, Tachycardia: 0, Syncope: 0 (0), Dizziness: 0, Headache: 3 (13.0), Upper respiratory tract infection: 4 (17.4), Urinary tract infection: 0, Hair loss: 0, Rash at injection site: 0, Joint pain: 0
Wen 2023 [66]	**Beinaglutide + metformin** 32 **Metformin** 32	**Beinaglutide + metformin** Diarrhea 0, Vomiting: 7 (21), Nausea: 8 (25), Abdominal distension: 0 **Metformin** Diarrhea: 8 (25), Vomiting: 2 (6), Nausea: 13 (40), Abdominal distension: 10 (31)	**Beinaglutide + metformin** Headaches: 3 (9), Fatigue: 1 (3), Injection site pruritus: 13 (40), Subcutaneous induration: 15 (46) **Metformin** Headaches: 0, fatigue: 0, Injection site pruritus: NA, Subcutaneous induration: NA
Xing 2022 [64]	**Metformin** 25 **Liraglutide + metformin** 27	Mild gastrointestinal side effects, such as nausea, heartburn, vomiting, and diarrhea, occurred in both groups during the first two weeks of treatment with a higher proportion of these adverse reactions in the COM group.	Two participants had one episode of hypoglycemia, while one participant in the COM group developed a rash at the injection site. Most adverse reactions were mild and spontaneously resolved after 2 weeks of treatment.

GI = gastrointestinal; TEAE = treatment-emergent adverse event.

6 Long term analyses

6.1 Meta-analyses for metformin+

BMI (kg/m^2)



Footnotes

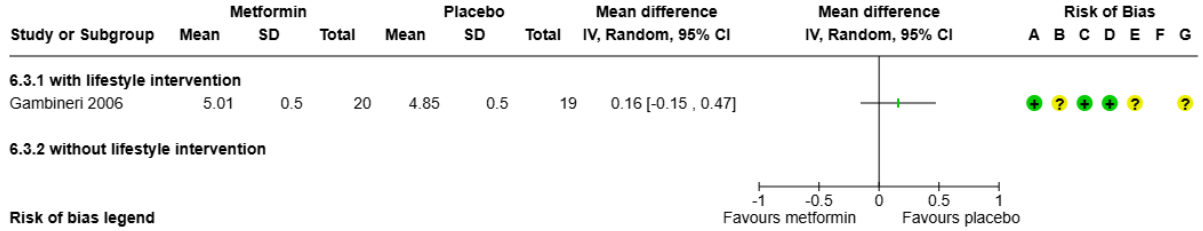
[a]CI calculated by Wald-type method.

[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

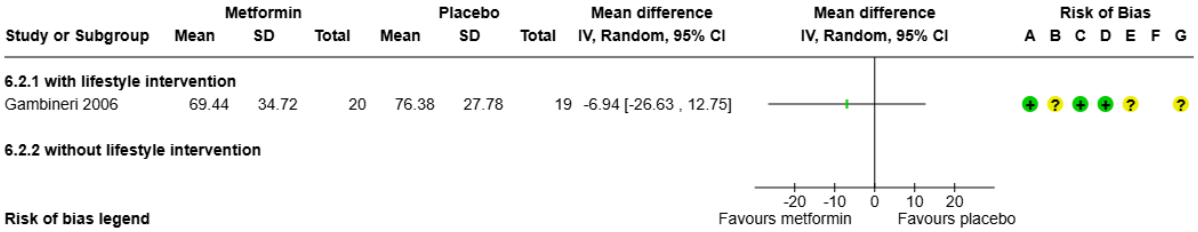
Fasting glucose (mmol/l)



Risk of bias legend

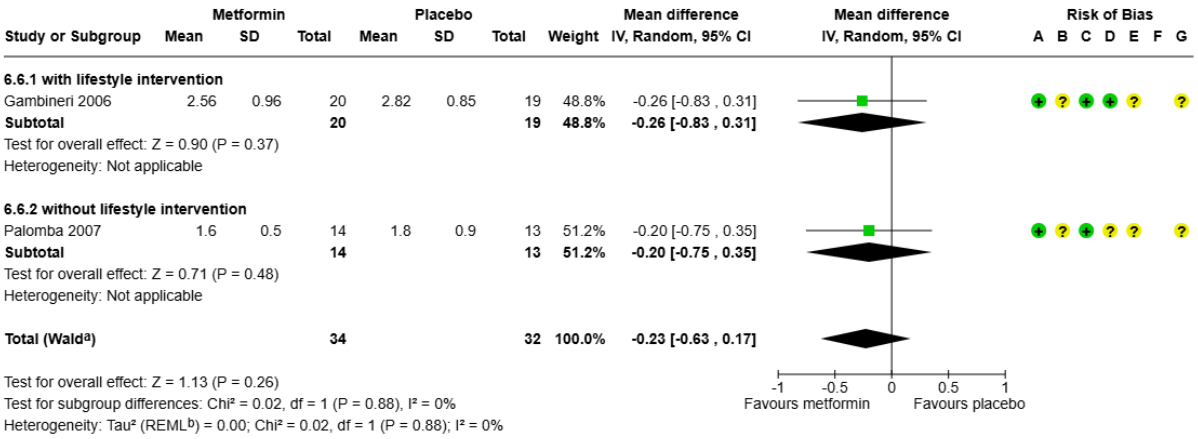
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Fasting insulin (pmol/l)



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

LDL (mmol/l)

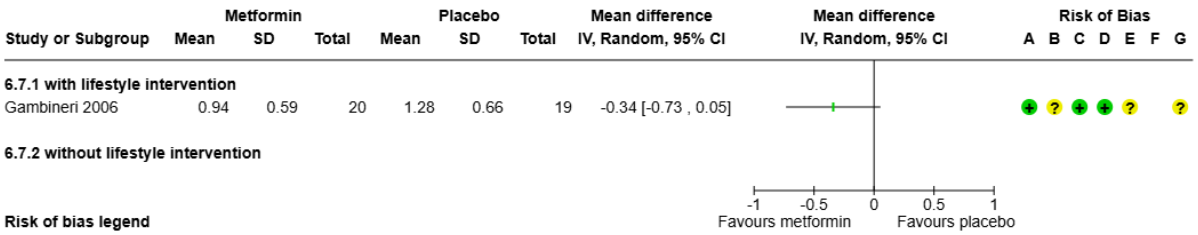


Test for overall effect: Z = 1.13 (P = 0.26)
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%
Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

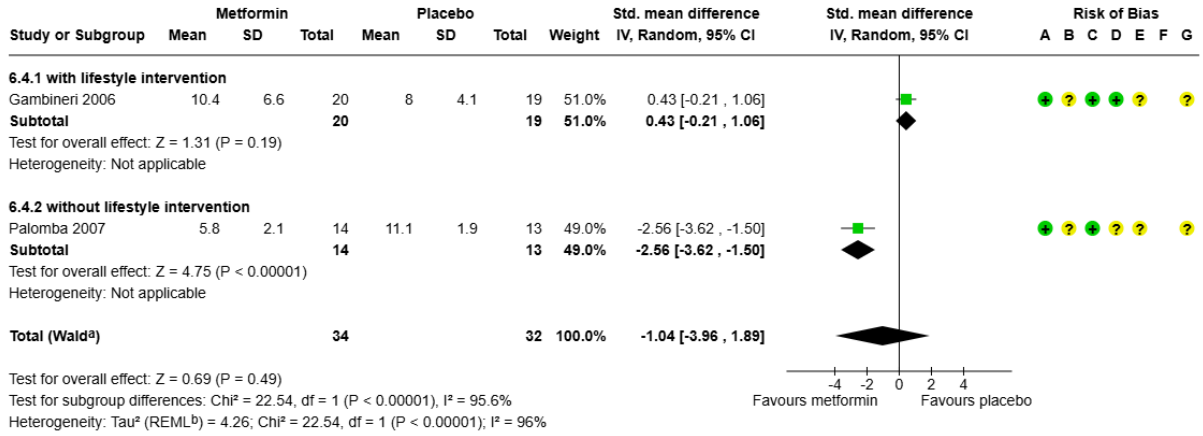
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Triglycerides (mmol/l)



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

Hirsutism



Footnotes

[a]CI calculated by Wald-type method.

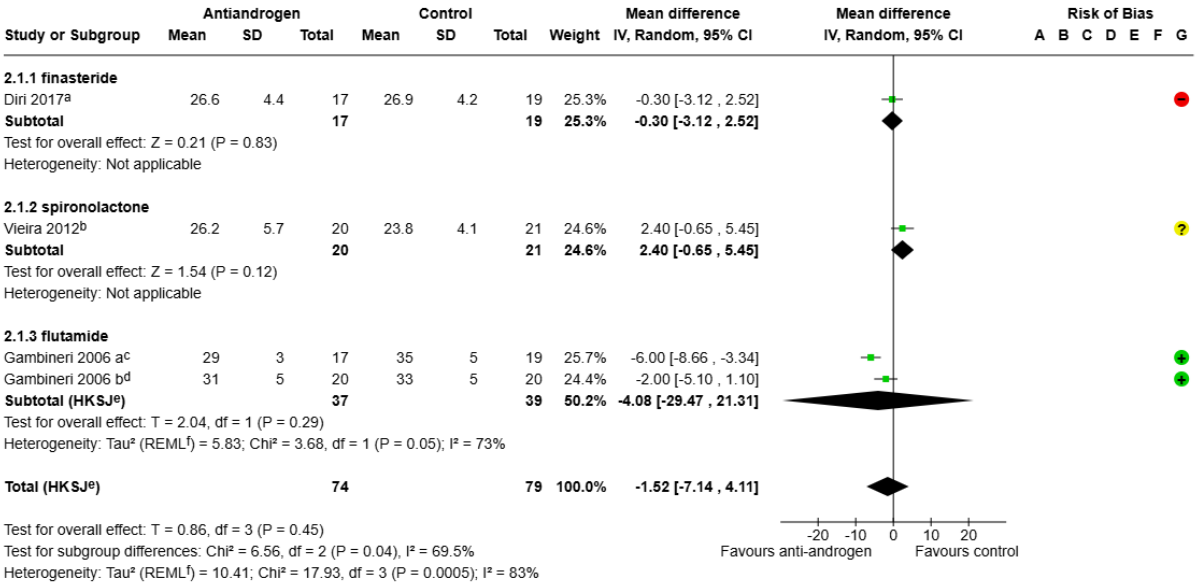
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Conflict of interest
(G) Overall risk of bias

6.2 Meta-analyses for antiandrogens+

BMI (kg/m²)



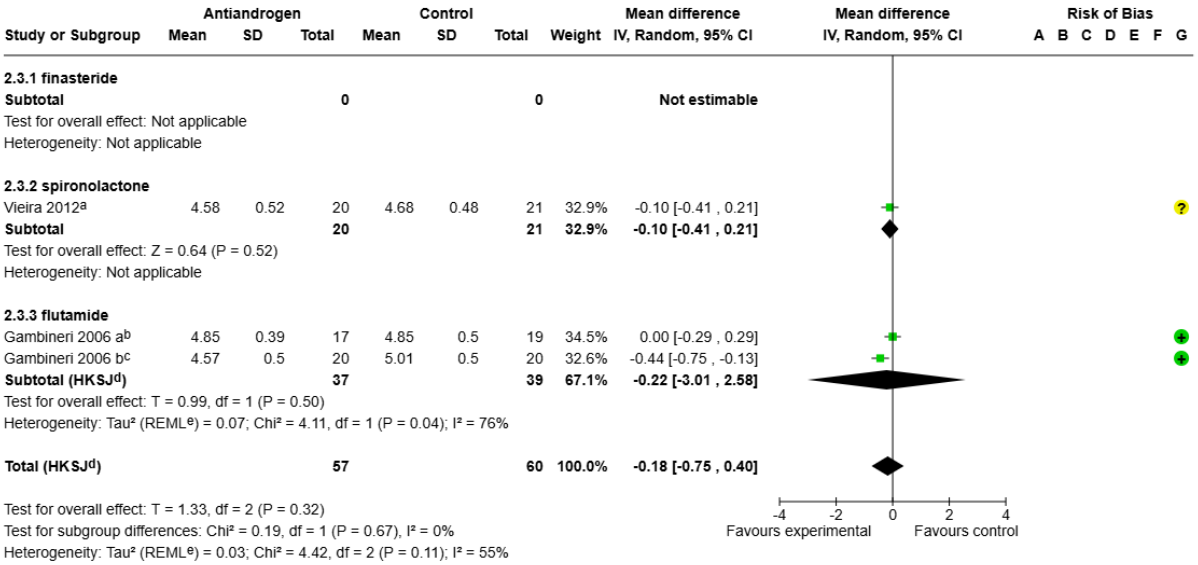
Footnotes

[a]with metformin for both groups
[b]with oral contraceptives for both groups
[c]with lifestyle intervention for both groups
[d]with metformin and lifestyle intervention for both groups
[e]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[f]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Fasting glucose (mmol/l)



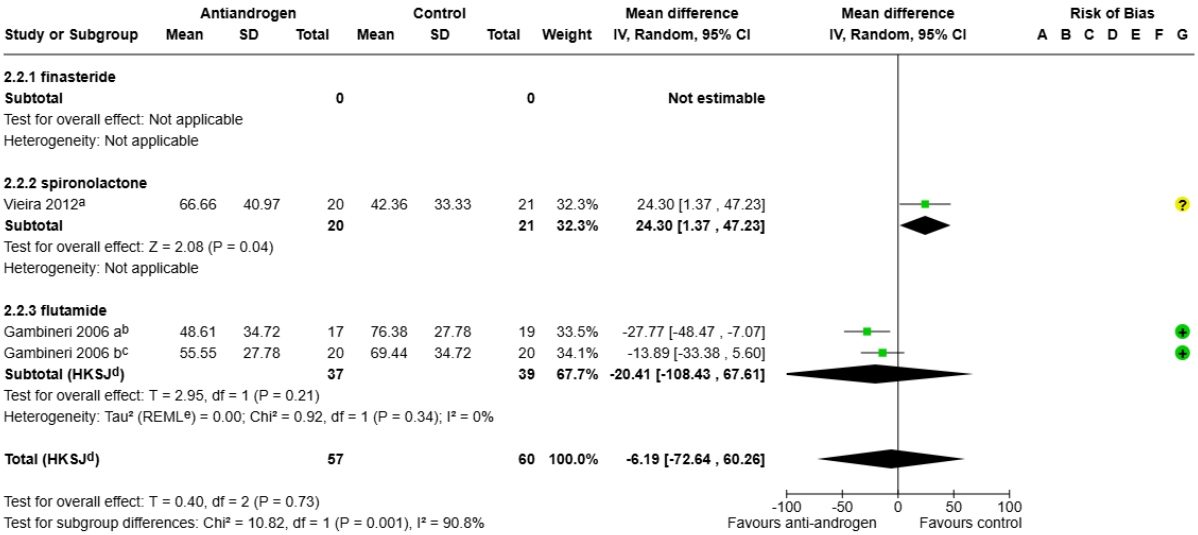
Footnotes

[a]with oral contraceptives for both groups
[b]with lifestyle intervention for both groups
[c]with metformin and lifestyle intervention for both groups
[d]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[e]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Fasting insulin (pmol/l)



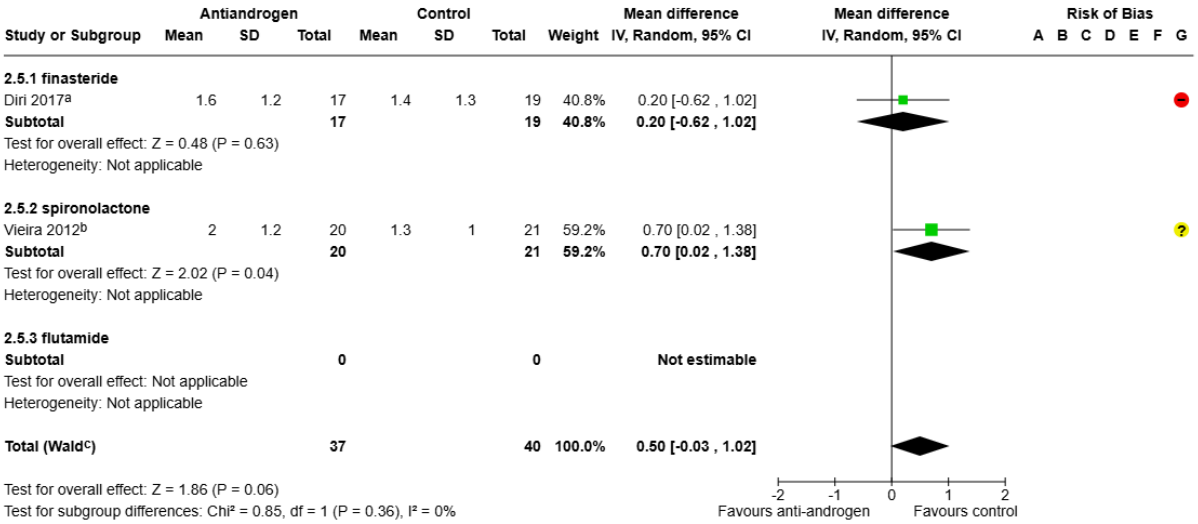
Footnotes

[a]with oral contraceptives for both groups
[b]with lifestyle intervention for both groups
[c]with metformin and lifestyle intervention for both groups
[d]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[e]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

HOMA-IR



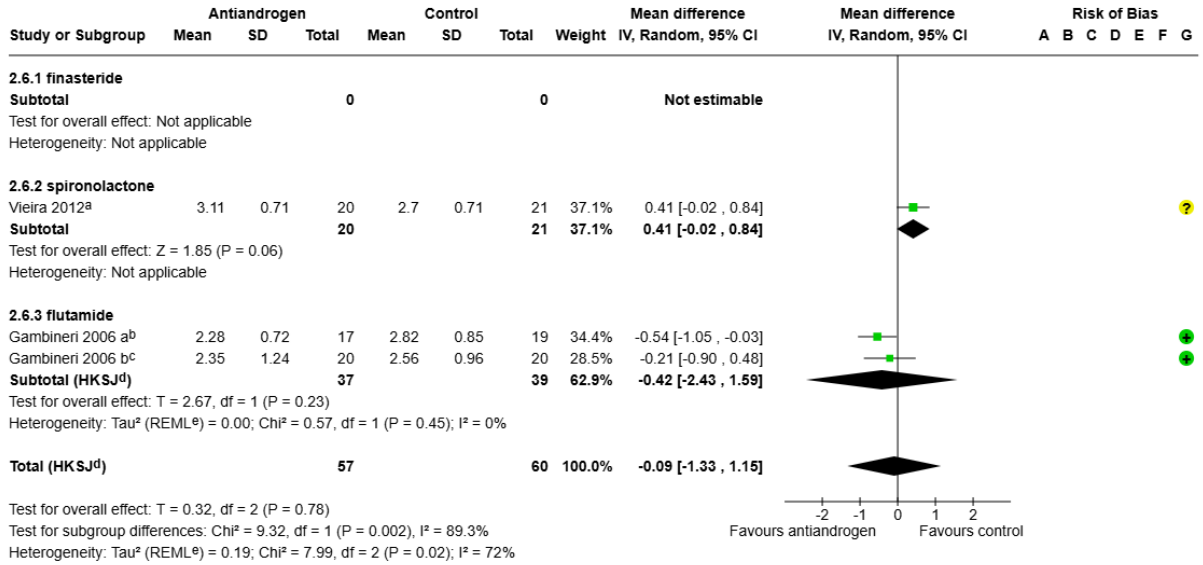
Footnotes

[a]with metformin for both groups
[b]with oral contraceptives for both groups
[c]CI calculated by Wald-type method.
[d]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

LDL (mmol/l)



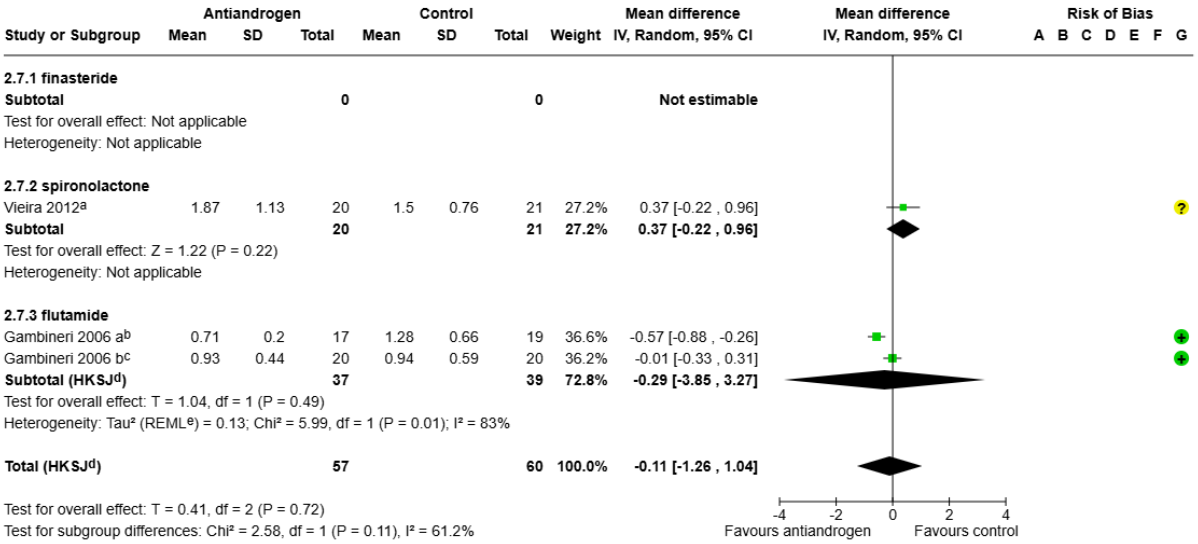
Footnotes

[a]with oral contraceptives for both groups
[b]with lifestyle intervention for both groups
[c]with metformin and lifestyle intervention for both groups
[d]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[e]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Triglycerides (mmol/l)



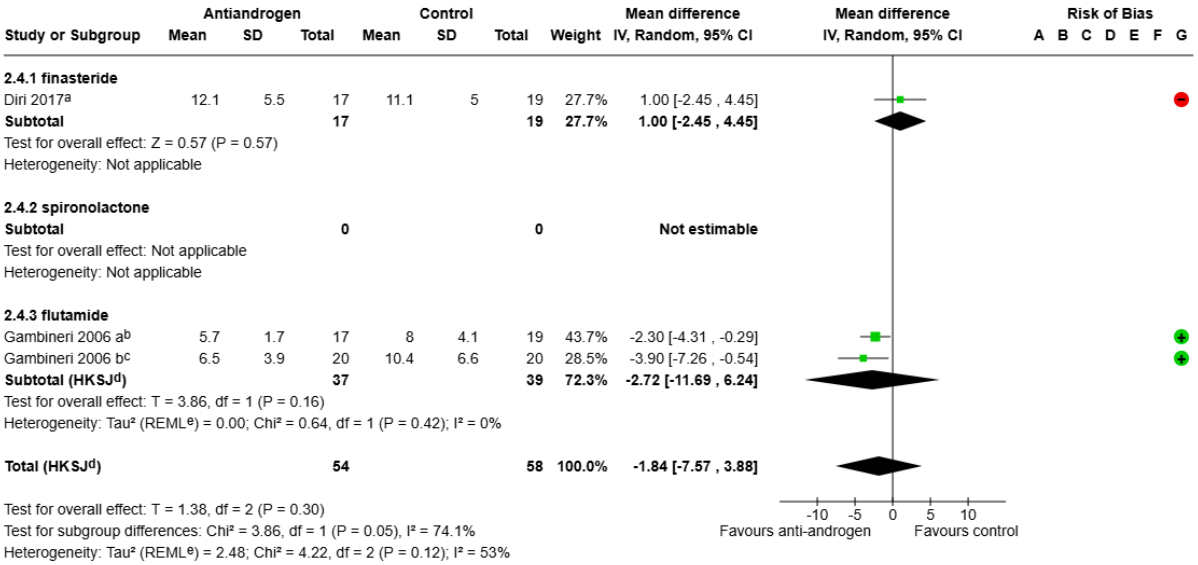
Footnotes

[a]with oral contraceptives for both groups
[b]with lifestyle intervention for both groups
[c]with metformin and lifestyle intervention for both groups
[d]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[e]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Hirsutism



Footnotes

[a]with metformin for both groups
[b]with lifestyle intervention for both groups
[c]with metformin and lifestyle intervention for both groups
[d]CI calculated by Hartung-Knapp-Sidik-Jonkman method.
[e]Tau² calculated by Restricted Maximum-Likelihood method.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

7 References for summary of findings tables

Table 52 *Antiandrogens (references for table 5.1 in main report).*

Outcome	Metaanalysis (MA) References Narrative analysis (NA) References
BMI	MA: [16-20, 22, 24] NA: [23]
WHR	MA: [16, 20] NA: No studies
Glucose	MA:[16, 18-20, 22, 24] NA: No studies
Insulin	MA: [16, 18-20, 22, 24] NA: No studies
HOMA-IR	MA: [17, 20, 22, 24] NA: No studies
LDL	MA: [16, 19, 22, 24] NA: [21, 23]
TG	MA: [16, 19, 22, 24] NA: [21, 23]

Hirsutism	MA: [14, 16, 17, 19, 20, 22] NA: [21, 23]

Table 53 Metformin+ (references for table 5.2 in main report).

Outcome (patients according to BMI class)		Metaanalysis (MA) References Narrative analysis (NA) References
BMI	All	MA: [16, 19, 26-28, 32, 34, 36, 39, 40, 42-44, 46-52] NA: [37, 38, 45]
	≥25	MA: [19, 26-28, 34-36, 40, 43, 47, 49] NA: [37, 38]
	<25	MA: [32, 34, 35, 42, 46, 48] NA: [45]
WHR	All	MA: [16, 28-30, 32, 34, 35, 40, 42, 44, 47, 49-51] NA: [38, 39]
	≥25	MA: [28, 34, 35, 40, 42, 47, 49] NA: [38]
	<25	MA: [32, 34, 35, 42] NA: inga studier
Glucose	All	MA: [16, 19, 26, 28-30, 32-36, 39-44, 47, 50, 52] NA: [37, 38, 45, 49]
	≥25	MA: [19, 26, 28-30, 34-36, 40-43, 47] NA: [37, 38, 49]
	<25	MA: [29, 30, 32, 34, 35, 42] NA: [45]
Insulin	All	MA: [16, 19, 26, 28, 39, 41-44, 47, 50, 52] NA: [29, 30, 36-38, 45, 49]
	≥25	MA: [19, 26, 28, 41-43, 47] NA: [29, 30, 36-38, 49]
	<25	MA: [42] NA: [29, 30, 45]
HOMA-IR	All	MA: [39, 41, 50] NA: [29, 30, 37]
	≥25	MA: [28, 34, 35, 41, 42] NA: [29, 37]
	<25	MA: [34, 35, 42] NA: [29, 30]
LDL	All	MA: [16, 19, 26-30, 36, 40, 41, 43, 44, 46, 48, 50] NA: [38, 45]
	≥25	MA: [19, 26-28, 36, 40, 41, 43] NA: [38]
	<25	MA: [46, 48] NA: [45]
TG	All	MA: [16, 19, 26-28, 39-41, 43, 44, 49, 50] NA: [36, 38, 45]
	≥25	MA: [19, 26-28, 40, 41, 43, 49] NA: [36, 38]
	<25	MA: No studies

		NA: [45]
Hirsutism	All	**MA**: [16, 19, 26, 31, 43, 44, 46, 48] **NA**: [16, 19, 26, 27, 29-32, 36, 37, 39, 41, 43, 48, 49, 51, 52, 65]
	≥25	**MA**: [19, 26, 31] **NA**: [37]
	<25	**MA**: [46, 48] **NA**: No studies
Menstruation	All	**NA**: [16, 19, 26, 27, 29-32, 36, 37, 39, 41, 43, 48, 49, 51, 52, 65]

Table 54 GLP-1 analogues (references for table 5.4 in main report).

Outcome	Metaanalysis (MA) References Narrative analysis (NA) References
BMI	**MA**:[56-60, 64, 66] **NA**: [63]
WHR	**MA**: [56-60, 66] **NA**: [66]
Glucose	**MA**: [56, 61-64, 66] **NA**: No studies
Insulin	**MA**: [61-64] **NA**: [66]
HOMA-IR	**MA**: [55-60, 63] **NA**: [61, 62, 66]
LDL	**MA**: [55-60, 66] **NA**: [63]
TG	**MA:** [56, 63] **NA**:[61-63]
Hirsutism	**MA**: No studies **NA**: [57-60]
Menstruation	**NA:**

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