

## **Insulin Sensitizers for the Treatment of Hirsutism: A Systematic Review and Meta-analyses of Randomized Controlled Trials**

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## **ABSTRACT (260 words)**

**Context:** Insulin sensitizers, including metformin and thiazolidinediones (TZDs) improve hyperinsulinemia and reproductive dysfunctions in some women with hyperandrogenism. The extent to which these agents improve hirsutism remains unclear.

**Objective:** To conduct a systematic review and meta-analyses of randomized controlled trials of metformin or TZDs for the treatment of hirsutism.

**Data sources:** We searched the following databases: MEDLINE, EMBASE, and Cochrane CENTRAL (up to May 2006). Review of reference lists and contact with hirsutism experts further identified candidate trials.

**Study selection:** Reviewers working independently and in duplicate, with acceptable chance-adjusted agreement ( $\kappa = 0.72$ ), determined trial eligibility. Eligible trials randomly assigned women with hirsutism to  $\geq 6$  months of insulin sensitizers or control, and measured hirsutism outcomes.

**Data extraction:** Reviewers working independently and in duplicate determined the methodological quality of trials and collected data on patient characteristics, interventions, and outcomes.

**Data synthesis:** Of 348 candidate studies, 16 trials (22 comparisons) were eligible. The methodological quality of these trials was low. Random-effects meta-analyses showed a small decrease in Ferriman-Gallwey scores in women treated with insulin sensitizers compared to placebo (pooled weighted mean difference (WMD) of -1.5, 95% confidence interval (CI) -2.8, -0.2, inconsistency ( $I^2$ ) = 75%). There was no significant difference between insulin sensitizers and oral contraceptives (WMD of -0.5, CI, -5.0, 3.9;  $I^2$  = 79%). Metformin was inferior to both spironolactone (WMD of 1.3, CI, 0.03, 2.6) and flutamide (WMD of 5.0, CI, 3.0, 7.0;  $I^2$ =0%).

**Conclusions:** Imprecise and inconsistent evidence of low to very low quality suggests that insulin sensitizers provide limited or no important benefit for women with hirsutism.

## **Introduction**

Clinical features of hyperandrogenism, including hirsutism, acne, and androgenic alopecia, are common in polycystic ovary syndrome (PCOS) (1, 2). Indeed, women with PCOS often present with hirsutism, a cause of psychosocial distress to patients, which moves health care providers to exclude other, more ominous, causes of hyperandrogenism. Insulin sensitizers, including metformin and thiazolidinediones (TZDs), have been used for the treatment of the metabolic abnormalities (e.g., diabetes mellitus) and the reproductive derangements (e.g., chronic anovulation) present in women with PCOS. However, their clinical role in the improvement of hyperandrogenism manifestations, and in particular hirsutism, remains unclear.

Some effects of insulin sensitizers may favorably impact patients with PCOS and hyperandrogenism. Metformin decreases hepatic glucose production(3) and lowers insulin levels with improved insulin sensitivity. TZDs improve the action of insulin in the liver, skeletal muscle, and adipose tissue(4). By reducing hyperinsulinemia, both metformin and TZDs may also reduce adrenal and ovarian androgen biosynthesis, raise levels of sex hormone binding-globulin, and improve gonadotropin secretion(5). The net effect could plausibly cause improvement of hirsutism.

Systematic reviews can enhance the ability of clinicians and patients to make sense of disparate and small clinical trials. These trials tend to yield imprecise answers and apply to only a narrow set of patients. Pooling such trials together, if the trials are consistent, can yield precise estimates that are more broadly applicable (6).

To clarify the role that insulin sensitizers play in the treatment of hirsutism, we conducted a systematic review and meta-analyses of randomized trials of metformin or TZDs, alone or in combination with other therapies (oral contraceptive pills (OCPs) or antiandrogens), for the treatment of hirsutism. The Endocrine Society Task Force on Hirsutism, assembled to produce clinical practice guidelines,

commissioned these meta-analyses to support the formulation of evidence-based recommendations.

## **Methods**

We developed a systematic review protocol (available upon request) with extensive input from the expert members of the commissioning Task Force. We prepared this report in adherence with the Quality of Reporting of Meta-analyses (QUOROM) standards for reporting systematic reviews of randomized trials (7). The authors of this report have not received financial contributions or research support from makers or distributors of insulin sensitizers, antiandrogens, or OCPs, for this project or at any other time.

### *Eligibility Criteria*

Eligible studies were fully published randomized trials that enrolled women of age 12 and older with varying degrees of hirsutism and treated them for at least 6 months with metformin or TZDs, alone or in combination with OCPs or antiandrogens, or with placebo or active control (OCPs or antiandrogens). For this review, OCPs included single pill preparations, some of which contained a low dose (2 mg) of cyproterone acetate. We considered higher doses of cyproterone acetate separately as antiandrogens.

Eligible trials had to measure hirsutism as an outcome. Patients, clinicians, or researchers could use subjective methods (the Ferriman-Gallwey score (FGS), typically), or researchers could use objective methods (e.g., measurement of hair diameter, length, or rate of growth) to measure hirsutism.

We excluded studies enrolling patients with hirsutism due to etiologies other than PCOS, idiopathic hirsutism, or presumed late-onset congenital adrenal hyperplasia. Trials in which patients received gonadotrophin releasing hormones, clomiphene, or glucocorticoids were also ineligible. Language of publication was not an eligibility criterion.

### *Study Identification*

An expert reference librarian (P.J.E.) designed and conducted the electronic search strategy with input from an endocrinologist (V.M.M.) with expertise in conducting systematic reviews. The systematic search included MEDLINE, EMBASE, and Cochrane CENTRAL electronic databases from their inception through May 2006. The detailed strategy is available upon request. To identify additional candidate studies, we reviewed the reference lists of the eligible primary studies, narrative reviews, and systematic reviews, and we queried the expert members of the commissioning task force.

#### *Study selection*

Working independently and in duplicate, reviewers (M.C., B.A.S., D.M.K., and V.M.M.) screened all abstracts and titles. After obtaining all potentially eligible studies in full text, these reviewers, again working independently and in duplicate, determined eligibility with acceptable chance-adjusted interobserver agreement (kappa statistic ( $\kappa$ ) = 0.72). Disagreements were resolved by consensus or arbitration (by V.M.M.).

#### *Data collection*

Using a standardized data extraction form and working in duplicate, M.C., B.A.S., and V.M.M. abstracted the following descriptive data from every study: description of trial participants (age, body mass index or body habitus (e.g., lean or obese), etiology of hirsutism, presence of hirsutism as an explicit criterion for enrollment, degree of hirsutism at baseline, prior treatment that may have affected hirsutism, and characteristics of treatment and control interventions (medication type, dose, frequency, route, and duration).

We also abstracted specific hirsutism outcomes from every study. We collected end-of-study hirsutism scores or, when these were not reported, change-from-baseline scores. Outcomes collected were at the longest point of complete follow-up while patients were still exposed to the interventions. When authors seemed to have collected data but failed to report these, or reported data only with a statement of change or significance (e.g., ‘no

change’ or ‘not significant’), we contacted the authors to obtain full details.

#### *Quality Assessment*

To ascertain the reported methodological quality of eligible trials, pairs of reviewers (M.C., B.A.S., D.M.K., M.L.L., R.J.M., and V.M.M.), working independently and with adequate reliability, determined the adequacy of allocation concealment ( $\kappa$  = 0.56) and blinding of patients ( $\kappa$  = 0.69), health care providers ( $\kappa$  = 0.63), and outcome assessors ( $\kappa$  = 0.88). The proportion of participants randomized for whom the trial authors did not report hirsutism outcomes (i.e., the extent of loss to follow-up) was also noted.

#### *Statistical Analyses*

##### *Meta-analyses*

Due to a small number of randomized trials reporting patient self-assessment and objective evaluation of hirsutism, we focused our quantitative analyses on subjective assessment by a health care professional. We determined the pooled weighted mean difference between treatment and control interventions and the associated 95% confidence interval (CI) using a DerSimonian and Laird(8) random-effects meta-analysis as implemented in RevMan 4.2 (Cochrane Collaboration)(9) and in StatsDirect statistical software(10). We quantified inconsistency using the  $I^2$  statistic which describes the proportion of variance across studies not due to chance, thus describing the extent of true inconsistency in results across trials:  $I^2 < 25\%$  and  $I^2 > 50\%$  reflect small and large inconsistency, respectively(11).

##### *Subgroup analyses*

The following were *a priori* hypotheses to explain potential heterogeneity across eligible trials: study quality (blinding status and loss to follow-up); patient population characteristics (age, hirsutism etiology, and degree of hirsutism at baseline); and treatment and control interventions (type, dose, and length of treatment). To explore these hypotheses, we estimated the difference in treatment effects between subgroups or treatment-subgroup interactions (12).

## Results

### Search results

The search identified 348 candidate studies for review, of which 16 trials were confirmed eligible (**Figure 1**) contributing to 22 comparisons. One trial reported the results separately by patients weight groups (lean, overweight or obese)(13) and 2 trials evaluated multiple interventions(14, 15); we abstracted each intervention of interest as a separate comparison while avoiding duplicate counting of the control group within the same meta-analysis.

### Methodological quality

**Table 1** summarizes the methodological quality of the eligible trials. Several trials lacked details regarding the use of methodological features that protect against bias, while in other trials it was clear that the techniques were not used. Four trials (18, 20, 22, 32) reported procedures consistent with allocation concealment which protects the randomization, and only two (18, 19) clearly reported blinding of the outcome assessors (i.e., the researchers estimating each patient's degree of hirsutism). Loss to follow-up was, in some cases, substantial with 7 trials (13, 17, 19, 20, 22, 33) losing more than 20% of the randomized participants.

### Clinical characteristics

**Table 2** describes the characteristics of the eligible trials. Enrolled participants were typically young women with median (calculated as median of the mean age of the patients in each trial) age 27 with PCOS (defined either by NIH or Rotterdam criteria) and hirsutism quantified using FGS in all studies. Baseline mean hirsutism scores varied widely across the trials (FGS range: 6.9 to 22.8) with 4 trials (15, 18, 19, 22) requiring a minimal degree of hirsutism for enrollment. Nine studies (13, 14, 18, 20, 21, 31, 32, 33, 34) contributing to twelve comparisons included obese and overweight women (body mass index > 25 kg/m<sup>2</sup>), 4 studies (13, 15, 24, 35) contributing to 6 comparisons enrolled lean women (body mass index < 25 kg/m<sup>2</sup>), and 4 studies (17, 19, 22, 23) contributing to 4 comparisons did not have a weight eligibility criterion. Included trials evaluated the efficacy of either 1000 to 2000 mg

metformin daily or TZDs (600 mg troglitazone daily or 4 mg rosiglitazone daily) for 6 to 12 months. The eligible trials involved two antiandrogens (50 mg spironolactone daily or 62.5 to 500 mg flutamide daily) and three OCPs (35 micrograms ethinyl estradiol with 250 micrograms norgestimate daily, 35 micrograms ethinyl estradiol with 2 mg cyproterone acetate daily, or 30 micrograms ethinyl estradiol with 300 micrograms drospirenone daily).

### A. Meta-analyses of clinician's subjective assessments of hirsutism

**Figure 2** summarizes the results of the meta-analyses. The **Appendix** includes each of the meta-analytic plots for the analyses listed.

### Insulin sensitizers vs. placebo

Meta-analysis of the nine placebo-controlled comparisons found a small effect of insulin sensitizers on hirsutism (pooled weighted mean difference (WMD) of -1.5; CI, -2.8, -0.2), with large inconsistency across the trials ( $I^2 = 75\%$ ).

Subgroup analyses showed that one 11-month trial found troglitazone was better than placebo(16, 17) (-2.4; CI, -3.8, -1.0) while meta-analysis of the 8 comparisons of metformin vs. placebo (13, 14, 18-21) found no significant effect (-1.4; CI, -2.8, 0.1;  $I^2 = 77\%$ ). However, we found no significant interaction between sensitizer type (troglitazone vs. metformin) and the magnitude of the treatment effect ( $P_{interaction} = .31$ ). Further planned analyses found no subgroup-treatment interactions across subgroups defined by blinding status, extent of loss to follow-up (less or more than 20%), degree of hirsutism (less or more than the median FGS of 13.5), length of treatment ( $\leq 6$  months vs.  $> 6$  months), or type of reported outcome (i.e., end-of-study FGS or change in FGS from baseline). A *post hoc* analysis revealed that studies enrolling participants described as overweight or obese (or who had a mean body mass index that was 2 standard deviations above 25 kg/m<sup>2</sup>) or enrolling a mixed population of lean and obese women (WMD - 2.3, CI -3.4, -1.2) had a significantly different result ( $P_{interaction} = .02$ ) than the study enrolling lean women exclusively (1.1, CI -1.6, 3.8); **Appendix Figure S1**).

### *Insulin sensitizers vs. OCPs*

Five trials compared insulin sensitizers to OCPs. Meta-analysis of these comparisons found no significant difference in FGS between these treatments (-0.5; CI -5.0, 3.9), but with large inconsistency across these studies ( $I^2 = 79\%$ ; **Appendix Figure S2**).

One subgroup analysis, length of therapy, yielded a significant subgroup-treatment interaction. Trials assessing interventions delivered for 6 months or less (1.7; CI, -0.6, 4.0;  $I^2 = 0\%$ ) had a significantly lower overall treatment effect ( $P_{\text{interaction}} = .01$ ) than the 12-month trial of metformin (-8.5; CI, -12.6, -4.4)(22). All other planned subgroup analyses were noncontributory.

### *Metformin vs. antiandrogens*

Meta-analysis of the three trials of metformin vs. antiandrogens (there were no trials of TZDs vs. antiandrogens) found a significant difference in favor of antiandrogens (-3.7; CI -6.8, -0.6) but with large inconsistency across trials ( $I^2 = 80\%$ ). A significant type-treatment interaction partly explains this inconsistency ( $P_{\text{interaction}} = .002$ ): metformin was much less effective compared to flutamide(14, 15) (5.0; CI 3.0, 7.0;  $I^2 = 0\%$ ;) than to spironolactone(23) (1.3; CI 0.03, 2.6; **Appendix – Figure S3**). Other planned subgroup analyses were noncontributory.

### *Metformin in combination with other treatments*

One 9-month trial of metformin and flutamide vs. OCPs (24) found no significant difference in hirsutism between the two groups (-0.5; CI, -2.7, 1.7; **Appendix - Figure S4a**). Meta-analysis of two comparisons of metformin and flutamide vs. flutamide alone (14, 15) also found no difference between groups (0.9; CI, -0.4, 2.2;  $I^2 = 0\%$ ; **Appendix - Figure S4b**). Meta-analysis of two comparisons of metformin and flutamide vs. metformin alone (14, 15) found that the combination led to significantly lower hirsutism scores than metformin alone (-4.6; CI, -7.9, -1.3;  $I^2 = 40\%$ ; **Appendix - Figure S4c**). We found no significant subgroup-treatment interactions to account for the moderate inconsistency.

### *B. Summary of studies reporting patient self-assessments of hirsutism*

Three RCTs reported results of patient self-assessment of hirsutism along with FGS and laboratory measurements(16, 17, 19, 22).

#### *Metformin vs. placebo*

In a crossover trial, Kelly et al (19) asked 10 women to assess their hirsutism scores before and after 6 months of metformin or placebo. Compared to placebo, metformin significantly improved self-assessed hirsutism scores ( $P = .014$ ), matching the reported improvements in clinician-ascertained FGS and laboratory measurements (e.g., hair growth velocity).

#### *TZDs vs. placebo*

Guyatt et al(16) validated a self-administered health-related quality of life questionnaire (PCOSQ) in women with polycystic ovary syndrome. The PCOSQ included 26 questions addressing five areas of concern including body hair in women treated with troglitazone or placebo for 44 weeks. The changes in the self-reported hair growth domain of the PCOSQ significantly correlated ( $r = -.22$ ,  $P < .01$ ) with the clinician-assessed FGS (reported in the study by Azziz et al(17)).

#### *Metformin vs. OCPs*

In the study by Harborne et al (22), investigators asked patients to assess their hirsutism status using a visual analogue scale and with a questionnaire about the change in hair quality and need for cosmetic removal of excess hair. After 12 months, the patients taking metformin scored their hirsutism lower than the OCP group ( $P = .01$ ) matching the improvement in clinician-assessed FGS in the same group; there was no difference in hair quality between the two groups at 12 months.

## **Discussion**

### *Principal findings*

Our systematic review and meta-analyses suggest that overall insulin sensitizers provide a small benefit for women with hirsutism when compared against placebo and no significant benefit when compared with OCPs, and antiandrogens. Subgroup analyses showed that insulin sensitizers appear to be more effective

than placebo when used in women who are overweight or obese, and metformin was more effective than OCPs in one small study that treated women for more than 6 months. The addition of metformin to either antiandrogens or OCPs provided no significant advantage.

#### *Weaknesses and strengths*

Readers should interpret the results of these meta-analyses with caution for several reasons. We could not conduct meta-analyses of patient-reported hirsutism outcomes, the outcome of most relevance, as only three studies measured these outcomes. When measured and reported, however, these outcomes appear to correlate with clinician-assessed FGS. Publication bias could affect our review despite our extensive search procedure, and we did not contact drug manufacturers. We found only a small number of patients studied and trials published. Our meta-analyses include published RCTs only; potential unpublished studies may have been missed. Therefore, overestimation of treatment effect due to publication bias cannot be excluded.

Most studies include patients with a wide range of hirsutism severity at baseline, in some studies hirsutism was not even an explicit patient inclusion criterion, and several trials had baseline hirsutism scores that were not equivalent across intervention and control groups. Differences in how clinicians would score hirsutism in patients of different ethnic backgrounds and other limitations of the hirsutism scores need to be acknowledged (1). While these limitations do not bias individual randomized trials (as they are likely to affect both arms) or their summary (i.e., this review), they argue for using patient-reported outcomes rather than subjective physician assessments of hirsutism in future clinical trials.

Also, the majority of eligible RCTs had methodological limitations (a lack of, or no reporting of, adequate allocation concealment and appropriate blinding, and significant loss to follow-up). Furthermore, the often important between-study inconsistency in results remained largely unexplained. Overall, the quality of evidence informing the use of insulin sensitizers

for the treatment of hirsutism is low to very low (25) and this therefore weakens clinical inferences and the corresponding clinical practice recommendations.

Our work has several strengths. We have summarized the best available evidence about the efficacy of insulin sensitizers for the treatment of hirsutism. Almost all eligible trials reported their findings in a way that allowed their inclusion in our meta-analyses, limiting reporting bias. The thorough systematic literature search, explicit eligibility criteria, extent of agreement between abstractors, and focused analyses with subgroup explorations strengthen the validity of this systematic review and the meta-analyses.

Since the completion of our review, we know that 4 pertinent trials have been published (36-39). In general, these trials found that insulin sensitizers provided no significant benefits on hirsutism when compared with antiandrogens or OCPs, results that support the findings and conclusions of our review.

#### *Comparison with prior studies*

There are two meta-analyses reporting on the effect of insulin sensitizers on hirsutism in patients with PCOS, both published in the Cochrane Database of Systematic Reviews. Lord et al summarized trials (up to March 2004) of insulin sensitizers for the treatment of PCOS(26) against placebo or no treatment. This review included two trials with a total of 24 participants, both reporting no significant effect. The combined effect of these two trials, one using metformin alone(21) and one including metformin combined with clomifene(27) favors metformin, largely due to the latter study and only after excluding patients that did not fulfill the NIH consensus criteria for PCOS diagnosis (WMD -5.12,  $p=0.006$ , 95% CI -8.77 to -1.47). Costello et al(28) included a total of four trials comparing metformin vs. OCPs and two trials of metformin combined with OCPs vs. OCPs alone; they concluded that limited data demonstrated no difference in effect between metformin and OCPs, alone or in combinations. Our analyses included a larger number of studies; nevertheless, our results are consistent

with the findings of these earlier and smaller reviews.

#### *Implications for clinical policy and research*

The overall quality of the evidence informing the use of insulin sensitizers for the treatment of hirsutism is low to very low using the GRADE system(25), and the current evidence suggests that insulin sensitizers are not effective agents for hirsute women.

Furthermore, there is limited reporting of adverse effects in these trials. Prolonged use of TZDs has led to heart failure, edema, and bone fractures in otherwise normal women at risk of, or with newly diagnosed, diabetes (29, 30). The uncertain safety of these agents during the first trimester of pregnancy may require the study of these agents alongside effective contraception. Given the positive findings associated with troglitazone use versus placebo, further research on TZDs and hirsutism will be warranted as long as these potential harms associated with TZDs are acceptable to women with severe hirsutism who are unable to use or benefit from hair removal procedures, OCPs, and antiandrogens.

The accompanying clinical practice guidelines, based on the evidence from this review along with the values, preferences, and expertise of the Task Force members, provide clinicians and patients with current recommendations.

#### *Unanswered questions*

The poor methodological quality of the evidence summarized here highlights the research needs in this field. Investigators with nonprofit funding need to conduct large and rigorous randomized trials in women with different etiologies of hirsutism; using the various types and doses of insulin sensitizers, alone and in combination with other interventions (mainly OCPs in fertile women not seeking pregnancy); for longer periods of follow-up; and measuring blinded patient self-assessments of hirsutism as the primary outcome. Randomized trials to fully clarify both the efficacy and safety of insulin sensitizers may have a greater likelihood of finding an important treatment effect in overweight women, a *post hoc* finding of our

review that requires confirmation in new studies. Also needed are trials comparing insulin sensitizers with biological (e.g., eflornithine) and mechanical (e.g., shaving, depilation, electrolysis, and laser epilation) modifiers of hair growth.

#### *Conclusion*

Imprecise and inconsistent evidence of low to very low quality suggests that insulin sensitizers provide limited or no important benefit for women with hirsutism.

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## Figure legends

**Figure 1: QUOROM flow chart of study selection.** Results of the systematic review with QUOROM flow of studies for eligibility into the review and into each meta-analysis. IS, insulin sensitizers; OCPs, oral contraceptive pills; AA, antiandrogens.

**Figure 2. Overall summary of meta-analyses results.** Overall summary of random-effects meta-analyses of randomized controlled trials of insulin sensitizers for the treatment of hirsutism. The vertical line represents no treatment effect. Squares and horizontal lines represent the weighted mean differences in Ferriman-Gallwey Scores and their associated 95% confidence interval (CI) for each comparison, respectively. Where appropriate, we report inconsistency using the  $I^2$  statistic.

**Table 1: Methodological quality of eligible studies**

Comparison First author, year	Allocation concealment	Blinding			Loss to Follow-up	Study Funding
		Patients	Caregivers	Assessors		
<b>SINGLE AGENT</b>						
<b>Insulin sensitizers vs. placebo</b>						
<i><b>Troglitazone</b></i>						
Azziz, 2001(16, 17)	NR	Yes	Yes	NR	25%	For-profit agency
<i><b>Metformin</b></i>						
Hoeger, 2004(20)	Yes	Yes	No	No	33%	Not-for-profit agency
Kelly, 2002(19)	NR	Yes	Yes	Yes	38%	Not reported/Can't tell
Maciel, 2004(18)	Yes	Yes	Yes	Yes	15%	Not reported/Can't tell
Moghetti, 2000(31)	NR	Yes	Yes	NR	0%	Not-for-profit agency
Onalan, 2005(13)	NR	Yes	Yes	NR	11%	Not reported/Can't tell
Pasquali, 2000(21)	NR	Yes	Yes	NR	10%	Not reported/Can't tell
Gambineri, 2004(14)	NR	Yes	No	No	10%	Mixed sources
Onalan, 2005(13)	NR	Yes	Yes	NR	22%	Not reported/Can't tell
<b>Insulin sensitizers vs. OCPs</b>						
Allen, 2005(32)	Yes	No	No	No	11%	Not reported/Can't tell
Harborne, 2003(22)	Yes	No	No	No	35%	Not reported/Can't tell
Lemay, 2006(33)	NR	No	No	No	39%	Mixed sources
Morin-Papunen, 2000(34)	NR	No	No	No	28%	Not-for-profit agency
Morin-Papunen, 2003(35)	NR	No	No	No	15%	Not-for-profit agency
<b>Insulin sensitizers vs. Antiandrogens</b>						
Ganie, 2004(23)	NR	No	No	No	16%	Not reported/Can't tell
Ibanez, 2002(15)	NR	No	No	No	0%	Not-for-profit agency
Gambineri, 2004(14)	NR	Yes	No	No	5%	Mixed sources
<b>COMBINATIONS</b>						
<b>Insulin sensitizers + Antiandrogens vs. OCPs</b>						
Ibanez, 2004(24)	NR	No	No	No	0%	Not-for-profit agency
<b>Insulin sensitizers + Antiandrogens vs. Antiandrogens</b>						
Gambineri, 2004(14)	NR	Yes	No	No	5%	Mixed sources

Ibanez, 2002(15)	NR	No	No	No	0%	Not-for-profit agency
<b>Insulin sensitizers + Antiandrogens vs. Insulin sensitizers</b>						
Gambineri, 2004(14)	NR	Yes	No	No	0%	Mixed sources
Ibanez, 2002(15)	NR	No	No	No	0%	Not-for-profit agency

NR = Not reported; OCPs = oral contraceptive pills

**Table 2: Trial and comparison characteristics**

Comparison First author, year	Patients	F-G Score		Treatment	Follow-up (months)
		Insulin sensitizer	control		
<b>SINGLE AGENT</b>					
<b>Insulin sensitizer vs. placebo</b>					
<i>Troglitazone</i>					
Azziz, 2001(16, 17)	410 women (mean age 30) from USA with PCOS; hirsutism not explicit eligibility criteria	14.4	14.2	600 mg troglitazone vs. placebo	11
<i>Metformin</i>					
Hoeger, 2004(20)	18 women (mean age 28) from USA with PCOS; hirsutism not explicit eligibility criteria	15.1	13.6	1.7 g metformin vs. placebo	12
Kelly, 2002(19)	16 women (mean age not described) from UK with PCOS; inclusion if FG > 8	17.7	17.7	1.5 g metformin vs. placebo	6
Maciel, 2004(18)	34 women (mean age 21) from Brazil with PCOS; inclusion criteria FG > 8	8.4	8.7	1.5 g metformin vs. placebo	6
Moggetti, 2000(31)	23 women (mean age 23) from Italy with PCOS; hirsutism not explicit eligibility criteria	8.9	12.7	1.5 g metformin vs. placebo	6
Onalan, 2005(13)	65 women (mean age 26) from Turkey with PCOS; hirsutism not explicit eligibility criteria	9.1	6.9	1.7 g metformin vs. placebo	6
Pasquali, 2000(21)	20 women (mean age 31) from Italy with PCOS; hirsutism not explicit eligibility criteria	14.8	11.5	1.7 g metformin vs. placebo	6
Gambineri, 2004(14)	20 women (mean age 27) from Italy with PCOS; hirsutism not explicit eligibility criteria	16	13.5	1.7 g metformin vs. placebo	6
Onalan, 2005(13)	74 women (mean age 27) from Turkey with PCOS; hirsutism not explicit eligibility criteria	12.4	11.7	1.7 g metformin vs. placebo	6
<b>Insulin sensitizer vs. OCP</b>					
Allen, 2005(32)	35 women (mean age 15) from USA with PCOS; hirsutism not explicit eligibility criteria	8.4	12.4	1 g metformin for 2 wks, then 2 g metformin vs. 0.035mg EE + 0.25 mg norgestimate	6
Harborne, 2003(22)	52 women (mean age 32) from UK with PCOS; inclusion if FG > 8	20.3	22.8	1.5 g metformin vs. 0.035 mg EE + 2 mg CPA	12
Lemay, 2006(33)	28 women (mean age 24) from India with PCOS; hirsutism not explicit eligibility criteria	16.7	17.1	4 mg rosiglitazone vs. 0.035 mg EE + 2 mg CPA	6
Morin-Papunen, 2000(34)	25 women (mean age 30) from Finland with	9.6	7.6	1 g metformin for 3 mo then 2 g metformin	6

Morin-Papunen, 2003(35)	PCOS; hirsutism not explicit eligibility criteria 20 women (mean age 28) from Finland with PCOS; hirsutism not explicit eligibility criteria	7.9	5.2	for 3 mo vs. 0.035 mg EE + 2 mg CPA 1 g metformin for 3 mo then 2 g metformin for 3 mo vs. 0.035 mg EE + 2 mg CPA	6
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### **Insulin sensitizer vs. Anti-androgen**

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Ganie, 2004(23)	82 women (mean age 23) from India with PCOS; hirsutism was an explicit eligibility criteria, but FG score not specified	12.5	12.9	1 g metformin vs. 50 mg spironolactone	6
Ibanez, 2002(15)	18 women (mean age 19) from Spain with a mixed etiology of hirsutism; inclusion if FG > 8	18	14.1	1.275 g metformin vs. 250 mg flutamide	9
Gambineri, 2004(14)	20 women (mean age 27) from Italy with PCOS; hirsutism not explicit eligibility criteria	16	11.5	1.7 g metformin vs. 500 mg flutamide	6

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### **COMBINATIONS**

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#### **Insulin sensitizer + Anti-androgen vs. OCP**

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Ibanez, 2004(24)	Women (mean age 15) from Spain with PCOS; hirsutism not explicit eligibility criteria	15.3	15.1	62.5 mg flutamide + 850 mg metformin vs. 0.03 mg EE + 0.3 mg drospirinone	9
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#### **Insulin sensitizer + Anti-androgen vs. Anti-androgen**

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Gambineri, 2004(14)	20 women (mean age 27) from Italy with PCOS; hirsutism not explicit eligibility criteria	12.9	11.5	500 mg flutamide + 1.7 g metformin vs. 500 mg flutamide	6
Ibanez, 2002(15)	23 women (mean age 19) from Spain with a mixed etiology of hirsutism; inclusion if FG > 8	16.2	14.1	250 mg flutamide + 1.275 g metformin vs. 250 mg flutamide	9

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#### **Insulin sensitizer + Anti-androgen vs. Insulin sensitizer**

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Gambineri, 2004(14)	20 women (mean age 27) from Italy with PCOS; hirsutism not explicit eligibility criteria	12.9	16	500 mg flutamide + 1.7 g metformin vs. 1.7 g metformin	6
Ibanez, 2002(15)	21 women (mean age 19) from Spain with a mixed etiology of hirsutism; inclusion if FG > 8	16.2	18	250 mg flutamide + 1.275 g metformin vs. 1.275 g metformin	9

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CPA = cyproterone acetate; EE= ethinyl estradiol. FG = baseline mean or median Ferriman-Gallwey score. PCOS = polycystic ovary syndrome.

Figure 1

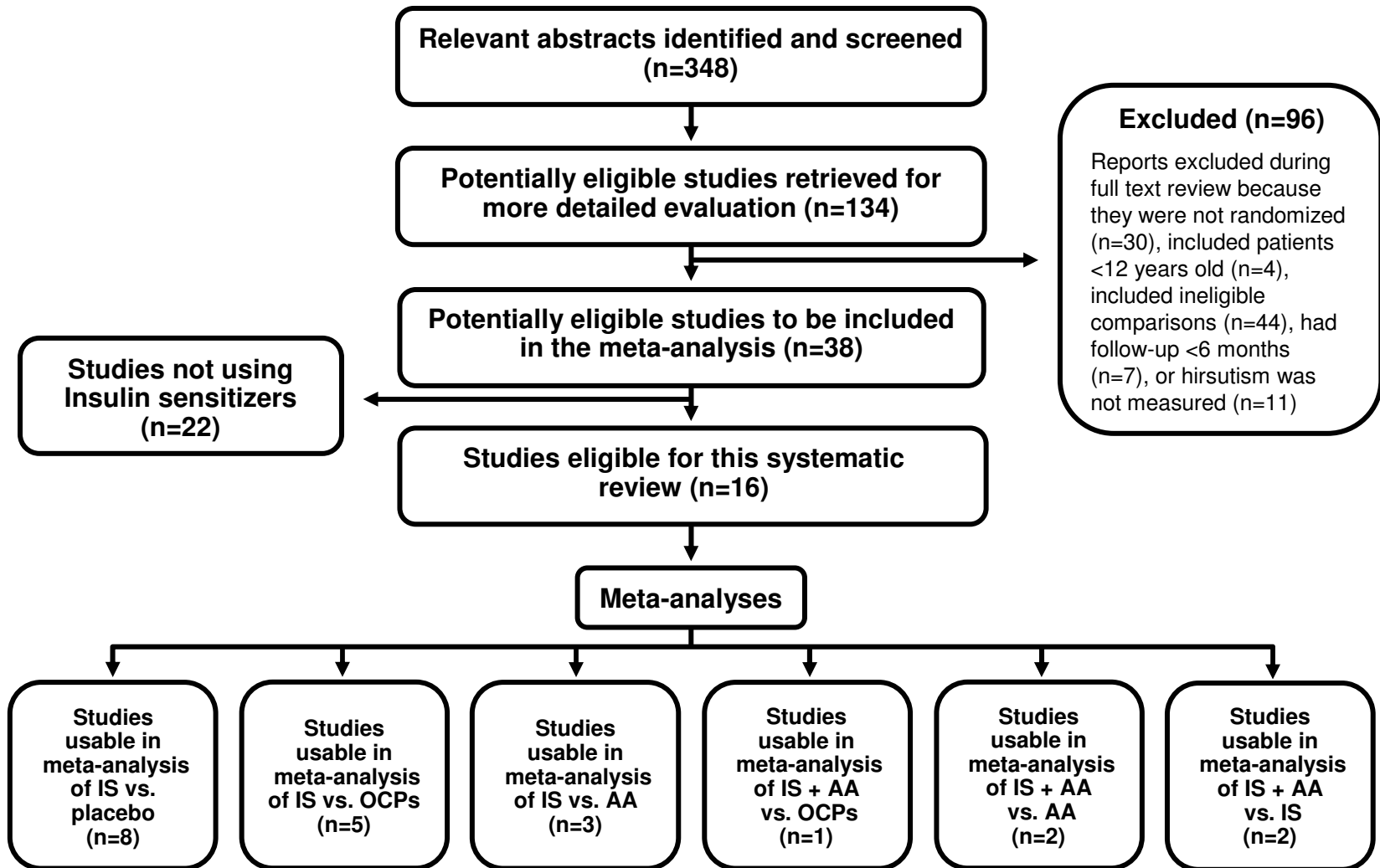
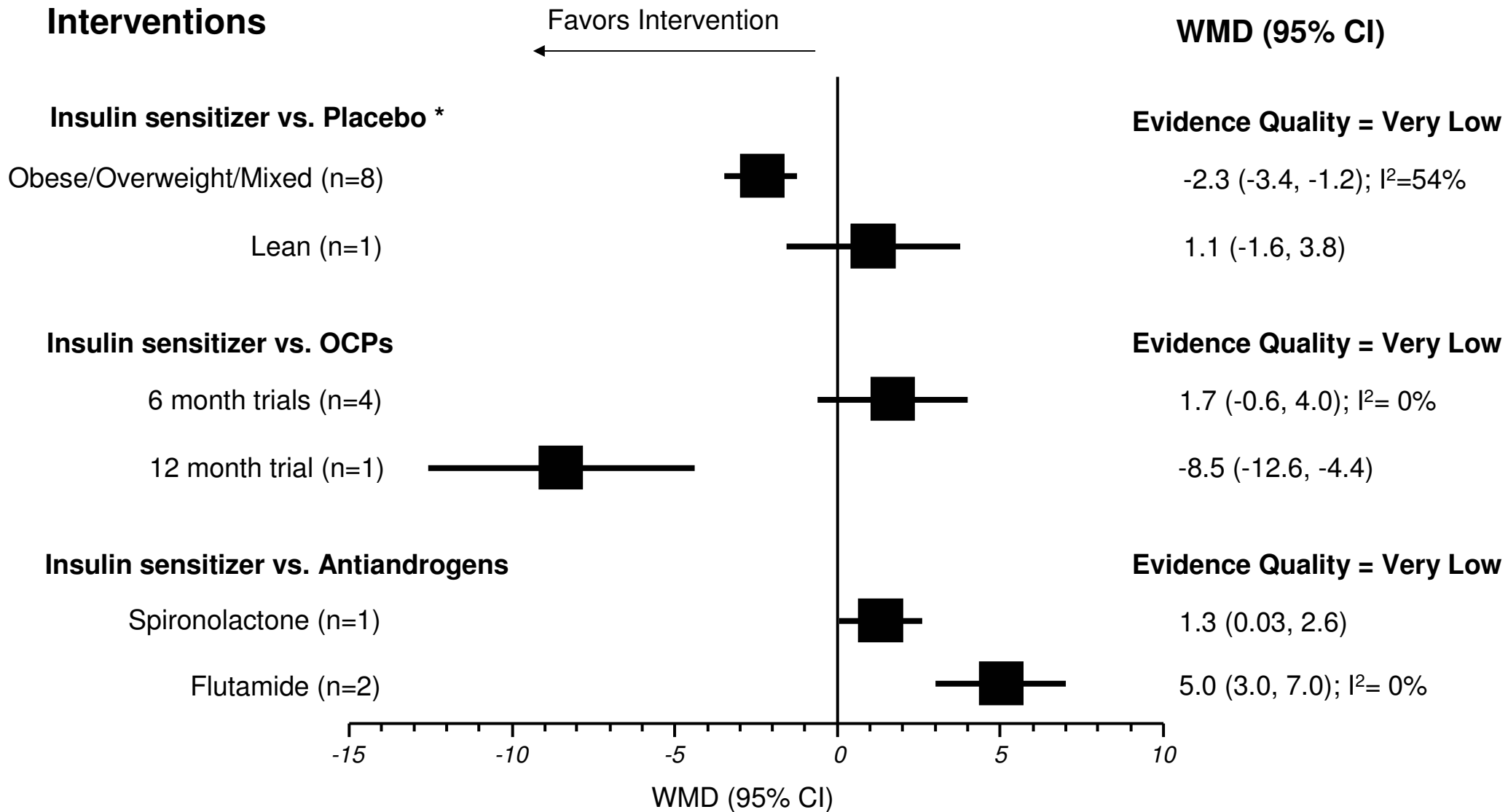


Figure 2



\* This is a post-hoc analysis