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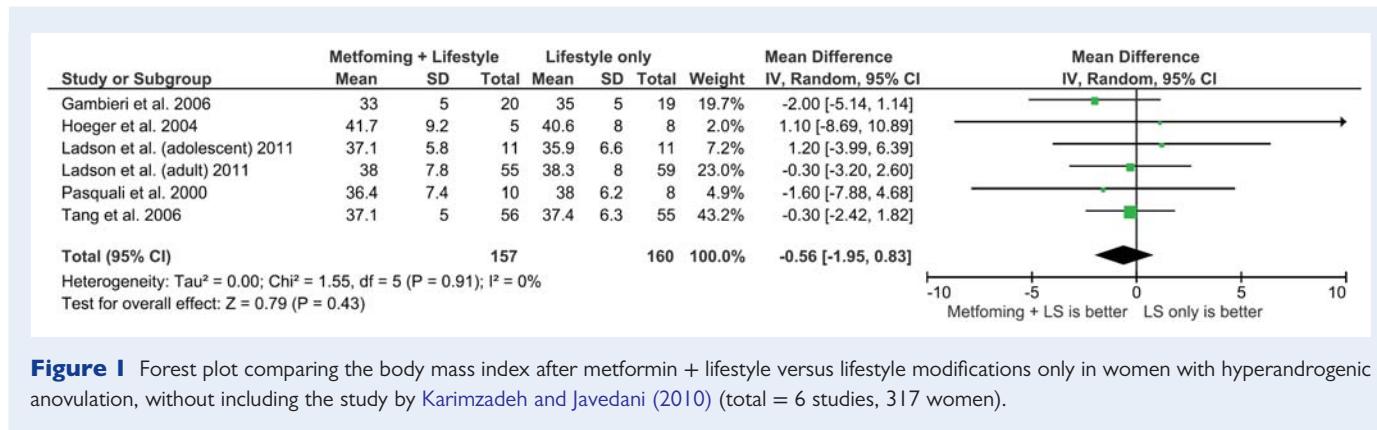
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doi:10.1093/humupd/dmv062

Advanced Access Publication on January 10, 2016

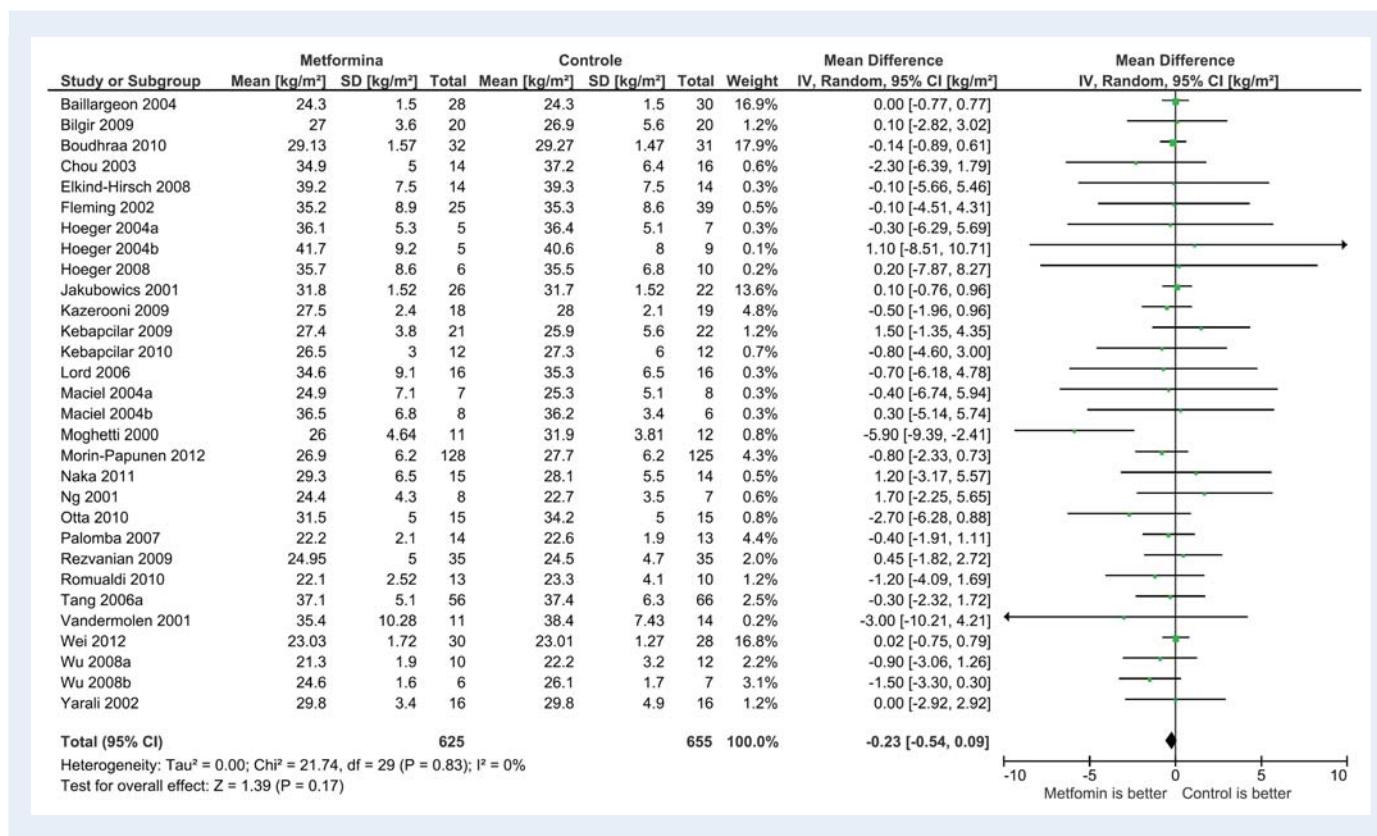
## Metformin for women with hyperandrogenic anovulation

Sir,

I read with great interest a systematic review comparing metformin and lifestyle modification in women with hyperandrogenic anovulation (Naderpoor *et al.*, 2015) where the authors concluded that metformin + lifestyle modification is able to reduce body mass index (BMI). However, reading the forest plots, I noticed that >90% of the weight of the pooled estimated comes from only one study (Karimzadeh and Javedani, 2010). When reading this study, which is at high risk of bias (no details regarding randomization or allocation concealment are



**Figure 1** Forest plot comparing the body mass index after metformin + lifestyle versus lifestyle modifications only in women with hyperandrogenic anovulation, without including the study by Karimzadeh and Javedani (2010) (total = 6 studies, 317 women).



**Figure 2** Forest plot comparing metformin versus placebo or no intervention in women with hyperandrogenic anovulation (total = 30 studies, 1280 women).

available and there was no blinding), I understand that they have compared metformin versus lifestyle modification and not lifestyle modification + metformin versus lifestyle modification. Moreover, there is no information in the report regarding the BMI after the intervention.

If we exclude the data from this study, there will be no significant difference between groups (Fig. 1). When comparing all studies comparing metformin versus placebo or no intervention published until 2012, I also didn't observe any significant benefit of metformin in BMI (Fig. 2).

Additionally, it would be very interesting if authors provide the quality of the evidence, according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group recommendation (<http://www.gradeworkinggroup.org/>).

## References

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doi:10.1093/humupd/dmv064

Advanced Access Publication on January 22, 2016

## Reply: Metformin for women with hyperandrogenic anovulation

Sir,

Thank you for the opportunity to respond to the letter by Dr Martins (Martins, 2016) regarding our article entitled 'Metformin and lifestyle modification in polycystic ovary syndrome: systematic review and meta-analysis' (Naderpoor et al., 2015).

Our team, who have extensive experience in systematic reviews and meta-analyses, completed a systematic review and meta-analysis with adherence to rigorous international best practice, independent data extraction by two reviewers and statistical analysis by a biostatistician. However, when checking the points raised by Dr Martins an error was detected. Some baseline data points were incorrectly transferred from extraction tables to RevMan analysis software. This resulted in an error in the analysis of BMI at 6 months comparing lifestyle + metformin treatment with lifestyle  $\pm$  placebo. The error in the transfer of one data frame from the extracted data table to the RevMan software resulted in the inclusion of baseline data from three studies (Karimzadeh and Javedani, 2010; Ladson et al., 2011a, b) rather than the 6 month data in comparing the BMI outcome of lifestyle + metformin and lifestyle  $\pm$  placebo.

To overcome this, we contacted the initial authors and requested BMI data at 6 months. With limited data available at 6 months, we requested data on change in BMI over 6 months and did a new meta-analysis, which demonstrates a better, although no longer statistically significant, outcome with lifestyle + metformin (95% CI: -0.85, 0.01,  $P = 0.06$ ) compared with lifestyle  $\pm$  placebo. This supports the results of the original analysis and further highlights the need for larger scale randomized trials.

The Journal has published a Corrigendum (Naderpoor et al., 2016) correcting all identified errors.

With regard to the study by Karimzadeh and Javedani (Karimzadeh and Javedani, 2010); this article is relevant as all study participants received a lifestyle intervention with dietitian review. Hence, the lifestyle alone group can be compared with the metformin group who also had lifestyle intervention with a dietitian and education. Therefore, this study should be included in the meta-analysis.

Overall, current available evidence is suggestive of a greater benefit regarding weight management with lifestyle + metformin compared with lifestyle  $\pm$  placebo in patients with PCOS over 6 months; however, more research is required to affirm this.

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doi:10.1093/humupd/dmv065

Advanced Access Publication on January 22, 2016