Reviewer's report

Title: The effect of statins on testosterone in men and women, a meta-analysis of randomized controlled trials.

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Reviewer: Bu Yeap

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Schooling and colleagues report a meta-analysis of RCTs involving statin vs placebo, in which treatment effects on testosterone (T) were reported. 11 of 28 trials were included in the analysis, in 5 RCTs with 501 men statins lowered T by 0.66 nmol/L. In 6 heterogenous RCTs in 368 young women with PCOS, statins lowered T by 0.40 nmol/L. This information is useful as observational (cohort) studies have not been wholly consistent. Overall, the article is informative and of interest. The following comments are offered for consideration.

- Major Compulsory Revisions

1. This analysis cannot answer the hypothesis that pleiotrophic effects of statins could be due to (or coincide with) lowering of androgens. It can only address the question of whether statin use is associated with a change in T levels. This presentation of study aims needs to be carefully stated, eg in the abstract background, introduction and discussion.

2. In the discussion (page 7), the authors hypothesise that statins might cause diabetes due to the side-effect of lowering T. The analysis cannot address this question, so it remains speculative.

3. The discussion (page 7) touches on an important concept, namely the gender difference in physiology and associations of T with insulin resistance. In adult men lower T is associated with reduced insulin sensitivity. However, in young women with PCOS, higher T (albeit still much lower than normal circulating levels in men) is associated with insulin resistance. Therefore, if statins lower T in both groups, any flow on effect on diabetes risk is likely to differ between sexes. Perhaps a more conservative interpretation might be that the reduction in T with statin treatment is modest (4% in men and 11% in young women with PCOS), and this difference may or may not be sufficient to modulate diabetes risk. It would be helpful to comment on the larger extended duration statin trials looking at CVD events, whether the excess of diabetes risk was present in both men and women. There may be three distinctions to be drawn, ie between men and young women with PCOS, between men and middle-aged or older women, and between young women with PCOS and middle-aged or older women.

4. In the second paragraph of page 8, the discussion is slightly speculative and should be presented as such (and more concisely) while acknowledging the limitations of the present analysis to address these issues.
5. In the concluding paragraph, the finding that statin use is associated with reduced T, does not in itself suggest that altered T plays a role in statin modulation of diabetes or CVD risk. It does raise this issue as a question to be addressed in future research.

6. General comment: overall, the length of the discussion and number of references could be reduced to make the paper more concise. However, space should be found for a brief comment on the results of cohort studies in men reporting T levels with statin use as a covariate, to compare the magnitude of attributable changes in T with the current meta-analysis of RCTs.

- Minor Essential Revisions

1. Introduction: First paragraph: the discussion re statins vs other lipid lowering treatments could be shortened and the number of references reduced, as the focus of this analysis is statins not other lipid-lowering drugs. Please either remove or adequately reference the assertion that statins are associated with a lower risk of hormonally modulated cancer.

2. Introduction: Second paragraph could be made more concise. The situation of F to M transsexuals is interesting but does represent an very marked alteration in hormonal profiles, compared to the relatively modest changes in T reported with statin treatment. Similar caveats apply to the citing of these studies in the discussion.

- Discretionary Revisions

1. Page 6 line 1, convert T to nmol/L for consistency.

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

No competing interests to declare.