Author's response to reviews

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

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Author's response to reviews: see over
19th October 2012
Dear Dr D'Souza,

Thank you very much indeed for your consideration of our paper. We have carefully revised in the light of the reviewers’ thoughtful and insightful comments, which we feel has helped us make it into a better paper. We have also carefully edited the paper to ensure that we followed the recommendation to make the paper shorter, to avoid speculation and to keep the number of references down. Overall, we have reduced the length from 2511 (with correct reference formatting) to 2362 words, we have also kept the number of references the same, despite adding substantial new material in response to the reviewer’s helpful suggestions.

We have provided a detailed point by point response to each of the reviewer’s comments. Our responses are in italics. Any text from the paper is in bold surrounded by quotes. Any next text is also underlined. We also uploaded both a ‘clean’ version and a version in track changes.

Thank you again for your consideration of our paper and the valuable insights provided.

Regards
Mary Schooling

Version: 1 Date: 18 September 2012
Reviewer: Allan A Sniderman
Reviewer's report:
1. Major Compulsory Revisions:
   This paper comes across like someone whispering fire in a theatre. Could there be yet another major- and unanticipated- problem with statins? Please do not mistake my views- this is a well-written and, I think, so far it goes, a well-executed study, which may or may not be meaningful. And that is my concern. The authors identify a potential problem and they are, appropriately, careful and cautious in the conclusions that they draw. The differences in testosterone levels produced by statins are small. Moreover, they are the average differences and I presume the authors have no idea what the distribution of differences is. They assume they are normally distributed and they may well be. If so, I suspect they may not matter. But the effect could also be more extreme in some rather than others. Drugs are like that sometimes. If so, then the consequences could be more important. I recognize the authors do not have access to the original data and so they cannot distinguish these alternatives However, from the SD and from clinicians, can they suggest more clearly than they have whether the changes might be physiologically significant? I accept the answers can not be definitive but I think they need to try harder than they have.
   Clinical endocrinologists should have some sense of what these differences might mean and I think their insights need to be incorporated.

   Please accept our apologies. We focused here on the population level effects rather than individual level effects. At an individual level the difference in testosterone is small and the normal range of testosterone is wide. The most likely effect of statins reducing testosterone concerns sexual functioning, which does not seem to be very sensitive to differences in testosterone across the normal range. There do also seem to be some men who are particularly vulnerable to the effects of statins, where much larger changes in testosterone (and libido) can occur. However, this is uncommon. Erectile dysfunction is a very rare side effect of statin therapy, which may generally be compensated for by improvements in sexual function due to the favourable cardiovascular effect of statins. We have included this explanation in the text, by changing the following section.

   From:
   “Consistent with our a priori hypothesis this meta-analysis of randomized controlled trials found statins lowered testosterone. Nevertheless, despite our hypothesis’ potential explanatory power statins’ effects on testosterone could be of little clinical significance. However, given the very wide use of statins even a relatively small change in androgen levels could have an impact on population health that should not be dismissed without any consideration. Statins causing diabetes could be another side effect of testosterone lowering.”

   To:
   “The clinical significance of this reduction in testosterone with statins is difficult to gauge; the normal range of testosterone is wide and sexual function similar across the range. Erectile dysfunction is a rare side effect of statins, perhaps because statins’ have beneficial effects on cardiovascular function which would
counteract changes of this magnitude in testosterone. However, large changes in testosterone (and libido) can occasionally occur, which are reversible by statin withdrawal. The impact on population health may be more germane, where statins causing diabetes could be another side effect.”

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Reviewer's report
Title: The effect of statins on testosterone in men and women, a meta-analysis of randomized controlled trials.
Version: 1 Date: 27 September 2012
Reviewer: Bu Yeap
Reviewer's report:
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.

Please do accept our apologies for not being clear. We did not intend to imply that this study tests whether all the pleiotropic effects of statins are due to statins lowering testosterone, because that would require very many studies. In the abstract and the introduction we are simply giving a motivation, both theoretical and practical, as to why we think that assessing whether statins lower testosterone is an important research question. We have changed the abstract background, the introduction and the discussion to make the helpful point you raise clearer.

In the abstract background.
From: “Physiologically statins would be expected to lower testosterone and statins’ pleiotropic effects coincide with the physiological effects of lowering testosterone.”
To: “Physiologically statins would be expected to lower testosterone, because statins inhibit production of the substrate for the local synthesis of testosterone, and statins’ pleiotropic effects are somewhat similar to the physiological effects of lowering testosterone, so we hypothesized that statins lower testosterone.”

In the introduction, we have also provided further clarification, where we amended the crucial last two lines explaining the study as follows:
From: “Given statins’ physiological mechanism would be expected to reduce androgens as well as the similarity between the effects of statins and of reducing androgens, we hypothesized a priori that the pleiotropic effects of statins could be due to lowering of androgens. As a preliminary test of this hypothesis, we carried out a meta-analysis of placebo-controlled randomized trials, to avoid bias by indication, in men and women to examine whether statins reduced total testosterone.”
To: “Given statins’ physiological mechanism would be expected to reduce androgens as well as the similarity between the effects of statins and of reducing androgens, we hypothesized a priori that the pleiotropic effects of statins could be due to lowering of androgens, i.e., that statins lower androgens and that lower androgens might mediate the pleiotropic effects of statins. Here, we carried out a meta-analysis of placebo-controlled randomized trials, to avoid bias by indication, in men and women to examine whether statins reduced total testosterone.”
In the discussion, we have been careful to point out that we have tested whether statins lower testosterone, but we could not test whether lower testosterone mediates the pleiotropic effects of statins, by adding to the last paragraph of discussion:

“This finding does not demonstrate that androgens mediate any health effect of statins.”

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.

Thank you, we agree this suggestion remains speculative. We have added these words as follows:

“...statins causing diabetes could be a side effect of testosterone lowering. We are not aware of any study examining whether lowering testosterone mediates the effect of statins on diabetes, as this possibility has not, to our knowledge, been considered before, and 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.

Thank you very much indeed for raising these issues. We could not find any clear evidence from RCTs that statins have different effects on the development of diabetes by sex. However a recent large, well-conducted observational study in a cohort of women found statins associated with diabetes. Observational studies are always open to confounding, however, such confounding is more likely to bias estimates of intended effects (such as protection against CVD) than unintended effects (incident diabetes), so we think this study provides good evidence that statins do cause diabetes among women.

The gender difference in physiology and associations of T with insulin resistance is a very important concept, which does lead to the prediction that if statins lower testosterone they should increase diabetes in men but decrease diabetes among women. We previously argued that this important concept was based on observational evidence that could be confounded rather than causal and provided evidence concerning interventions where high doses of testosterone in female to male transsexuals appeared to improve glucose metabolism, however, we agree that might not be relevant to older women or effects may vary with dose. We also suggested a parsimonious model might be more persuasive. Notably, one of the lessons of the HRT, where observational evidence was refuted by RCTs, was that we should be cautious of treatment effects that ‘cross’ by gender. However, we fully accept that these arguments are may not be persuasive, so we have examined the experimental evidence again.

We could not find any RCTs designed to assess the effects of testosterone on diabetes among women. We did find RCTs where testosterone has been used as a treatment in older women for low sexual desire and in young women for androgen deficiency or HIV wasting. These RCTs did not indicate that testosterone adversely affected glucose metabolism in postmenopausal women, nor is impaired glucose metabolism seen as side-effect of testosterone treatment for low sexual desire in post-menopausal women. In younger women, the RCTs indicated that testosterone at low doses had no effect on glucose metabolism or even improved it slightly, consistent with the effects of higher doses in interventions among transsexuals. We have rewritten this section to be more cautious, to reflect all the possibilities you suggest and to be better grounded in the experimental evidence.

From:

“Observational studies suggest that the association of serum testosterone with diabetes varies by sex, and that testosterone is positively associated with diabetes among women.” Causal inference from observational studies is complicated by confounding and reverse causality. These observations could simply be the result of
confounding by obesity which causes diabetes and lower testosterone among men but causes diabetes and higher testosterone among women. Consistent with these observations possibly being confounded, interventions where female to male transsexuals are given testosterone results in lower, not higher, fasting glucose, similar to the effect of testosterone on glucose metabolism among men. Thus, in contrast to the less definitive observational evidence, the experimental evidence suggests a simpler model where lowering testosterone impairs glucose metabolism in both sexes.”

To:
“Moreover, observational studies suggest serum testosterone has sex-specific physiological effects on diabetes, negative among men and positive among women, when statins increase diabetes in both sexes. We could not identify any RCT confirming testosterone therapy increases diabetes incidence among women. In postmenopausal women, RCTs of testosterone indicate little effect on glucose metabolism. In younger women, some RCTs indicate that low doses of testosterone may improve glucose metabolism; female to male transsexuals given high doses of testosterone have improved glucose metabolism. Nevertheless, distinct effects of testosterone on diabetes may occur by dose, sex and age with the reduction in testosterone with statin treatment insufficient to modulate diabetes risk consistently.”

Finally, we also qualified the conclusion to focus more on men, because the evidence concerning men is more coherent and given men’s higher levels of testosterone than women’s, the role of testosterone may be more important among men than women. We have made the following change in the conclusion.

From:
“This finding does not demonstrate that androgens mediate any health effects of statins, but raises the question as to whether testosterone modulation plays a role in the diseases for which statins are detrimental (diabetes) or protective (cardiovascular disease).”

To:
“This finding does not demonstrate that androgens mediate any health effects of statins, but raises the question as to whether testosterone modulation plays a role in statins’ effects on health, particularly among men where testosterone is a more important hormone.”

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.

Thank you for this helpful comment. We have shortened this paragraph as you suggest (215 to 147 words) and ensured it is less speculative as given below.

From:
“More importantly, this meta-analysis also raises the question as to whether lowering testosterone is a side effect of statin therapy which should be counter-acted by testosterone therapy for maximum cardiovascular benefit, or whether testosterone lowering contributes to statins’ mode of action, and could form the basis for new treatments and prevention policies. Observational evidence suggests testosterone is inversely associated with cardiovascular mortality, although it is unclear whether these observations reflect a causal role of testosterone, or testosterone acting as marker of health status. We are not aware of any randomized controlled trial of testosterone therapy which has shown any reduction in cardiovascular events, but two randomized controlled trials of testosterone therapy have been halted because of adverse, mainly cardiovascular events, among men allocated to testosterone. Natural experiments suggest that lower testosterone protects against specifically ischemic heart disease mortality, with a relatively lower risk in men legally castrated or with Klinefelter’s syndrome. Physiologically lowering testosterone would be expected to reduce thromboxane and platelet activation, thereby providing protection against specifically ischemic heart disease, but not diabetes. Given accumulating evidence that estrogen cannot explain the dramatically lower ischemic heart disease risk among women, the alternative hypothesis, i.e., that androgen reduction could protect against ischemic heart disease and be one mechanism of statins, should not be dismissed without consideration.”

To:
“This meta-analysis also raises the question as to whether lowering testosterone is a side effect of statin therapy which should be counter-acted by testosterone therapy for maximum cardiovascular benefit, or contributes to statins’ mode of action, which could inform new treatments and prevention policies. Observationally testosterone is inversely associated with cardiovascular mortality, but whether testosterone is causal or a marker of health is unknown. No RCT has shown testosterone therapy reduces cardiovascular
events; two RCTs of testosterone therapy were halted because of adverse, mainly cardiovascular events, among men allocated to testosterone. Natural experiments suggest lower testosterone protects against specifically ischemic heart disease mortality, with a relatively lower risk in men legally castrated or with Klinefelter’s syndrome. Physiologically lowering testosterone may reduce thromboxane and platelet activation, specifically relating to ischemic cardiovascular disease, but not to diabetes. However, whether lowering testosterone with statin treatment modulates cardiovascular disease has not been examined.”

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.

Thank you for pointing this out, we have amended the concluding paragraph to follow your suggestion as follows: From: “This study based on experimental evidence shows that statins reduce testosterone, and thereby suggests that testosterone modulation may have a role in the diseases for which statins are detrimental (diabetes) or protective (cardiovascular disease).” To: “This study based on experimental evidence shows that statins reduce testosterone. This finding does not demonstrate that androgens mediate any health effect of statins, but raises the question as to whether testosterone modulation plays a role in statins’ effects on health…”

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.

We agree completely that short papers are preferable. We have checked. BMC Medicine does not have any limit on length or the number of references. We have covered the standard topics in our discussion, i.e., a paragraph summarizing the results, a paragraph comparing our study with similar studies, two paragraphs on explanations for and implications of our findings, a paragraph of limitations and a concluding paragraph. We do not think we could delete any of these sections, so we have made each paragraph shorter, and combined the two paragraphs on the implications and interpretation of our findings. We have also added the new text as requested by the reviewers. Nevertheless we have still succeeded in shortening the discussion from 1174 to 1074 words. The original discussion had 23 references, from which we removed 6 references, to ensure we answered the reviewers’ comments thoroughly and did not introduce any unreferenced statements, we added 11 references to the discussion. However, we also went through and removed any unnecessary references elsewhere, so the net effect is the same number of references as in the original submission, but now covering a much wider set of material. We hope this is acceptable.

Please accept our apologies for lack of clarity. To our knowledge, there are two large cohort ‘type’ studies reporting changes in testosterone following statin use, and several very small such cohorts giving testosterone ‘before and after’ statin use. We previously referenced the two large studies reporting changes in testosterone following statin use in the discussion, but we did not include all the small cohorts in the discussion in the interests of avoiding too many references. However, we referred to these two cohort studies as ‘before and after’ studies which may have been confusing. We have now clarified this section and provided a comparison of the effect sizes, which adds to the paper by demonstrating a dose response. Thank you very much indeed for this suggestion. We have also rewritten the second paragraph of the discussion to be clearer about this point, as below.

From: “However, our findings are consistent with other experimental studies. Two before and after studies among men found statins lowered testosterone, by about 10%. In contrast, observational studies are less clear, as would be expected from studies which are inevitably open to un-correctable biases from residual confounding, reverse causality and over-adjustment due to an imperfect understanding of the underlying causal pathways.” To:
Two trials comparing simvastatin 80 mg/day with simvastatin 40 mg/day among 640 men found median testosterone lower by 10.3% and 7.5% respectively after 48 weeks, consistent with the 4% reduction here mainly among men mainly using simvastatin 20 mg/day, suggesting a possible dose response of statins on testosterone.

We could not find any observational cohort studies reporting statin use at baseline and then assessing testosterone later. A number of cross-sectional studies have reported on the association of statin use with testosterone. We previously alluded to these studies but did not cite them. We have explicitly cited these studies, by making the following change

From:
“In contrast, observational studies are less clear, as would be expected from studies which are inevitably open to un-correctable biases from residual confounding, reverse causality and over-adjustment due to an imperfect understanding of the underlying causal pathways.”

To:
“Finally, cross-sectional studies were not included, because these provide evidence from which it is difficult to assess causality. The larger cross sectional studies only considered men and generally observed lower testosterone among statin users than non-users.”

- 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.

Thank you for pointing this out. Your comment makes us realize we were not quite clear. We mentioned the contrast with other lipid lowering drugs because statins have effects for cardiovascular outcomes that are not strongly related to cholesterol. We have clarified this point. As you suggest we have also made the first paragraph in the introduction much shorter (208 to 144 words) and reduced the number of references about other lipid lowering drugs from 7 to 3. In order to keep the length and number of references down we removed all text concerning statins and cancer. Given, that statins do differ from other lipid-modulated therapies in their effects on cardiovascular disease and their pleiotropic effects, we feel it is important to provide this information for the reader to set the scene.

2. Introduction: Second paragraph could be made more concise. The situation of F to M transsexuals is interesting but does represent a 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.

We have made the second paragraph in the introduction shorter (282 to 236 words) with fewer references (17 to 14) even though we have included additional clauses clarifying our hypothesis. We deleted information about the situation of F to M transsexuals from the introduction. In the discussion, we have focused much more on the more relevant question of the effect of testosterone at low doses on glucose metabolism in women from RCTs, and thus given less emphasis to F to M transsexuals. Thank you for helping us clarify and improve the paper here.

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

Thank you, we have made this change.

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.

Response to editors notes

We have changed the headings, added all the authors’ emails and checked the PRISMA checklist, where we have made the following changes.
1. We changed the title to include the words “systematic review”
2. We have included more information about the consideration of within study bias, where we have added a quality score to Appendix Table 1 and a sensitivity analysis excluding the lower quality studies. We amended the “Data extraction and quality assessment” section of the methods to:
   “The reviewers (CMS and SLAY) independently used an established tool to evaluate the quality of each trial,” and a sensitivity analysis was done excluding the lower quality trials.”
We also amended the third paragraph of the results by adding the following “and the estimate [among men] was similar (-0.73 nmol/L, 95% CI -0.20 to -1.26) including only the higher quality trials. The estimate for women was also similar, but included no effect, (-0.50 nmol/L, 95% CI 0.06 to -1.06) when including only the higher quality trials. The estimate for [men and women] when only including the higher quality trials (-0.57, 95% CI -0.12 to -1.02).”
In view of this sensitivity analysis we also amended the first paragraph of the conclusion to be more cautious about the findings for women, by adding:
   “and our findings were less robust for women than men”
We also amended the last paragraph of the discussion to put more emphasis on men, as follows
   “This finding does not demonstrate that androgens mediate any health effect of statins, but raises the question as to whether testosterone modulation plays a role in statins’ effects on health, particularly among men where testosterone is a more important hormone.”

Reference List


