Author’s response to reviews

Title: Unintended effects of statins from observational studies in general population: systematic review and meta-analysis

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Author’s response to reviews: see over
The authors would like to thank all the comments and suggestions kindly sent by the reviewers. All of them were considered valuable and have been incorporated into a revised manuscript (changes highlighted in blue). The quality of the manuscript improved and we hope that it is now acceptable for publication. All the editorial requests were also addressed. The questions/comments of the reviewers are answered point-by-point:

Reviewer: Michael J Blaha
Reviewer’s report:
1. Major Compulsory Revisions
   - None.
   - I find this to be a high quality manuscript with no obvious methodological concerns (at least ones that have not already been pointed out by the authors themselves).
   - I would like to congratulate the authors on this huge undertaking.
2. Minor Essential Revisions
   - There are a few spelling mistakes in the text, but nothing major that cannot be fixed during copyediting.
3. Discretionary Revisions
   - I think the abstract could be much better
   The abstract was revised in order to improve it.

   - In the background section, "safety" is used in the first sentence and "unintended effects" in the next sentence. These aren't necessarily the same thing. A drug may be unsafe through an intended effect (hypoglycemic for a hypoglycemic drug, etc). Safety is commonly reported in trial, however I agree that unintended effects are not commonly reported. Consider changing word "safety" in first sentence.
   - In the background, "from general populations" is much too vague. Consider removing this phrase all together.
   - In last sentence of background, use the RCT abbreviation you have defined.
   In the Background section, all the suggested changes were accepted and made.

   - In methods, "hospital based cohort studies" is not a clear description to me.
   Consider being more specific, or at least describing more in the body of the text.
   The Method section was revised to clarify that “hospital based cohort studies” are cohort studies where the participants were selected among patients admitted to a certain hospital.

   - In results, please give total number of patients studied with mean follow-up time, total years at risk, or some other measured of duration of follow-up available.
   Table S1 presents the number of participants and follow-up duration of each study. The forest plots in the main paper also present the total number of participants included in the studies pooled for each outcome. Any attempt to present these data in a single number (total patients and follow-up) for all the unintended effects studied is not straight forward because some studies, for example references 102 and 103, included sub-groups of participants from the same project (“The Blue Mountains Eye Study”), and we have no information on how these two samples overlap.
   We revised the Results section in order to call attention to all the information presented in Table S1: “Table S1 summarizes the characteristics of the 86 articles included, regarding study design, dataset, study population, sample size, follow-up duration and statin type.”
- In results, recommend also giving effect sizes for the "positive" outcomes: myopathy, liver, diabetes.
The Results section includes information on effect sizes for the “positive” outcomes (highlighted in blue).

- In conclusion, first sentence appears to be a general methodological statement and doesn't even mention statins. Consider "We show that systematic review and meta-analyses of high quality observational data may can provide critical data on unintended effects of statins missing from RCTs"
- In conclusion, the last sentence should specifically mentions statins as a class of drugs. Consider: "The absolute excess risk of harmful unintended effects of the statin class of drugs is very small compared to the beneficial effects on major cardiovascular events."
- please consider the following new citation: http://www.ncbi.nlm.nih.gov/pubmed/24095248
The new reference was added.
We are thankful for the valuable suggestions that improved our Conclusion (now revised):
“Our systematic review and meta-analyses indicate that high quality observational data can provide reliable and relevant evidence on unintended effects of statins to add to the evidence from RCTs for health care guidance. Comparisons of the observational findings with RCTs, where possible, showed similar estimates, indicating that our approach is capable of making plausible inferences on unintended effects. The absolute excess risk of the observed harmful unintended effects of the statin class of drugs is very small compared to the beneficial effects of statins on major cardiovascular events.”

Reviewer: Kosmas Paraskevas
Reviewer’s report:
1. Is the question posed by the authors new and well defined? Yes.
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work? Yes.
3. Are the data sound and well controlled? Yes.
4. Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes.
5. Are the discussion and conclusions well balanced and adequately supported by the data? Yes.
6. Do the title and abstract accurately convey what has been found? Yes.
7. Is the writing acceptable? Yes.

Minor Compulsory Revisions
Several reports have described an effect of statins on asthma and on sepsis. Could the authors extend their study to discuss these issues as well? Some unintended effects (e.g. ventricular arrhythmia, intracerebral hemorrhage, sepsis) were not covered in this meta-analysis as they were not reported in population based studies, but from case reports and clinical case series which provide weaker evidence of causal association.

Reviewer: Yoon Kong Loke
Reviewer’s report:
Major compulsory revisions
I have focused my comments mainly on the Methods:
The search is now two years out of date; last conducted January 2012.
If you used the BMJ Cohort studies filter, how well do you think it would have worked in picking up Case-Control studies?
The optimal search strategy for specifically identifying reports of unintended effects has yet to be established. No search filter seems to have high sensitivity and specificity in both Medline and Embase databases (Golder S, Loke YK, 2012). Therefore, it is advisable to combine several approaches to maximize the likelihood of identifying relevant studies. We screened 12,010 titles and abstracts identified by keywords and supplemented that search with reference lists of 110 identified studies and more than 30 reviews. We also contacted 71 authors asking for additional relevant articles and unpublished studies. We believe all the relevant observational studies were identified.

The Discussion section should mention the important Limitation that Data Extraction and Validity Assessment were mainly carried out by a single reviewer (I appreciate that a random 10% of the extraction was checked). The Discussion section was revised to include this limitation: “We also recognize the limitation of having a single reviewer assessing all data extraction and validity; although no discrepancies were identified in a random sample of 10% of the titles and the numbers extracted.”

Sensitivity analyses – the cut-offs for various subgroups seem somewhat arbitrary, I assume that these were categorized posthoc? Why use the threshold of 8 for NOS quality? The subgrouping according to sample size is somewhat meaningless when there are different study designs in this review. For instance, you could have a very large cohort study with very few events of interest, whereas you could have a much smaller case-control design that has hundreds of cases with outcomes of interest.

In NOS studies score one star for each area addressed, with scores between 0 and 9 (highest level of quality). The threshold of 8 for NOS quality corresponds to studies with small overall risk of bias and confounding. The Method section was revised to clarify this issue, saying “Studies score one star for each area addressed, with scores between 0 and 9 (highest level of quality).”

The sensitivity analysis according to sample size is part of several exploratory analyses, also by study type and NOS quality. The stratification of results by sample size is useful to verify the stability of the results and it was decided a priori.

In the situation exemplified by the reviewer, where the pooled effects would be driven by a smaller case-control design with a large number of events of interest, in comparison with a large cohort study with very few events; we would expect to observe differences between the overall pooled results stratified by study type or by sample size, that could lead to further exploratory analyses. Since no discrepancies were identified no further sensitivity analysis were conducted.

This review does not seem to consider outcome reporting or publication bias. Case-control studies may only have reported drug use or exposure where a significant association was found. Similarly cohort studies may only have provided numerical estimates of the association where significant findings were noted, and there may have been outcomes where the primary studies simply stated no significant harm was found. These data would not have been included in the present meta-analysis; hence I view it likely that the pooled effect sizes may potentially be exaggerated by this bias. I appreciate that this is hard to deal with or to address, but the major limitation should be acknowledged.

This is a very important remark. The Discussion section was revised to include this limitation: “Publication bias is a particular threat to the validity of meta-analysis of observational studies. Although we contacted authors asking for unpublished studies, publication bias is possible since observational studies with significant outcomes are more likely to be published,
therefore over-represented in our meta-analysis. The pooled effect sizes may potentially be exaggerated by this bias.”

Results section:
I think you should present an Online Supplement with Forest Plots of each outcome showing effect estimates and 95% CI from the individual primary studies. This gives a better visual depiction of the heterogeneity amongst studies when considering the pooled value within the meta-analysis.
The Forest Plots of each outcome are now provided as online supplement.