Author's response to reviews

Title: Industry sponsorship and publication bias among animal studies evaluating the effects of statins on atherosclerosis and bone outcomes: a meta-analysis

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Version: 2 Date: 23 January 2015

Author's response to reviews: see over
13 January 2015

Dear BMC Medical Research Methodology Editor:

On behalf of my coauthors I’m pleased to re-submit to BMC Med Research Methodology the manuscript entitled:

Industry sponsorship and publication bias among animal studies evaluating the effects of statins on atherosclerosis and bone outcomes: a meta-analysis

We have addressed the reviewers’ concerns in this manuscript.

Reviewer 1

MAJOR COMPULSORY REVISIONS

1. The methods used are not clear. The paper is about comparing publication bias in two systematic reviews: one of industry funded trials and one of other trials. This simple point was not quite clear in the abstract or the body of the paper until p9. It is a great design and needs to be made clear for non-specialists in the abstract and the body of the text.

Response: Thank you for pointing out this point of confusion to us. We have clarified in the paper that this is actually a publication bias analysis of two reviews—one which evaluated atherosclerosis outcomes and one which evaluated outcomes concerning various bone outcomes. Each of these reviews contained both industry sponsored and non-industry sponsored studies. We stratified our results by industry sponsorship to see if there were differences in publication bias between subgroups of industry sponsorship. This point is now made clear in the abstract and earlier in the text, as well.

2. A main finding — that non-industry studies yielded greater effect sizes — is counter intuitive and different from similar reviews of clinical studies. The authors do not discuss the potential reasons for the discrepancy between animal and clinical studies in the manuscript. (One reason could be that the authors conducted anomalous reviews, see point 3 below.)

Response: We have added further discussion regarding the conflicting results from reviews of clinical studies to the discussion. In the discussion we note the work performed by ter Riet et al and though there may be true differences in the reasons for publication (or lack thereof) between industry and non-industry authors, we acknowledge that the true reasons are unknown (lines 414-425). Furthermore, we had added a reference in the discussion which further elucidates the differences in effects seen in industry and non-industry studies (lines 395-405), though these differing effects were not replicated in a more recent analysis of animal data. We call on further investigation of funding bias in larger cohorts of animal studies. It is difficult to compare the findings to our study as it (ter Riet et al) is a survey of researchers’ opinions and our study is a quantitative estimate of publication bias.

3. The fact that the conclusions are based on just two reviews needs to temper the conclusions. Perhaps they cannot be generalised.

Response: Publication bias is typically assessed in systematic reviews. And systematic reviews of similar clinical questions are not often repeated, though they may be updated years later. We have made it clearer in the discussion that our results are only generalizable to the research questions specifically reviewed in the two systematic reviews (lines 481-485).
MINOR COMPULSORY REVISIONS
4. The background section is very interesting, but not concise. I would make it about half as long.
Response: We have reduced the size of the background section as recommended.

Reviewer 2
1. The methods are appropriate and have been used in other studies to assess for publication bias. My only reservation is the number of comparisons included in each subgroup analysis. The minimum number of comparisons that are generally used for these types of analyses in our group are 25 comparisons. It may be worth describing this limitation in more detail in the discussion section of the manuscript.
The data are sound however I recommend that the authors include more details on the number of comparisons included in each subgroup analysis.
Response: We have added the number of comparisons in each subgroup to the text and tables. We have also added a bit more to the limitations regarding the limited number of studies compared and the implications (lines 471-475). Though we wholeheartedly agree that a larger sample would help us in better understanding these relationships, we are unsure of the evidence for specifically recommending a minimum of 25 studies. In fact, the Cochrane Handbook specifically recommends a minimum of 10 studies.

2. The authors acknowledge that this work builds upon a previously published systematic review. However, the reference for this previous review needs to be corrected.
Response: This has been corrected.

Response: Thanks for correction!

4. References, reference number 14 (Line 554). Spelling error. “CAMRADES” should read “CAMARADES”.
Response: This has been corrected.

5. Background, fifth paragraph. “few registries of animal studies exist” the authors reference www.CAMARADES.info. A more specific reference would be useful?
Response: The reference we use is the most specific we could find for access to the CAMARADES database.

6. Background, fifth paragraph. I cannot identify this statistic “most abstracts of animal studies (75%) submitted to a conference were never published” in the publication by Timmer et al. is referenced in the text. Can the authors clarify that this statistic is from this reference?
Response: This should read “most abstracts of experimental studies (76%) submitted to a conference were never published” and has been corrected. This information is in Timmer et al, page 7 under the subheading Reasons for Non-Publication.

7. Methods, second paragraph. “For further details about inclusion and exclusion criteria, see our previous review [20].” This reference is the systematic review by Krauth et al. “Instruments for assessing risk of bias and other methodological criteria of published animal studies: a systematic review” but I’m not sure how the details on inclusion/exclusion criteria provided in this earlier review are relevant to the present review. Should reference 20 be the following publication: Nonindustry-Sponsored Preclinical Studies on Statins Yields Greater Efficacy Estimates Than Industry-Sponsored Studies: A Meta-Analysis. David Krauth, Andrew Anglemyer, Rose Philipps, Lisa Bero (2014) DOI: 10.1371/journal.pbio.1001770?
Response: Thanks for the great editorial catch! This reference has been corrected.

8. Methods, third paragraph. Should reference 20 be the above publication (Krauth et al. 2014)?
Response: This reference has been corrected.
9. The title “Statistical Analysis - Publication Bias Assessments” should be in bold.
Response: This has been done.

10. Results, first paragraph. The authors should state the number of atheroscleroris outcomes as they have done for the bone outcomes. E.g. We identified 49 unique studies evaluating x atherosclerosis outcomes in 3948 animals...”
Response: This information has been added.

11. Results, second paragraph. To avoid over-interpretation of non-significant results the final sentence should be changed to read “There was no significant difference in beneficial bone outcomes between industry sponsored (0.13; 95% CI -0.48, 0.73) and non-industry sponsored studies (0.48; 95% CI -0.10, 1.06) (p value= 0.41).
Response: Thanks for the recommendation. This has been edited.

12. Results, third paragraph. It would be useful to include the number of comparisons for each subgroup (Atherosclerosis industry-sponsored/atherosclerosis non-industry sponsored/atherosclerosis no statement and the equivalent subgroups for bone outcomes).
Response: Good recommendation. Though we had this information in Table 1, we have added this information to the first paragraph in the results, as well.

13. Results, third paragraph. The first sentence should be changed to indicate how publication bias was assessed by the funnel plots e.g. Across all studies, (Figure 1; panels a, e) there appears to be publication bias in both atherosclerosis and bone studies as assessed by funnel plot asymmetry.
Response: Thanks for the recommendation—we have addressed this.

14. Results, third paragraph. Please state how many comparisons are included in each funnel plot. It has been suggested for these types of publication bias analyses that you need at least 25 comparisons for the analysis to be sufficiently powered. There may not be enough comparisons to draw conclusions from funnel plots and trim and fill analysis.
Response: As per comment #10 above, we have addressed this in the first paragraph in the results section. Regarding the suggested minimum of 25 studies, we have further addressed this limitation in the discussion.

15. Results, fourth paragraph. Similarly, we would recommend a minimum number of 25 comparisons for Egger’s regression.
Response: See response to comment #14 above.

16. Discussion, second paragraph. Extra full stop in second last sentence.
Response: This has been fixed.

17. Discussion, sixth paragraph. The authors state “reporting has improved slightly since the publication of ARRIVE guidelines.” Is there any evidence to support this? We would expect reporting to improve since the introduction of ARRIVE but I do not know if this has been observed.
Response: In our previously published atherosclerosis article (Krauth et al. 2014), we showed that randomization, whether all animals were accounted for, and sample size were reported more frequently after publication of the ARRIVE Guidelines. Randomization was reported in 11 of the 15 (73.3%) studies that were published post-ARRIVE compared to 19 of the 48 (39.6%) studies published pre-ARRIVE. All animals were accounted for in 12 of the 15 (80%) studies published post-ARRIVE compared to 27 of the 48 (56.3%) studies published pre-ARRIVE. Sample size was reported in all 15 studies published post-ARRIVE compared to 41 of 48 studies (85.4%) published pre-ARRIVE. These results are referenced in paragraph 7 of the discussion.

Discretionary Revisions

18. Methods, fifth paragraph. The authors calculated the effect of statins using a standardised mean difference (SMD) for each outcome and pooled using a random-effects model. The authors state the null hypothesis and the meaning of a negative or positive value. I suggest that the wording of “that the statin increases the risk of atherosclerosis harms outcomes or beneficial bone outcomes when compared to control or placebo” should be changed to “that the statin increases the risk of atherosclerosis outcomes or increases the likelihood of beneficial bone outcomes when compared to control or placebo” Similarly, I suggest the converse description should be changed to “that the statin reduces the risk of atherosclerosis outcomes or reduces the likelihood of beneficial bone outcomes when compared to control or placebo.”
Response: We agree with this suggestion and have made these changes.
The study by Riet and colleagues appears to contradict the findings of the present study. Riet et al. report that only 10% of for-profit research would be published whereas 80% of non-industry sponsored research would be published. However, the present study identified potential evidence of publication bias to be more prominent in non-industry sponsored studies. Perhaps discuss the potential reasons for the different findings.

Response: Thank you for the suggestion. We have added this point to our discussion. We reference the ter Riet study in the introduction (lines 135-137) because it adds important background information. However, it is difficult to compare the findings to our study as it is a survey of researchers opinions and our study is a quantitative estimate of publication bias. We do discuss potential reasons for the difference in the discussion (lines 414-425), as well as other possible explanations for our observed publication bias among non-industry funded researchers.

Reviewer 3

Minor Essential Revisions-

1. The authors state that articles were classified into those funded by industry and those that were not. However, I’d like to see a better description of how this classification was made. For instance, if article corresponding authors listed a private company but the article contained no disclosure statement - did that count as industry? Some of this information may be present in their companion paper - but it seems crucial to report it here as it is the anchor on which this analysis pivots.

Response: As stated on lines 198-199, the source of sponsorship for each study was categorized as:

(1) Any Industry, meaning that as long as the study was funded in part by a private company, it received an “Any Industry” code, regardless of the other sources of funding

(2) Non-Industry, meaning that the study was fully funded by sources other than industry.

(3) No Sponsorship Statement

We have clarified this in line 199.

For the sensitivity analysis, studies that did not disclose a funding statement were assigned to the “Any Industry” grouping (lines 256-257).

The second set of issues concern the imputation of publication bias. This paper reports little about the properties of the studies analyzed- which makes it difficult to rule out rival explanations for the differences (there is more information in their companion paper). For example:

2. based on the figures, industry-funded studies tend to have much lower variance (i.e. clustering on the tops of funnels). Does this reflect that industry uses larger sample sizes? If so, one might imagine a factor causing funnel plot is that people invest more effort in performing- hence reporting- a larger study. Another variable is species or choice of outcome measure for effect size. If industry is trying to measure a somewhat different disease response- a more subtle one- is it not possible that the patterns observed here would be recapitulated? Another variable is duration of study. So in short, the paper might be enhanced by greater description of the two populations, and a discussion- and explanation- of why rival hypotheses are unlikely to explain the differences observed between the two groups.

Response: The sample sizes between the industry and nonindustry are all small and further, we have acknowledged these limitations in the discussion (e.g., small sample sizes, disparate outcomes, species, durations of follow-up, and different statins). For further details, please refer to our accompanying paper (Krauth 2014). These changes have been made in lines 475-481.

3- I’d be interested to know the frequency with which studies of a statin were performed by companies with competing products. Both would count as industry funded, but one can easily imagine, say, Pfizer using preclinical studies to discredit Merck’s product by performing preclinical studies showing a small or modest effect- and Merck doing the reverse. In which case the effects of publication bias would tend to cancel each other out and create the appearance of symmetry in funnel plots, etc.
Response: This is a very interesting point. However, we feel that competition is not a factor because all industry funded studies evaluated their own product for new indications, some small companies evaluated non-generic or soon-generic products for new indications. It is important to remember that these are preclinical animal studies, not studies of approved indications.

To summarize the 19 industry funded studies for the atherosclerosis dataset:
- Pfizer sponsored 5 studies and assessed only atorvastatin in all 5 studies.
- Bistol Myers Squibb sponsored 3 studies and assessed pravastatin and simvastatin in 1 study and only pravastatin in 2 studies
- Merck sponsored 4 studies (one study assessed only lovastatin; 3 studies assessed only simvastatin)
- AstraZeneca sponsored 3 studies and assessed only rosuvastatin in all 3 studies
- GlaxoSmithKline sponsored 1 study and assessed only atorvastatin
- Banyu Pharmaceutical sponsored 1 study and assessed only simvastatin
- Dong-wha Pharmaceutical Industrial Co., LTD, Korea sponsored 1 study and assessed only simvastatin
- Mitsubishi Pharma Research Foundation sponsored 1 study and assessed only fluvastatin

*Simvastatin was evaluated by Bristol Myers Squibb in 3 studies, Banyu Pharmaceutical in 1 study, and Dong-wha Pharmaceutical Industrial Co., LTD, Korea in 1 study.
*Atorvastatin was evaluated by Pfizer in 5 studies and GlaxoSmithKline in 1 study

To summarize the 6 industry funded studies for the bone dataset:
- Proctor and Gamble sponsored 1 study and assessed only cerivastatin
- Astrazeneca sponsored 1 study and assessed only rosuvastatin
- Bayer sponsored 1 study and assessed only cerivastatin
- Merck sponsored 1 study and assessed only simvastatin
- Zimmer, Inc. sponsored 1 study and assessed only lovastatin
- Synthges AG Oberdorf sponsored 1 study and assessed only simvastatin

*Both Proctor and Gamble and Bayer assessed cerivastatin. Similarly, both Merck Co. and Synthges AG Oberdorf assessed simvastatin.

Simvastatin = Merck
Atorvastatin = Pfizer
Pravastatin = Sankyo, Bristol-Myer Squibb, TEVA
Rosuvostatin = Astrazeneca
Fluvastatin = Novartis
Cerivastatin = Bayer / P and G

4- I’d also like to know more about the characteristics of the drugs that are tested. My own work shows it is very difficult to access preclinical efficacy data for drugs early on in development- and if drugs are not ultimately licensed. I suspect the direction of publication bias may be reversed for drugs that are not yet licensed. I also suspect the direction might run in reverse for preclinical toxicology studies. The authors may want to consider this in their discussion.
Response: All were licensed (although one has been taken off the market in many countries). The preclinical studies were exploring new unapproved indications.

Discretionary Revisions:
5- I found figures difficult to read. Very compressed. For example, in figure 3, y-axes have different scales, making it difficult to visually compare plots for industry vs. nonindustry.
Response: We have improved the quality of the figures.

6- Authors should cite their companion paper (!) in PLoS Biology- all the more so as this one cannot be interpreted without viewing that one.
Response: This error in references has been corrected.
7- I’ve published a few papers in this area and I think they are relevant for the introduction and analysis. Anderson/Kimmelman Nat Biotechnology 2012 is relevant to making the case for animal study registration, for example.
Response: *We have added reference to this work in our present work.*

Please do not hesitate to email or call me if you have any questions regarding this manuscript.

Thank you for your consideration,

Andrew Anglemyer, PhD