Reviewer's report

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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Reviewer: Jonathan Kimmelman

Reviewer's report:

This paper follows up on the authors' previous report- in PLoS Biology- that industry funded preclinical studies of statins for atherosclerosis and bone outcomes show more modest effect sizes than academically funded studies. One possible explanation for the difference is publication bias, and the authors set out to use three methods- funnel plot, trim and fill analysis, and Egger’s regression- to test this hypothesis.

Briefly, they stratify their sample into industry and nonindustry funded studies, plot the data, and apply tests for publication bias. Their hypothesis is confirmed insofar as industry-funded produce less asymmetry in funnel plots, less adjustment for effect size using trim and fill, and less evidence of bias using Egger’s regression.

To my knowledge this is the first paper to rigorously test publication behavior for industry vs. nonindustry studies, and will therefore be of interest to those following the developing literature on preclinical research, reporting, and bias. It is also a logical complement to their previous paper.

I am not a statistician, so I am not qualified to comment on analyses- except to say that similar methods have been used recurrently in the preclinical systematic review literature.

Minor Essential Revisions-

There were, nevertheless, some analytical and interpretive issues that caught my attention- I’d feel better for having them addressed.

The first is easily fixed. 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.

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:

1- 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.

2- 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..

3- 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.

Discretionary Revisions:

1- 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.

2- Authors should cite their companion paper (!) in PLoS Biology- all the more so as this one cannot be interpreted without viewing that one.

3- 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.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:

I declare that I have no competing interests