Author's response to reviews

Title: Systematic review of methods for individual patient data meta analysis with binary outcomes

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Author's response to reviews: see over
Dear Editor,

Thank you for your response dated March 13, 2014. We have read your comments and those of the two reviewers and have revised the manuscript substantially based on their comments. Based on the instructions provided in your email we uploaded the file of the revised manuscript on the journal’s website.

As you will notice, we have revised the manuscript by modifying the Abstract, Introduction, Methods, Results and Discussion sections, based on the comments made by the reviewers. Accordingly, we have uploaded a revised copy of the manuscript with all the changes made during the revision process.

Appended to this letter is our point-by-point response to the comments raised by the two reviewers. We agreed with all the comments raised by the reviewers. We would like to take this opportunity to express our sincere thanks to the reviewers who identified areas of our manuscript that needed corrections or modification. We would like also to thank you for allowing us to resubmit a revised copy of the manuscript.

I hope that the revised manuscript is accepted for publication in BMC Medical Research and Methodology.

Sincerely Yours,

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We thank the Reviewer for their thoughtful and detailed review. We have tried to address each point raised, and we think that the manuscript is much improved as a result of these revisions.

Reviewer's report:

Major compulsory revisions:

1. There are several ways in which a meta-analysis may be classified, and the authors attempt to describe all of them to some degree. However, I am concerned as to whether these facets are adequately separated, and whether the manuscript is too confused as a result. For clarity, I refer to:
   a) aggregate-data vs IPD
   b) one-stage vs two-stage
   c) adjusting the treatment effect for (prognostic) confounding vs analyzing treatment effect modifiers (e.g. with interaction terms)
   d) random trial effects vs random treatment effects.
   e) [there may be others]

   We have read through the article very carefully, trying to be clarify where possible.

   The authors state that "a one-stage approach... reduce[s] the potential for ecological bias that may occur when meta-regression is used in conventional two-step MA". However, methods exist for analyzing treatment-covariate interactions with a two-stage (IPD) approach, and these in fact are guaranteed to be free of ecological bias (see e.g. Fisher, JCE 2011).
   
   *A correction was made to this sentence. We agree that both the one- and two-approaches can reduce the risk of bias only through the exclusion of across-trial information. However, there is a trade-off between increase power of the analysis and risk of bias for the one-step approach.*

   In a later paragraph, the authors state "IPD-MA are not prone to ecological bias" which is only true if the data are analysed correctly -- this should also be clarified.

   *Corrected in the text to clarify.*

   In the section "The effects of covariates", the sentence "these studies included the covariate and/or interaction terms between treatment and covariates" requires clarification. Are the authors enumerating all studies that included any covariate and/or interaction adjustment? To me, a treatment effect adjusted for confounder(s) is quite different from a model estimating treatment-covariate interaction(s), and the two should be enumerated separately. Indeed, what exactly is the difference between the 58% of MAs here and the 67% of MAs in the subsequent sentence?

   *We have substantially improved this section based on comments from Reviewer 1 and Reviewer 2. We now consider three uses of covariates: to investigate subgroup*
effects, to adjust for potential confounders and to identify predictors. Please see the section in the results “Covariates”.

2. The introduction states, justifiably, that a "random-effects" approach may involve random-effects on the trial coefficient and/or the treatment coefficient, and the authors' ambition in describing the use of both possibilities is admirable. However, their subsequent use of the terms "random-effects" and "fixed-effects" is then made a bit more vague, and should be clarified. For instance, in the "Statistical methods" section, it is stated "all patient data from these studies were combined in a GLMM, accounting for clustering among patients in the same trial by including random effects". Is this really true -- that *no* MAs used a fixed trial-membership effect? We have tried to clarify throughout the text whether random intercepts and/or random slopes were used. See e.g. Table 3 in the revised manuscript.

Minor essential revisions

3. In the section "Heterogeneity", the sentence "it was unclear if any measure of heterogeneity was used in about six? Studies" needs correcting. Corrected in the text.

4. The 5th paragraph of "Discussion" ends "this likely reflects the greater comfort with and availability of [the] random effects model in health research". I assume the authors are implying that the only thing previously holding researchers back from using one-stage models was the lack of random-effects routines in mainstream statistical packages? If so this could be made clearer -- possibly with reference to other outcome types, e.g. time-to-event outcomes, where one-stage random-effects routines are still not generally available. We cannot make this claim as we have not studied the methods used for IPD-MA of survival type outcomes. We have clarified the sentence somewhat to reflect the idea that random effects models for binary outcomes are increasingly used in health research and that they are available in most statistical packages,

5. The 10th paragraph of "Discussion" (beginning "heterogeneity should be quantified and described") is currently badly worded and requires revision. (although I agree with the point being made.) We have edited this sentence.

Discretionary revisions:

6. It would be helpful for the included MAs to be explicitly referenced somewhere within main text -- possibly in the second paragraph of "Results"? (I am aware that the MAs are explicitly listed in the Supplementary Information, which is great.) References were added in the text, at the beginning of the results section.

Reviewer: 2
We thank the Reviewer for their thoughtful and detailed review. We have tried to address each point raised, and we think that the manuscript is much improved.

Reviewer’s report:

General issues

- The decision to limit this review to binary outcomes is regrettable in my view as several issues under investigation equally apply to other types of outcomes (time-to-event, continuous.

We agree with this and may follow up with another review on methods used in IPD-MA of time-to-event outcomes. We have addressed this limitation in the discussion section.

- The number of IPD meta-analysis is still rather moderate. A 2-year period would have been more insightful.

We agree with this reviewer’s concern, but the methodological contents are unlikely to differ substantially to those included in the one-year. We have addressed this limitation in the discussion section.

Major compulsory revisions

- It appears that the authors focused on intervention reviews, otherwise I expected to see IPD reviews of diagnostic and prognostic reviews as these can also examine binary outcomes. The restriction to intervention reviews is not clear from the inclusion criteria. Please provide further details.

We did not limit our search to intervention studies. We have now clarified the goals of the IPD-MA and stratified some of our results according to the goal of the IPD-MA. See e.g. Table 1 in the revised manuscript.

- A crucial question is in this field is to IPD or not. A tabulation of potential reasons why these IPD’s might have generated additional information compared to traditional meta-analysis of aggregate data is informative.

We revisited each IPD-MA and extracted the reason stated for conducting an IPD-MA. This information is now contained in Table 2 in the revised manuscript, and described in the results section.

- A major potential benefit of IPD is the greater flexibility, validity, and power when examining variation in treatment effects across patient groups. More detail should be given to this issue, which might include the type and number of patient subgroups examined, if based on a continuous characteristic (e.g. age) how handled in the analysis, how these examinations were reported (p-values, relative or absolute differences etc.), whether the consistency in subgroup effects across studies were examined, etc.

We have substantially revised the section on covariates. Now we have included information on the number of and type of subgroups, how they were handled in the analysis and how they were reported. See the Covariates subsection in the results section.
- The observation that 50% of the IPD meta-analyses included data from both randomised and non-randomised studies is an interesting one. Please provide more information about these IPD meta-analyses, like the type of review question(s) they address; the rationale for including non-randomized studies; whether it led to a specific statistical approach. 

_We have added some of this information. We have classified IPD-MA that included observational studies or only RCTs according to the goal of the analysis. (See Table 1). We have also addressed some of these points in the section on Covariates in the results section._

- Missing data in an IPD setting can be handled in different ways. Please provide data how missing data were handled in the IPD meta-analyses. 

_Information on missing data was not present very often. We have extracted and summarized what information was presented in the Missing Data section of the results section._

Minor essential revisions

- In Abstract the Methods section I would rephrase the sentence “methods to adjust for the effects of covariates” because the issue is also about examining whether the treatment effect is different between subgroups of patients.- Provide more numbers in the Results section of the Abstract rather than most, some form, most-used etc. 

_Correction was made to the text._

- Table 2: the “Other measures” group is relatively large and interesting. Please list in more detail. 

_Amendments were made to the Heterogeneity section in the paper. Also, the number of this table has been changed to Table 4._

_Other measures use to quantify heterogeneity were the reporting of the magnitude for the estimated variance from a random or mixed effect model._

Table 3. I assume that several IPD meta-analyses examined more than 1 type of covariate. How were these counted because there appears to be no double counting? A table that would start with the total number of covariates examined, the type of covariates they were (patient-level or study-level), and how they were handled in the analyses would be a more informative structure of this table. 

_We have removed Table 3 and replaced it by information in the text. We consider subgroup effects, adjusting for confounders and identifying predictors now. We have also considered the type and number of subgroups, the type of confounders, etc. Please see the subsection “Covariates” in the results section._
- Table 3: it is unclear where “Both” and “Unclear” stands for, especially as it doesn't match the numbers in Table 1. For instance, in table 1 there is only one unclear study and apparently no IPD review having a mixture of analytical approaches. Please clarify and make consistent.

_We have removed this Table._

Discretionary revisions

- Results section the paragraph on Heterogeneity: there is a question mark in the 5th sentence that is out of place.

_Correction was made to the text_

- Figure 1 prints-out very badly

_Improvements made to the Figure 1_

- Figure 1. At the bottom the number of reviews is 55, one layer above it is 57. Please explain. Furthermore, I assume that some IPD review examined different types of outcomes, how are these counted.

_Some typographical errors were made but it is now corrected. Also, if articles had multi-outcomes, we presented information on only the primary outcome of the main analysis._

- Table 1 in additional files. Please explain difference between Chi squared test and Q statistic.

_There is no apparent difference between the Chi squared test and the Cochrane Q statistic, since the Q statistic has a central chi square distribution under the null hypothesis. Hence, the two can be used interchangeably and the results of the two were merged in Table 4. However, the chi-squared test was replaced as the Q statistic in Table 1 of additional files._

- Table 1 in additional files. The heterogeneity column has an entry “Not described”. Does it mean “Not examined” or is it examined but the approach how it was done has not been described?

_Not described does mean that heterogeneity was not examined and not quantified in these meta-analyses. Changes were made to the file._