Author’s response to reviews

Title: The judgement of biases included in the category “other bias” in Cochrane systematic reviews of interventions: a systematic survey

Authors:

Andrija Babic (babic.andro@gmail.com)
Andela Pijuk (ap71417@mefst.hr)
Lucie Brazdilova (lucie.brazdilova@seznam.cz)
Yuliyana Georgieva (jgeorgieva95@abv.bg)
Marco Antonio Raposo Pereira (a30883@fcsaude.ubi.pt)
Tina Poklepovic Pericic (tinapoklepovic@gmail.com)
Livia Puljak (livia.puljak@gmail.com)

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Author’s response to reviews:

Dirk Krüger
BMC Medical Research Methodology

Re: Revision of the manuscript BMRM-D-18-00215

Dear Dr. Krüger,

Thank you and your reviewers for providing feedback about our manuscript titled The judgement of biases included in the category “other bias” in Cochrane systematic reviews of interventions: cross-sectional study (BMRM-D-18-00215). We did our best to address the comments we received, and we provided a point-by-point response. We highlighted all the changes made in the manuscript using track changes. In addition to copying this response into the online submission system, we also uploaded this response letter, in the original formatting, as a supplementary material, for easier reading.

Technical Comments:

1. Please include email addresses for all authors on the title page
Response: We added co-authors’ email addresses on the title page.

2. Please change the ‘introduction’ header to ‘Background’ to conform to journal style

Response: We changed the header accordingly.

3. Please define abbreviations in the text at first use and provide a list at the end of the manuscript text; the list should be placed immediately after the main Conclusions section, and should be followed by the Declarations section

Response: We defined abbreviations in the text at first use and provided a list at the end of the manuscript text immediately after the main Conclusions section.

Reviewer reports:

Evangelos Kontopantelis, Ph.D. (Reviewer 1):

1. The introduction is all around the Cochrane tool, understandably, but the authors fail to describe it and explain what aspects of bias ARE already covered.

Response: Thank you for your suggestion. We changed the ‘introduction’ header to ‘Background’ to conform to the journal style. Initially, due to the length of the manuscript, we did not describe all domains of Risk of bias in Cochrane systematic reviews, but we have now described and explained all domains of Risk of bias, as suggested.

2. The aims of the paper, expected at the end of the intro, are "... to analyze the scoring and support for judgement of the category 'other bias' in a large...". This is not an aim. "Analysing" is not an aim. "Support for judgement of the category 'other bias'" is also relatively meaningless - it is not clear how quantifying reported sources of bias and their variability or whatever will imply something and why. Not here, not in the methods section, not anywhere in the paper. What does the paper plan to achieve and how?

Response: Thank you for your observation and for the opportunity to clarify our aim. There are very few examples of “other bias” in the Cochrane Handbook, and after reading many Cochrane reviews we realized that Cochrane authors have the very heterogeneous approach with this RoB domain and that they often use ‘other bias’ domain to describe bias which actually falls into one of the first six domains. We recognized this as an issue and decided to conduct a research on a large sample of Cochrane reviews, to determine what exactly Cochrane authors consider to be “other bias”. Our aim was to define which issues would author consider as “other bias”, and to determine the prevalence of those categories. Moreover, we considered important to quantify the
qualitative data which support the assessment of other bias to determine the reasons for giving a score in the category “other bias”. We revised our aims accordingly.

We also added an explanation of the term ‘support for judgment’ in the Methods. The revised sentence now is: We extracted judgments (high, low or unclear risk) and supporting explanations for judgments (qualitative data which support the assessment to determine the reasons for the judgment) from the ‘other bias’ section of RoB table in Cochrane reviews.

3. There is no justification for the study period. Why a year? Why that year? What are the implications of that?

Response: Thank you for your excellent comment. We already stated in the limitations section that our analysis was focused on one year since this type of study is very labor intensive. For the purpose of this study, we had to manually extract more than 30,000 data units from more than 10,000 trials included in analyzed Cochrane reviews. Therefore, we did not opt to extract RoB data from all Cochrane reviews ever published. Going back too long in time would not make sense anyway since the manuscript about Cochrane RoB tool was published in 2011, and these methods made their way into Cochrane reviews subsequently. For this reason, we decided to choose a recent sample. This was a convenience sample, and we estimated that taking Cochrane reviews published within one year would give us a sufficient number of reviews and trials for analysis, to capture the variability of ‘other bias’ domain. We started the analysis in the second half of the year 2016, and then we took reviews that were published within the past year at the moment of search.

We do acknowledge that the findings in our research could possibly be different if we chose another time period, and this is already indicated in our limitations. However, we consider that the differences would be small, due to the fact that the instructions for Cochrane authors regarding RoB assessment did not change in the time since 2011. To accommodate comment of the reviewer, we will include more elaborate acknowledgement regarding the chosen time period in the limitations section, accordingly.

4. Language corrections are needed.

Response: We have sent our manuscript to a professional translator and it was revised accordingly.

5. "Non-standard domains" are mentioned on page 6 and later, and we are not told what they are.

Response: We appreciate the opportunity to clarify what we mean by this expression. “Non-standard domains” are domains which are not covered by the seven “standard” domains in the assessment of other bias. The explicit statement has been added in the manuscript. These non-standard domains are presented in Table 3, examples are ‘sample size’ or ‘time of outcome assessment’ – these issues are not covered with the standard domains of the Cochrane RoB tool.
6. The outcomes section on page 7 was pretty confusing. The second sentence was not clear - needs to be rephrased to explain what are the characteristics, for example.

Response: Thank you for the opportunity to clarify our methods. We have rephrased the text accordingly. The new text is, as follows:

We analyzed number, type, judgments and inconsistencies in judgments for certain comments about other risk of bias. These inconsistencies were judged as follows: we analyzed whether Cochrane authors used different RoB judgments for the same supporting comment. We quantified Cochrane reviews in which authors did not use ‘other bias’ domain for any of the included RCTs to determine whether they used some non-standard additional RoB domain instead of ‘other bias’. We conducted quantitative and qualitative analysis of these non-standard domains.

7. The secondary analysis (primary analysis, first para, last sentence) is confusing. I could not follow what the authors meant and why.

Response: Thanks for your observation. In the primary analysis, we wanted to analyze separately Cochrane systematic reviews that assessed Risk of bias in included studies using standard Cochrane Risk of bias tool in the context of our study, i.e. reviews which had ‘other bias’ domain. In the secondary analysis, we analyzed reviews that either did not have other bias domain in the Cochrane risk of bias tool, or they had this domain, but also had other non-standard domains in the tool, i.e. domains not specified by the Cochrane RoB tool. We revised the text in the manuscript to clarify.

8. The whole premise of the paper, although not explicitly stated as previously mentioned, is around variability in the "other" bias section. So what? Why is that a problem? The authors have failed to make this point throughout out the paper.

Response: Thank you for your question. Cochrane Systematic Reviews are perceived as highest-quality evidence currently available. It is widely accepted that the main reasons for high standards of quality of Cochrane reviews is well defined and strict methodology in the overall process, from protocol writing to reporting. Our own experience with Cochrane reviews indicated that domain ‘other bias’ is vague, that the instructions for Cochrane authors regarding this domain are insufficient, and that Cochrane authors often mention as ‘other bias’ issues that actually belong to the other six Cochrane RoB tool domains. Basically, the aim of our manuscript was manifold: we wanted to explore what the Cochrane authors mention as ‘other bias’, to see whether supporting comments used to support ‘other bias’ domain are consistently judged across different Cochrane reviews, whether Cochrane authors in this domain mention issues that belong to other six domains, and which non-standard domains they use. The ultimate purpose of this manuscript is also manifold. First, results of this manuscript will provide more comprehensive information for Cochrane authors regarding ‘other bias’ domain – we present many sources of other bias that Cochrane authors recognize, and that are not mentioned in the Cochrane Handbook. Second, we showed mistakes that Cochrane authors are doing when they
mention in ‘other bias’ domain issues that actually belong to other six domains of Cochrane RoB tool. Third, we are also pointing out to mistakes that Cochrane authors are doing despite explicit instructions from the Handbook, i.e. authors use sample size and funding to comment about potential bias, even though the Handbook explicitly warns against this. These informations are relevant not only for Cochrane reviews but also for non-Cochrane reviews that use Cochrane’s risk of bias tool. Therefore, our manuscript can help authors of Cochrane and non-Cochrane reviews to create better and more consistent reviews, to recognize additional potential sources of bias in trials they analyze, and to avoid mistakes that we have observed.

The importance and contribution of our results were now highlighted in the manuscript. Additionally, to avoid coming off as negative a priori, we changed the title somewhat, to give it a neutral tone. The new title is: The judgement of biases included in the category “other bias” in Cochrane systematic reviews of interventions: the cross-sectional study.

9. The manuscript is unnecessarily long (only descriptive statistics are reported) and unclear.

Response: We understand that the manuscript could be perceived as relatively long. However, we had a large pool of data, and we wanted to present our results in a comprehensive and clear way. The explanations in the discussion section were limited to the explanation of findings. The secondary analysis and data presentation have been already omitted from the manuscript and included in the Supplementary files. We believe that additional shortening of the manuscript would lead to the deficiency of explanation and loss of valuable information, and we did not think initially that the length of the manuscript should be a significant problem because this journal is an online publication only, so there are no usual limitations associated with print editions. Nevertheless, we will be ready to shorten the manuscript or move certain parts of it to additional supplements, if we can get specific advice about which parts of the manuscript the editors and reviewers would like us to reduce.

10. Title does not clarify what "other" bias implies. The title as it is, is meaningless.

Response: Thank you for your observation. We have revised our title which now states that we have assessed the biases included in the “other bias” category in Cochrane Systematic Reviews. We hope that the new title is more adequate. Further elaborations in the title would be very difficult because ‘other bias’ can include virtually any other bias that Cochrane authors have recognized beyond the first six domains of the RoB tool.

11. Risk of bias tools so not apply to all systematic reviews, not all types of studies are covered by guidelines. Guidelines are outcome oriented, so meta-analyses are covered but not systematic reviews.

Response: Your comment has a point, and we understand that we have not explicitly stated whether our results can be generalized. We have included this acknowledgement in the limitations section.
12. The number of reported RCTs will be smaller, since many will be reported in more than 1 systematic review. This needs to be clarified. If the authors accounted for that they need to report the overlap.

Response: Thank you for your comment. We understand your concern that one trial can be included in the several studies, and therefore increasing the proportion of categories of reasons for inclusion in “other bias” section. However, even if the one study has been included in the several systematic reviews, that study is being assessed for bias in both studies by different authors. Therefore, if a study received one score in one systematic review, the very same study does not need to receive the same score in another review, because it is being assessed by other authors and for different purposes. For those reasons, we have treated each study as an independent and had not accounted for the overlap. However, we do acknowledge the fact that we did not try to identify such studies and to report separately how different Cochrane authors have judged RoB in the same trials. This was not the aim of our study. Such study was conducted by Jordan et al., link: https://www.ncbi.nlm.nih.gov/pubmed/27622779. We indicated this as a limitation of the study.

Juan J Yepes-Nuñez, MD, MSc, Ph.D. (c) (Reviewer 2):

Comments to the Authors

1. This is a very interesting article. I have to admit that I have struggled with the "Other bias" domain every time I use the Cochrane RoB tool. It is nice to see that the issue has been raised through the purpose of this SR. I will provide my comments in the order of appearance throughout the manuscript with general comments.

Response: We are grateful to the reviewer for kind words about our manuscript, the time invested in this review and constructive feedback. We also hope that our study can help Cochrane authors to clarify what exactly is ‘other bias’, and what should not be used as ‘other bias’.

General comments

2. The major weakness of this study is a lack of systematic methodology to conduct the review regarding developing a protocol, the screening process (title and abstract, and full text), and the data extraction. There is no information about the SR protocol. Furthermore, the screening work was not done in duplicate, and there is no description of the full-text screening in the paper. Only 10% of that data extraction was checked for a second reviewer. Having done all these steps in duplicate will decrease the chance of missing important papers and information from the screening process and data extraction process respectively.

If the systematic review authors want to publish this study, I will encourage them to:
- Describe the protocol of the SR in supplementary material.

- Describe all steps for the title and abstract screening, full-text screening, and data abstraction processes.

- Follow the PRISMA statement for reporting this SR.

Response: We are sorry that we did not mention immediately in the title that our manuscript was not a systematic review, which can possibly lead the readers to misunderstandings. Now we have changed the title and immediately stated that this is the cross-sectional study. In this study we analyzed Cochrane systematic reviews of interventions as a methodological study, we did not aim to collate and appraise all available evidence on a certain clinical topic, as systematic reviews aim to do.

This manuscript was submitted in May 2018 and data extraction was done in 2016 and by the time it was submitted our methodology was as described in the manuscript: data extractors manually extracted information from the Risk of Bias (RoB) tables from Cochrane reviews and pasted them into Excel table. We considered that our methodology was adequate (namely: one person doing extraction, has a piloting period on the first batch of extractions, and subsequently another author verifies random 10% of extracted data) because RoB tables in Cochrane reviews are very straightforward, and the data extractors do not have to spend a lot of time in a review, making personal judgments about which data is relevant and what exactly they should extract. Cochrane RoB tables are easy to find in a review, and all domains are clearly specified. So all the extractors followed the same procedure and had to extract easily findable information. Of the 77 verified Cochrane SRs we found 3 SRs which were partially extracted (3.9%), which we consider to be a negligible percentage of discrepancy because it was not entirely wrong extracted (in 2 SRs a part of supporting explanation was missing and in one SR it was the wrong score for the judgement, unclear (U) instead low (L)).

However, with our evolving ideas on this topic, we ultimately faced a major problem with this type of data extractions, namely, that this is very, very time-consuming. For the purpose of this manuscript only we extracted more than 30,000 data items from more than 700 reviews and more than 10,000 trials included in those reviews. These data items were name and detail of a review, the number of included studies for each review, and the name of a trial, RoB judgment for other bias and comment for the risk of bias for each of more than 10,000 trials. This requires very large human effort to complete manual extraction. For this reason, we enlisted the help of a physician, Dr. Ognjen Barcot, who is also information specialist, and at the beginning of this year he created a software working as a parsing tool, which extracts specific data from Cochrane reviews if they are clearly delimited, and RoB tables are such type of data.

Therefore, in 2018, using this data parsing tool, we managed to extract clearly delimited data from Cochrane RoB tables, including data from the other bias domain, and by the time this review came in, we were able to compare data extracted manually by study authors and data extracted via software. We found only 12 data extraction errors in the entire sample, and these were all for the judgment, not for the comment. We acknowledged this now in the Methods, and contribution of Dr. Barcot in the Acknowledgements section.
Following this and because our paper is not systematic review it would not need to be done according to the protocol or Cochrane Handbook. This is the cross-sectional analysis of published Cochrane systematic reviews. PRISMA is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses. Out manuscript is not a systematic review or meta-analyses; instead this is a methodological study, and for this reason, we did not use PRISMA.

3. Finally, I will suggest to the authors to compare their findings with the new Cochrane RoB tool for RCT that was launched in the past Cochrane Colloquium deeper.

Response: We indicated in the manuscript that the new Cochrane RoB tool does not have ‘other bias’ domain. We can only, thus, indicate in our manuscript, that we think that the ‘other bias’ domain should remain a part of the Cochrane RoB tool, because the Cochrane authors did find many apparently relevant sources of bias in this domain, which are not covered with the standard domains of the original or revised RoB tool. This is now highlighted in the manuscript.

Specific comments

4. The authors may want to inform how many CSRs included RCT and NRS?

Response: Thank you for your question. In this study, we have included Cochrane systematic reviews that included both RCTs and non-randomized trials, but only RoB of RCTs was analyzed. This is because Cochrane RoB tool is only for RCTs. We did not analyze how many of them there were in each group, because we did not think it was important for the aims of our study.

5. Could you define what do you mean by specific partial data (page 10, row 181)?

Response: We appreciate the opportunity to define this phrase more clearly. We were thinking of SRs whose ‘other bias’ domains in RoB tables were not complete. We divided them into four distinct groups: the first group with 28 SRs that had judgments for 'other bias', but not all had accompanying comments, i.e. supporting explanations, second group with 4 SRs where only one included RCT did not have the ‘other bias’ domain, third group with one SR with included RCT without ‘other bias’ domain and included RCT with only judgment without comment, and fourth group with one SR where RoB table was completely missing for 6 included RCTs. The explicit explanation has been added in the manuscript.

6. This is critically important work that deserves to be published, but it is necessary to improve the methodology and the discussion sections.

Response: Thank you for your time and comments. We hope that the revised manuscript will be satisfactory.
Reviewer 3 (Reviewer 3):

General comments

1. This review highlights that when Cochrane review authors have the opportunity to assess and describe "other bias" this is frequently performed incorrectly with authors failing to clarify whether no other bias was found or, if it was, what the other bias was specifically.

I find learning about the various types of "other bias" reported by authors very interesting. The authors rightly highlight that version 2 of the Cochrane RoB will not have the "other bias" and in lines 327-329 highlight that some areas found would not fall under the more extensive updated RoB tool.

Response: We are grateful to the reviewer for kind words about our manuscript.

2. I would like the authors to go further here in elaborating the judgements of "other bias" found from this review that would not be covered by the new 2.0 tool. This is important for those working in this area who need to understand the limitation of new tools which are hoped to be improved versions of the old ones.

Response: We indicated in our manuscript that the new 2.0 tool would not have ‘other bias’ domain, and, as can be seen from our manuscript, there are issues that can introduce bias, and that are not covered in the domains of the RoB 2.0 tool. For this reason, we believe that the ‘other bias’ domain should remain in the new Cochrane RoB tool, but instructions for Cochrane authors regarding potential sources of other bias should be more elaborate, and reviewers + editors should be vigilant to point out errors that Cochrane authors do when they use ‘other bias’ domain to mention biases that are covered with other domains.

3. The authors allude to a similar study on attrition bias which is unpublished. Ideally this would be published, or at least in press, in order to be cited here.

Response: Your comment has a point. Our study on attrition bias was submitted to the BMC Medical Research Methodology in November 2017; we received the first reviewers’ comments two months ago, submitted the revised manuscript and the manuscript is now again in the ‘under review’ stage. Since we have now conducted several studies about the RoB in Cochrane reviews, we posted several of them, including results from the ‘attrition bias’ study on a preprint server, and we cited them now in this manuscript. Additionally, our detailed analysis of the ‘allocation concealment’ domain was just published a month ago in another journal, so we can cite that one too now in the manuscript.

Requested revisions
4. The overall interpretation could be more emphatic. Recently Cochrane has been under the spotlight for seeming to censor, by way of expulsion, board members who criticize Cochrane reviews. In this sense, the idea that these products will continue to be churned out without due consideration from authors is worrying to those with research integrity. How should the Cochrane Collaboration respond to the findings from this study?

Response: Indeed, we understand the concerns of the authors and we did not aim to create a non-empathetic manuscript. We tried now to do better and to be less harsh. We changed the title to give it a neutral tone; we changed conclusions also slightly to give them more neutral and optimistic tone, and we included a new section in the Discussion in which we explain the contribution of this manuscript: that we hope it will help authors of systematic reviews to recognize various potential sources of bias, and to avoid mistakes in the other bias domain.

Additional requests/suggestions

5. I have a problem with the acronym CSR because as a systematic reviewer this invariably means to me a clinical study report but here it applies to the Cochrane Reviews. I think many other readers in the field of this paper are likely to have the same association and I would prefer the acronym here to be CR.

Response: Thank you for your suggestion. To avoid any confusion with any other acronym, we have now used simply expression ‘Cochrane review’.

6. Some minor English/grammatical errors such as: "only RoB of RCTs was analysed" (should be plural).

Response: We have sent our manuscript to a professional translator and it was revised accordingly.

7. Please clarify what proportion of titles/abstracts were verified by the second author.

Response: Thank you for the excellent observation. The second author verified all the assessments of the first author. We added this information in the manuscript.

We hope that the revised manuscript will be satisfactory.

Sincerely,

Livia Puljak and co-authors