Author’s response to reviews

Title: Comparison of nuisance parameters in pediatric versus adult randomized trials: A meta-epidemiologic empirical evaluation

Authors:

Ben Vandermeer (bv1@ualberta.ca)
Ingeborg van der Tweel (i.vandertweel@umcutrecht.nl)
Marijke Jansen-van der Weide (jansen.mc@amc.uva.nl)
Stephanie Weinreich (s.s.weinreich@amc.uva.nl)
Despina Contopoulos-Ioannidis (dcontop@stanford.edu)
Dirk Bassler (dirk.bassler@usz.ch)
Ricardo Fernandes (fernandescunharicardo@gmail.com)
Lisa Askie (laskie@ctc.usyd.edu.au)
Haroon Saloojee (haroon.saloojee@wits.ac.za)
Paola Baiardi (paola.baiardi@fsm.it)
Susan Ellenberg (sellenbe@mail.med.upenn.edu)
Johanna van der Lee (j.h.vanderlee@amc.uva.nl)

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Author’s response to reviews:

Dear Editor,

We are grateful to you and to the Reviewer for your useful questions and comments, which have helped us to improve our manuscript. Below, we respond to each of your comments.

We hope that the responses are satisfactory, and that you consider the revised version of the manuscript suitable for publication in BMC Medical Research Methodology.
On behalf of all authors,

Yours sincerely,

Hanneke van der Lee

Reviewer 1.

1. In figure 2 and 4, it is best to add statistics to the side of the forest plot. Some readers may be interested in these statistics.

Response: We have attached alternative forest plots for these figures that include the numerical values of the risk ratios with 95% confidence intervals.

2. Since the authors are trying to investigate the age on CER-RR across meta-analysis, I suggest to add a meta-regression analysis and to examine whether the age had impact on the statistics. This is also a method to explore heterogeneity.

Response: We feel that the suggestion of a meta-regression is not feasible to this analysis for three important reasons:

1) Each entry in our meta-analysis is itself derived from a Cochrane meta-analysis that includes both pediatric and adult studies. Thus age is already incorporated in the effect size which is a ratio of CERs from the two groups.

2) By definition, all of these entries contain trials with both adult and pediatric data, so how can we categorize each with an age classification? The age range within each meta-analysis entry is designed to be heterogeneous, thus making it close to impossible to come up with a single age estimate for each.

3) The portion of our data-set comprising binary outcomes (for which we did the meta-analysis and to which a proposed meta-regression would apply) was taken from a previous publication’s data set, to which this level of detailed information is not available to us.

For these reasons we have not attempted to do any meta-regression related to age.
3. "Finally, we calculated the summary -CER-RR between pediatric and adult trials and their 95% confidence intervals across all meta-analyses by synthesizing the pooled logarithms of the CER-RRs within each meta-analysis again using the random effects model."---insert a reference here can be helpful (J Evid Based Med. 2016 Feb 9. doi: 10.1111/jebm.12191. ).

Response: We have added the reference as suggested.

4. Many topics have more than one meta-analyses, they were updated. how do you choose the one to be included in analysis?

Response: As stated, the meta-analyses were extracted from a previous study. These authors considered each meta-analysis within a review separately for inclusion, and included any that were eligible. We have added the following statement to our methods section:

"When a systematic review addressed different types of eligible comparisons of experimental versus control interventions, each comparison was considered for eligibility separately. [9]"

Reviewer 2.

In addition to significant differences/heterogeneity between pediatric and adult RCTs, the data also showed significant differences/heterogeneity among pediatric RCTs. It may have two implications. First, a use of the nuisance parameters from one to another pediatric RCT should be made cautiously too. This observation will lead to a stronger suggestion than the current conclusion of this study, but this is not the purpose of this study.

Response: We agree with this statement and its implications. We also agree that it is beyond the scope of this study. We have added the following statement to our discussion to emphasize these results and make this point more strongly:

“This suggests that not only should we be wary of extrapolating nuisance parameters for pediatric studies from adult studies, but we should be almost equally wary of extrapolating them from other pediatric studies.”

Second, this study may not be able to assume that all of the meta-analyses of a Cochrane review are similar enough for an imputation of nuisance parameters. The current result cannot exclude that the differences between RTCs came from the different populations. A random effect model cannot overcome this limitation. In practice, a further refinement of the inclusion criteria and a re-analysis based on the refined RTC data with a similar population structure (e.g., considering
more matching factors) may yield a more concrete conclusion. At least, an evaluation over this study limitation and detailed discussions on this limitation will be useful.

Response: While our study was designed to get a general overview of how the nuisance parameters compared, we do agree that such a study would be interesting and have added the following paragraph to our discussion to emphasize this issue:

“With these limitations in mind and given the results we have seen here, it would be interesting to do a further and more refined analysis as to which factors may lead to better concordance between the nuisance parameters of pediatric and adult studies. This would be a difficult endeavor, however, since these factors would likely be specific to a subject area, and not necessarily generalizable. Analysis would then have to be limited to those areas where there are enough studies to do it properly.”