Author’s response to reviews

Title: Subgroup effects despite homogeneous heterogeneity test results

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Author’s response to reviews: see over
Dear dr. Koutsos,

Please find attached the revised version of our manuscript “Subgroup effect despite homogenous heterogeneity test results” (MS 1198767956350389).

We thank the reviewers for their comments and useful suggestions. One of the issues raised in the reviews is the distinction between the proposed modification of the forest plot and ‘ordinary’ meta-regression analysis. We feel that, since meta-regression analysis provides the researcher with a (numerical) regression coefficient, this is likely to be interpreted in a quantitative way. Meta-regression analyses, however, might not be the appropriate method to quantify subgroup effects. An alternative method (the proposed modification of the forest plot), which is clearly qualitative, rather than quantitative, will not be falsely interpreted as a quantification of subgroup effects. Furthermore, it might be easier to interpret for clinicians, as it is related to the well-known forest plot.

We did our very best to meet the suggestions and requests made by the reviewers. In your email you indicated that it is important that our files are correctly formatted (i.e., include a methods, results, and discussion section to the manuscript). We are willing to change our manuscript accordingly, but feel that the clarity of the manuscript would suffer from it. We explicitly wrote the manuscript as a brief report and a tutorial, to make our message easily accessible to clinicians. As a result methods and results are intertwined and it is not straightforward to separate the two.

Please find below our response to each of the points raised by the reviewers. We look forward to your response.

Yours sincerely,
On behalf of all authors,

R.H.H. Groenwold, MD PhD

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Response to the review by Rose Baker

1. The reviewer suggests that nothing new is proposed in our manuscript, since exploration of meta-analyses for potential subgroup effects is already common, and can be done using meta-regression analysis.

We agree with the reviewer that such exploration can indeed be done using meta-regression analyses. Unfortunately, however, conduct and interpretation of meta-regression analyses are not straightforward to clinicians. A ‘simple’ forest plot on the other hand, or a modification to this, might be, as the forest plot is well-known to clinicians.

Furthermore, meta-regression analysis is not an appropriate method to quantify subgroup effects. As shown by Arends et al. (Stat Med 2000) ordinary least squares meta-regression can give biased estimates, since uncertainty around estimates (rather than true values) is not taken into account. Therefore, meta-regression analysis should not be the first choice when exploring for subgroup effects in aggregated data meta-analyses. In fact, aggregated data meta-analyses are inadequate to study subgroup effects, since the size of such effects can only
be correctly estimated in individual patient data meta-analysis. We discussed these issues in detail in the revised version of our manuscript.

2. The reviewer indicates that the quality of the figure should be improved.
We edited the figures to improve their quality.

We thank the reviewer for pointing out some type-o’s and issues that were unclear. In the revised version of the manuscript we clarified these and corrected the type-o’s.

Response to the review by Charles Green
1. The reviewer points out that there could be more reasons for heterogeneity than subgroup effects, e.g., methodology, ascertainment of outcome, etc.
This is indeed an omission, and we added other potential causes for heterogeneity to the revised version of the manuscript.

2. The reviewer suggests to rephrase “absence of statistical heterogeneity does not imply absence of clinical heterogeneity” into “lack of demonstrable statistical heterogeneity might obscure clinically relevant subgroup effects”.
We agree, and changed the manuscript accordingly.

3. The reviewer asks for a reference to a review about the statement that meta-analytic heterogeneity depends on the effect measure.
We included this reference, and added a short explanation to the manuscript.

4. The reviewer proposes to include references to the original publications on the heterogeneity tests that are discussed.
We agree, and included these references.

5. The reviewer wonders what the relative utility of each measure of heterogeneity is.
We briefly discuss the pro’s and con’s of the different measures in the revised version of our manuscript.

6. Our statement that ‘subgroup analyses in aggregated data meta-analysis are inappropriate to assess subgroup effects, since such assessments are observational by nature’, should be explained more fully.
In the revised version of the manuscript we explained this concept in more detail.

7. The reviewer suggests to conclude with a clear recommendation.
We included such a recommendation in the conclusion paragraph of the revised manuscript

8. The reviewer would like to see an additional example from the literature.
We intentionally tried to write a relatively brief report to make it easily accessible to a broad readership. Although additional examples might add to show the relevance of the proposed methodology, the size of the manuscript will increase, and it will no longer be as concise as it is. Therefore, we propose not to include such an additional example.

Response to the review by Michael Reade
1. **Major compulsory revisions:** The reviewer wonders what criteria for clinical heterogeneity (as opposed to statistical significant heterogeneity) are, since these may be very subjective. He proposes to discard the argument of clinical heterogeneity in the absence of statistical heterogeneity to explore the data for subgroup effect.

We agree with the reviewer that in the absence of statistical significant heterogeneity it may be very hard to communicate ‘clinical heterogeneity’. Indeed, clinical heterogeneity that is not statistically significant appears to be a subjective conclusion. However, absence of statistical heterogeneity in aggregated data meta-analyses does not imply absence of heterogeneity (i.e., subgroup effects) when looking at individual patient data, as shown by our example. Hence, in aggregated data heterogeneity appears to be absent, while this heterogeneity is in fact present (and statistically significant) at an individual patient data level. We emphasized this in the revised version of the manuscript. The reviewer also suggested (#4, minor essential revisions) to model heterogeneity as a function of predictor variables. We included this, and it also shows that measures of heterogeneity can be different for aggregated data meta-analysis and IPD meta-analysis.

What is important, is that the absence of statistical heterogeneity in aggregated data meta-analyses does not imply that exploration for potential subgroup effects is redundant, as these may have important clinical implications. We clarified this in the revised version of the manuscript.

2. **Minor essential revisions:**

The reviewer would like to see a clarification of the statement that meta-analytic heterogeneity depends on effect measure.

We added this clarification (see also 3. of the response to the review by Charles Green). Furthermore, we thank the reviewer for indicating some typographical errors in our manuscript and corrected these.

3. **Discretionary revisions:**

We thank the reviewer for his textual suggestions, and copied these in the revised version of our manuscript.