Reviewer’s report

Title: A comparison of the statistical performance of different meta-regression models for the synthesis of subgroup effects from randomized clinical trials

Version: 0 Date: 14 Jun 2019

Reviewer: Deborah Kunkel

Reviewer’s report:

Thank you for the opportunity to read the manuscript "A comparison of the statistical performance of different meta-regression models for the synthesis of subgroup effects from randomized clinical trials."

The authors address estimation of subgroup effects (treatment effect/covariate interaction) in meta-analyses. They perform a simulation study to compare estimates of a fixed interaction effect under several models with varying trial-specific fixed and random effects. They find that models using aggregate data differ substantially from those using individual participant data.

I appreciate the authors' efforts in studying the operating characteristics of a carefully-selected set of similar models. The simulation study appears well-designed and executed. The paper does not offer much insight into the differences among the models, however, which makes it difficult to learn from the simulation results. I think some reorganization and improved discussion of the models would improve this paper.

Major comments:

- The presentation of the models could be presented in a more readable way. Model 1 is the most complex model, with the subsequent models arising from zeroing out certain parameters. I wonder if presenting the models in a list or table that outlines these incremental differences could make the paper easier to follow. Then in the text, there could be less repetition and more nuanced discussion of the simplifying assumptions of each model and why the model is being considered.

- Relatedly, you might point out that the coefficient referred to as beta.interC is the key estimand in each model.

- The differences in the models 1-3 and 4-6 should be explained more clearly. Models 1-3 include a trial-specific fixed effect of the mean age in that trial—it might be helpful to emphasize that models 1-3 include an additional fixed effect, since the random effects in Model 4, for example, do in a way also separate between- from within-trial interaction. It seems as though the fixed effects in Models 1-3 induce a linear relationship among the means of the trial-specific intercepts, (where the ordering depends on the average age in the trials), while the trial-specific random intercepts (u_i) allow some deviation from this
ordering. This is a key element in the models being compared and I think readers could benefit from some discussion of this.

- When evaluating the bias of the AD model, what "true" value of the interaction effect is used? I think in the Model 7, the "beta.age" coefficient has a different meaning and in general, it is not something we would necessarily expect to be equal to the value used in simulating the data. Was this taken into account? It might still be interesting to point out that the coefficients tend to have different values, but "bias" might not be the best word since the interaction is captured by a fundamentally different coefficient.

- The low coverage in the IPD models is interesting/concerning. This may be unavoidable in fitting random effects models with such a small number of studies, but maybe warrants a conjecture as to why this occurs.

Minor comments:

- The description of the data generating mechanism might be better after the model description.

- The results shown in Tables 4, 6, and 7: It is difficult to look at the numbers and assess which differences are substantial relative to the standard errors. Could these numbers be displayed in a figure instead? Maybe in lieu of Figures 1 and 3, where it is difficult to see patterns in models 1-6 because of the scale.

- P9 line 34: what is beta.interCi?

- P11 line 14: parameters as defined in model 3?

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
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Yes

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