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

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Reviewer: Daisuke Yoneoka

Reviewer’s report:

This paper presents simulation results to compare the performance of different types of meta-regression formulation by using bias, MSE and coverage measures. This study introduces two novelties. Firstly, they focus on the estimation accuracy of the interaction term between patient and study-level characteristics. Secondly, they checked the performance of the estimation by comprehensive simulation experiments. In general, this is quite an interesting idea but I have a number of concerns both with respect to the methodology as well as the presentation of the results, which should be addressed before a decision on the manuscript is taken.

Major concerns

1. Theoretical background

The main findings of the manuscript are that 1) the use of AD or IPD and 2) the number of studies influence the performance of the estimation. But this fact has been well studied from a theoretical perspective such as Lin and Zeng (2010, Biometrika) and Zeng and Lin (2015, Biometrika). Although their focus is not on the efficiency in the estimation of the interaction term in terms of meta-regression approach, their results can be generalized to this case. Thus, it would be useful for readers to include some theoretical descriptions/proofs to support their claim.

2. Definition of heterogeneity between studies

The key idea of the manuscript is to check the estimation accuracy in the parameter of the interaction term between patient and study-level characteristics, which is defined in Eq. (4.1). And the heterogeneity is then defined as V2 to control the variance of the normal distribution, which is used to (randomly) sample the true parameter. However, as the authors mention in the discussion section, the definition of heterogeneity seems weird and arbitrarily. Heterogeneity between studies should be defined in terms of all relevant variance parameters that have the suffix i (study index) in Eq. (4.1). In the current setting, compared to the assumption of variance.age~N(49,1), the setting of V2 is relatively (very) small in the interaction term. It would be helpful for readers to include the results of larger V2 even if they seem implausible value in the real datasets of osteoarthritis. In addition, it would be also helpful to include the description about the heterogeneity of V2 from the total between-study variance point of view.

3. Model misspecification effect
As the authors discuss in the limitation section, one large potential problem is the issue of the model misspecification: i.e., given that the true model includes extra confounding variables in addition to age (such as the quality of study and the population difference), the fitted model (wrongly) includes only the age variable. In addition, although now they assume that age variable is continuous, it is possible to consider a discrete (categorical) variable instead of the continuous variable. These types of misspecification could occur frequently in practice. It would be helpful if the authors include some results of numerical experiments or description about the model misspecification.

4. Model parameter values

On page 6-8 and Table 2, the true parameter values in the model are described in different places. Thus, it is difficult to follow the simulation settings. For example, it is difficult to get information about the values of \( \sigma_i \) and \( \tau_i \) in Eq. (4.1). It would be helpful for reader to create a new table that include all parameter values in the simulation.

5. In conjunction with comment #4, there is no description about the cases where \( y_{ij} \geq 10 \) or \( y_{ij} < 0 \). The probability should be low, but it would be helpful to explain what the authors did in such cases.

6. Motivating real-data examples

Although their main focus is to check the performance of different meta-regression formulations via the numerical experiments, it would be necessary to include one or two real-data examples to clarify the practical performance.

Minor concerns

1. No figure title: I could not find figure titles and legends. Thus, it was difficult to check the quality of the figures.

2. Several citation mistakes: the authors mix the citation styles of "***. (# of ref)" and "*** (# of ref)."

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

No

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?
If not, please explain in your comments to the authors.

Yes

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Please indicate the quality of language in the manuscript:

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