Reviewer’s report

Title: Age-treatment subgroup analyses in Cochrane intervention reviews: a meta-epidemiological study

Version: 0 Date: 29 Jun 2019

Reviewer: Fujian Song

Reviewer's report:

1. This meta-epidemiological study of age-treatment subgroup analyses in a sample of 928 Cochrane Systematic Reviews is well conducted and fully reported. It was found that subgroup analyses by age were rarely performed in meta-analyses, and a few observed statistically significant subgroup effects by age in some systematic reviews were not considered seriously by reviewers themselves as well as by clinical guideline developers. These findings were similar or consistent to previous studies of subgroup analyses in meta-analyses. The common difficulties regarding subgroup analyses in meta-analyses are well known, include insufficient data reported in primary studies, and widely accepted sceptical attitudes regarding findings from subgroup analyses in clinical trials. The certainty of evidence from subgroup analyses in meta-analyses was usually rated very low, particularly when subgroup analyses were based on between-study comparison rather than within-study comparison, and given the retrospective nature of literature-based research synthesis.

2. The definition of, and approaches to, age-treatment subgroup analyses in meta-analyses need to be clarified. For example, subgroup analyses in meta-analyses may be conducted by between-study comparison or within-study comparison, or mixed with both. It is currently difficult for ordinary readers to understand how subgroup analyses were conducted. A conceptual framework to clarify the complex nature of subgroup analyses in meta-analyses should be provided.

3. Results of subgroup analyses in individual-participant data (IPD) meta-analyses are much more accurate and precise, compared to aggregate data meta-analyses, which has been largely ignored in the current study. Particularly, cumulative subgroup analyses using IPD data has been recommended for individualised medicine (Song & Bachmann: BMC Med. 2016 Dec 15;14(1):197). The use of IPD data will overcome insufficient data due to inadequate reporting, and non-standardised age groups in aggregate meta-analyses. Some Cochrane reviews are actually using IPD data. Authors should pay more attention on IPD meta-analyses, to resolve some difficulties met in aggregate data meta-analyses.

4. Page 6 the first sentence is unclear. "In order to understand the quality of evidence ..... ". However what listed as study aims were mostly about "how often", not really "quality".
5. Page 8, paragraph 2: "we then organized the trials by ascending year and noted .... " Is it possible to check changes in subgroup effect over time (or so called cumulative subgroup analysis)?

6. Table 1 seems very complex, difficult to understand.

7. Page 18 paragraph 1: "the prevalence of statistically significant P values from formal interaction testing was higher than what would be expected by chance (5%)." This statement is misleading, as the denominator should be the number of all tests conducted, which was actually unknown.

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.

Not applicable

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?
2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

'I declare that I have no competing interests'

Statement on potential review bias
Please complete a statement on potential review bias, considering the following questions:

1. Did you co-author any publication with an author of this manuscript in the last 5 years?

2. Are you currently or recently affiliated at the same institution as an author of this manuscript?

If you can answer no to all of the above, write 'I declare that I did not publish with these authors in the last 5 years and also meet the affiliation criteria". If your reply is yes to any, please give details below.

'I declare that I did not publish with these authors in the last 5 years and also meet the affiliation criteria

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal