Author's response to reviews

Title: The Ratio of Means Method as an Alternative to Mean Differences for Analyzing Continuous Outcome Variables in Meta-Analysis: A Simulation Study

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Author's response to reviews: see over
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Editorial Office
BMC Medical Research Methodology

Dear Sir/Madam:

RE: MS: 1233987214186979
The Ratio of Means Method as an Alternative to Mean Differences for Analyzing Continuous Outcome Variables in Meta-Analysis: A Simulation Study
Jan O Friedrich, Neill KJ Adhikari and Joseph Beyene

Thank you for sending us the comments of the three reviewers. As requested we are enclosing a revised version of the manuscript. We have also attached a point-by-point response to each of the Reviewers’ specific comments and state where we have made changes to the manuscript to incorporate their comments and suggestions.

Thank you for considering our revised manuscript. We look forward to hearing from you.

Sincerely,

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Reviewer 1 (Christopher Schmid’s) comments

We have moved the discussion of the ratio of means method and the derivation of its variance to the main text at the beginning of the Methods section starting on page 6 of the revised version of the manuscript. We have retained the material on random and fixed effects weights in the appendix since it is referred to multiple times in the main text.

A 2nd order Taylor series approximation for the variance of the natural logarithm of the ratio of means method, assuming normality for the sample mean (which usually holds true for large samples), leads to the following variance formula:

\[
Var \left[ \ln \left( \frac{D}{C} \right) \right] = \left( \frac{s_D}{\sqrt{n_D D}} \right)^2 + \frac{1}{2} \left( \frac{s_D}{\sqrt{n_D D}} \right)^4 + \left( \frac{s_C}{\sqrt{n_C C}} \right)^2 + \frac{1}{2} \left( \frac{s_C}{\sqrt{n_C C}} \right)^4
\]

(In this formula D refers to the experimental group, C to the control group, n to the number of patients in each trial arm, and s to the standard deviation in each trial arm.) We have added sentences describing the general form of the second order terms for the ratio of means method and numerically demonstrated how their inclusion would affect the bias on page 7-8 in the revised version of the manuscript.

We have moved the single table in Appendix II to the main text. It is Table 6 in the revised version of the manuscript.

As discussed in the Appendix, we used the corrected SMD by incorporating the correction factor \([1 – 3/(4N-9)]\) as described by Hedges et al (reference 5) to provide unbiased estimates of each individual study’s SMD. However, as discussed in references 5 and 6, the weighted combination of SMDs is still biased even with this correction factor when the inverse of the sampling variances are used as weights since the sampling variances depend on the value of SMD. We have clarified this point in the main text on page 6, as suggested by the reviewer.

Minor:

Page 7, line 4: parenthesis is added after “WMD =”

Page 8, para 2, line 1: “For” corrected.
Reviewer 2 (Malinee Laopaiboon’s) comments

We have added an explanation regarding the reason for the 88% coverage results when k=5 and sample size is 100 patients per trial arm in the discussion of the coverage results on p. 15-16 in the revised version of the manuscript.
Point-by-Point Response to Reviewers’ Comments

MS: 1233987214186979 (BMC Medicine Research Methodology)
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Reviewer 3 (Wim Van Den Noortgate’s) comments

Major Compulsory Revisions

None

Minor Essential Revisions

1. p.4: We agree that the commonly-used nomenclature is confusing since the so called weighted mean difference is in fact the weighted mean of mean differences and the so called standardized mean difference is the weighted mean of standardized mean differences. We agree that the terms and abbreviations suggested by the Reviewer, the overall mean difference (OMD) and the overall standardized mean difference (OSMD) would be less confusing. However, WMD and SMD are the terms that are most commonly used so we are hesitant to introduce two new terms and abbreviations, however, we would be agreeable to doing so if the Editors feel this is appropriate. We have specified that the WMD and SMD are actually weighted means of mean differences and standardized mean differences when these terms are first introduced on page 4 of the revised manuscript.

2. p.9:
   - We have clarified that by “extreme values” we mean deviating far from zero (page 12 in the revised manuscript).
   - We have added a sentence describing the separate effects of sampling variance and population heterogeneity on the bias towards zero (page 12 in the revised manuscript).
   - We agree with the Reviewer’s comment regarding the term ‘negative bias’ and have changed it to ‘bias towards zero or no effect’ in this section and throughout the manuscript. We have also made similar changes to references to ‘positive bias’ for RoM.

3. p. 11, line 9: In this section we were actually referring to the scenarios “without heterogeneity”. To make this clearer we have corrected the magnitude of the bias to “2-3%” from “3-4%” and added the following sentence on page 13 in the revised manuscript to make this explanation more clear: “(This bias is also present in the scenarios with heterogeneity and 10 patients per trial shown in Table 5; however, the overall bias in these scenarios is due to the combined effect of both this bias towards unity discussed in this section and a bias away from unity discussed in the next section.)”

4. p. 16: We agree that the standard deviations are necessary to calculate the weights for both RoM and SMD. The point we were trying to make was that clinicians interpreting the results of a meta-analysis using SMD (but not RoM) also require knowledge of this pooled standard deviation. We have re-phrased this sentence to more explicitly make this point and we have also added the statement that RoM is easier to interpret (page 18 in the revised manuscript). We feel that RoM is still calculable if the continuous variable is measured on an interval scale.

Discretionary Revisions

1. on p. 4: We have clarified that difference methods are commonly used in group comparison studies.
1. p. 5: We have added a sentence to state more explicitly that the RoM's are converted to their natural logarithms before being combined, and that the results are then back transformed.

2. p. 5: For each set of scenarios, the sampling variance is set the same for each study. When the sampling variance is changed (eg standard deviation increased from 10 to 70% of the mean value), the population heterogeneity is changed in the same proportion so that $\hat{I}^2$ remains constant (for a given number of patients per trial).

3. p. 14: We have added what the expected values for $\hat{I}^2$ are and described how they are calculated in the Methods section (page 10 in the revised version of the manuscript).

4. p. 29: We have added a sentence to this section (moved to the main text on page 7 of the revised manuscript) that describes the reason for the logarithmic transformation which allows approximation of the confidence intervals of the log-normal distributed function. This is similar to the approach applied to other ratio methods such as odds ratios and risk ratios, used for binary group comparison studies.