Author’s response to reviews

Title: Many continuous variables should be analyzed using the relative scale: a case study of β2-agonists for preventing exercise-induced bronchoconstriction

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Responsed indicated by HH+JF:

Reviewer #1: Manuscript Number: SYSR-D-18-00415
The title of the article is " Many continuous variables should be analyzed using the relative scale: a case study of β2-agonists for preventing exercise-induced bronchoconstriction". Hemilä H, et al conducted a specific article types as "Methodology". This article aimed to compare relative vs absolute scale pooled outcomes using data from a recently published Cochrane systematic review that reported only absolute effects of inhalatory β2-agonists on exercise-induced decline in forced-expiratory volumes in 1 second (FEV1).
This is an interesting topic that can benefit from more thorough reporting and discussion, and appears to be well performed in general and the manuscript is well written. This topic will aid in understanding the usefulness of the relative scale and some limitation of the absolute scales in the estimation of the effects of β2-agonists on exercise-induced FEV1 decline. However, the manuscript still could be further improved after some revisions.
Specific comment;
In Methods section, Selection of the β2-agonists on EIB. The authors state that "One trial that was excluded by Bonini et al. on the basis that there was no clear diagnosis of EIB reported IPD for exercise-induced FEV1 decline and was included in our IPD analysis. Another trial with IPD data was identified through perusal of the reference lists in included RCTs, and was included in our analysis [29], but had not been identified by Bonini. Thus, a total of 14 trials reporting IPD data suitable for this analysis were identified (Table 1)". It must know what method for trials selection, before interpretation and compare the results from Bonini et al (in Discussion section). Please clarify what methods or inclusion and exclusion criterion for trials selection or study flow chart of the trials selection.
HH+JF: In our Discussion section we explicitly state that “Our study did not intend to reproduce Bonini's main meta-analysis, which was labeled Analysis 1.1 in their paper [10]. There were some errors and data extraction inconsistencies, see Table S3 in Appendix 1. We used Bonini's review as an example to demonstrate that the calculation of absolute effects can lead to suboptimal effect estimates.”
In response to the reviewer’s comment we have better highlighted our inclusion and exclusion criteria in the Methods section which now state: “For the individual participant data (IPD) analysis, we systematically reviewed all the included and excluded studies and their reference lists in the studies identified by Bonini et al. [10], and included all placebo-controlled inhalatory β2-agonist cross-over randomized trials that reported IPD, 13 trials [16-28]. Bonini et al. excluded trials for a few reasons, one being "no clear diagnosis of exercise-induced bronchoconstriction". We did not exclude such trials for the following reasons: Clear dichotomous definition of EIB, such as a ≥10% FEV1 decline in an exercise test [11] is relevant in certain contexts such as in top level athletics; however, such a cut-off level is arbitrary and has no biological basis. Moreover, if participants with small FEV1 declines are included in the analysis, the range of FEV1 declines becomes wider and the comparison of the absolute scale (intercept) and the relative scale (slope) becomes statistically more powerful.”

2. Please clarify how you manage the different confounding factors such as different type of bronchodilators, different duration between the β2-agonist administration and the exercise test, different baseline in an EIB study or in some case you using the pre-drug level as the baseline. Did you re-analyzed of sensitivity analysis or subgroup analysis?

HH+JF: In response to the Reviewer’s comments we have added the following section to the Discussion clarifying our approach to managing the potentially confounding factors mentioned by the Reviewer: “Similar to Bonini’s analysis, we combined different β2-agonists to calculate one single estimate of effect. We took this approach because our primary goal was to compare two different methods in the analysis of FEV1 changes rather than estimating the effectiveness of a particular β2-agonist, or protocol for conducting an exercise test. If one β2-agonist or protocol is less effective than another, the lower effectiveness would be analyzed in both ways and thereby contribute equally to both the relative and absolute scale analysis. We tried to reduce the heterogeneity of comparisons by selecting salbutamol (or if not tested, salmeterol) when several β2-agonists were investigated in the same report, the shortest delay between β2-agonist administration and exercise test when exercise tests were repeated several times after the administration of a β2-agonist, and pre-drug FEV1 as baseline when possible. Furthermore, as described in the Methods section, we take into account the variations in β2-agonists and conduct of exercise tests used among different trials by using trial as a clustering variable in the analyses.”

3. In discussion section, please clarify, which cases did you prefer to use relative scale in limitation of relative scale?

HH+JF: We have modified this section in the revised version of the manuscript to highlight that there are different kinds of contexts where continuous outcomes are generated, and provide some conditions as well as specific examples where the relative scale may not be applicable.
4. In conclusion section, the author state "The absolute scale has been widely used in the analysis of FEV1 changes and it may have led to sub-optimal statistical analysis in some cases". There is an interesting point, please you clarify which cases that the outcome from "sub-optimal statistical analysis" can cause a clinical significant, in discussion part.

HH+JF: As to sub-optimal statistical analyses, in our paper we show that Bonini's estimate of 17.67 percentage points average effect of beta2-agonists is inconsistent with the three categories in Table 3: 30-39% decline after placebo, 40-49% decline after placebo, and &gt;50% decline after placebo. We describe this in our Discussion as follows: “The confidence intervals of the three groups with FEV1 decrease 30% and greater are all inconsistent with the 17.67 pp effect calculated by Bonini [10]. These three groups contain 61% (97 of 159) participants in Table 3. This illustrates that Bonini’s estimate of effect does not apply to a great proportion of people classified as having EIB.”

Another example of sub-optimal statistical analysis by the absolute scale in our Discussion is about the Cochrane review on vitamin C and asthma, as we write “one of the Cochrane reviews estimated the effect of vitamin C on EIB on the absolute scale and described the effect of vitamin C five minutes after exercise in the Schachter (1982) trial [45] as follows: “No significant difference between vitamin C and placebo: vitamin C mean: –0.24 (SE ± 0.06) L/s, placebo mean: –0.44 (SE ± 0.14) L/s, t = 2.13 (P = 0.057)” [39, p.46]. However, the slope of a linear regression analysis of the same study, which had reported the IPD [40], indicated that vitamin C’s relative decrease in FEV1 decline was highly significant: 55% (95% CI: 32 to 78%; P = 0.0003) [46]. This difference also illustrates that the calculation of the absolute effect, which is the custom in the Cochrane reviews, can lead to false negative conclusions.” We also list a few more Cochrane reviews that have used the absolute scale.

Thank you so much to let me having opportunity to work with this review.

Reviewer #2: I congratulate the authors with an excellent work and wish you a successful publication. I don't have any relevant comments or objections to the manuscript.

HH+JF: No responses needed