Author's response to reviews

Title: Exercise for patients with depression: a protocol for a systematic review with meta-analysis and trial sequential analysis

Authors:

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Version: 5 Date: 8 March 2015

Author's response to reviews: see over
For the editorial office at Systematic Reviews.

Copenhagen, March 8, 2015

On behalf of my colleagues, I would like to thank you for the opportunity to re-submit to the Systematic Review journal this manuscript containing a protocol for a systematic review entitled: **Exercise for patients with depression: a protocol for a systematic review with meta-analysis and trial sequential analysis**

Our resubmission includes a point by point response to reviewer comments.

On behalf of the authors

Sincerely,

Jesper Krogh
Reviewer's report
Title: Exercise for patients with depression: a protocol for a systematic review with meta-analysis and trial sequential analysis
Version: 4 Date: 5 January 2015
Reviewer: Alexander Tsertsvadze
Reviewer's report:

Study selection
• The following sentence on page 7 belongs to ‘search strategy’ section:
“Reference lists of relevant reviews will be searched for additional trials.”

Authors’ response
The sentence has now been removed accordingly.

• Will not the authors run into the risk of selection bias if both screening levels will be done by a single reviewer? Will not the second reviewer screen or at least cross-check the included and excluded studies?

Authors’ response
Two investigators will examine full text reports for inclusion or exclusion. This has now been mentioned in the study selection paragraph.

• Will the authors document the study flow and reasons for exclusions at full text screen level? If yes, will they use the PRISMA flow chart?

Authors’ response
The flow of trial reports and reasons for exclusions will be reported in the PRISMA flow chart. This is now mentioned in the ‘Search strategy’ paragraph.

• How will the reviewers reconcile any emerging conflicts/disagreements regarding inclusion/exclusion of any given record?

Authors’ response
We have now included the following sentence in the ‘Data extraction’ paragraph:

‘Any discrepancies in the data extraction or inclusion/exclusion of trials will be resolved by referring to the original papers. CG or MN will assist in the adjudication regarding disagreements.’

Risk of bias assessment
• I would suggest to move the explanatory paragraphs for each domain of risk of bias found on pages 8-10 (those in red font) from the manuscript to an appendix

Authors’ response
Specifications of bias assessment have now been removed to an appendix.
• The paragraph on publication bias should be moved to the end of ‘Data synthesis and analysis section’ (after subgroup analysis subsection)

Authors’ response
The paragraph has been removed accordingly.

• I suggest to delete the following sentence on page 10: “However, when we draw conclusions, we will remember that no or only few trials with low risk of bias existed. Hence, the chance to know the ‘true’ intervention effect is low or absent.”

Authors’ response
We have changed the sentence: However, in case no or few trials with low risk of bias will be included, we shall remember that the chance to know the ‘true’ intervention effect is low or absent.

Data synthesis and analysis
• On page 11, the authors state the following: “We will pool data from the experimental groups and compare to the control group.” Would not the greater effects (if present) in higher intensity groups be diluted by simply pooling the exercise intensity/dose arms? Although the authors address this issue in the ‘Subgroup analysis’ sub-section, they may need to make this provision here too (page 11), something in this fashion: “the pooling would be considered only if there is an assumption that these exercise intensity groups have similar effects”

Authors’ response
We respectfully disagree. The primary aim is estimate the effect of exercise on depressive symptoms. Secondly, to identify variables that potentially contributes to heterogeneity of trial results (e.g., the level of intensity). In the subgroup analyses according to level of or duration of exercise, we will be able to see if there is such a dilution of effect in the overall analysis. We find that the primary analyses ought to be the one with maximal power and precision, i.e., the one including most trials.

• On page 11, the authors explain that they would address the missing data for a particular binary outcome (lack of remission) using the standard imputation method and sensitivity analysis. Please, reword the following sentence to make this clear: “Regarding the outcome of lack of remission, we will include trials with incomplete or missing data in sensitivity analyses by imputing them according to the following scenarios.” Something like in this line: “…In case of missing data for the ‘lack of remission’ outcome, we will use the imputation technique such and such….and sensitivity analysis to check the effect estimate across different scenarios…”

Authors’ response
We have revised the sentence for clarity. Thank you.
• Please, place the above-mentioned information/paragraph (on imputation and scenarios for lack of remission) only after the paragraphs on primary outcomes (sequential analysis and Bayes factor) found on page 12 (flip the order in the text).

Authors’ response
The paragraphs have now been flipped.

• Will the authors mention anything on how they will handle missing data for their primary outcome (i.e., depressive symptoms measured on a continuous scale)?

Authors’ response
We have now added the following sentence that deals with missing data for the primary outcome assessed by a continuous scale:

‘To assess the potential impact of missing data (incomplete outcome data bias) we will assess a “best-worst” case scenario assuming that all participants lost to follow-up in the intervention group had a beneficial outcome (the group mean minus 1 standard deviation (SD)); and all those with missing outcomes in the placebo group have had a harmful outcome (the group mean plus 1 SD). We also plan to perform the reverse “worst-best-case” scenario analysis [26].’

Declaration of competing interests:
None.

Reviewer’s report
Title: Exercise for patients with depression: a protocol for a systematic review with meta-analysis and trial sequential analysis
Version: 4 Date: 11 January 2015
Reviewer: Jesse Berlin

Reviewer’s report:
Minor Essential Revisions:
1. I’m not making specific suggestions, but the writing could still benefit from some close editing.
Discretionary Revisions

Authors’ response
The manuscript has now been edited by a professional in English.

1. This is not a major point, but you plan to exclude studies that don’t have a “no
exercise” control group, but do look at different intensities of exercise. This isn’t a point on which I’d insist, but I would ask that you at least consider some sort of investigation of dose-response, which is probably best estimated within a given study (preserving the randomization). That would mean including these studies of different intensities in a separate analysis. It’s just a suggestion for your consideration.

Authors’ response
Thank you very much. We will assess the impact of intensity as a subgroup analysis. We will, however, not include additional trials that merely assess this aspect.

NOTE: On page 13, you say, “In addition, we will compare the effect of low-dose exercise to high-dose exercise in trials using different exercise intensities in the experimental groups as well as in trials allocating patients to different exercise doses versus a control group.” It’s not clear from this statement whether you plan to do some kind of summary of within-study comparisons of intensity or some kind of cross-study comparisons (i.e., the effect size for studies with high intensity compared with the effect size for studies with low intensity exercise). As I noted, I believe the stronger analysis of intensity would be based on within-study comparisons, if those are possible. In any case, it’s important to be clear about this distinction (between within-study and between-study comparisons).

Authors’ response
We agree with this reviewer and have specified that this sub-group analysis is a within-study analysis. Thank you.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests: I am a full-time employee of Johnson & Johnson. I see no conflict related to the topic of the paper.