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: 2
Date: 5 November 2014

Author's response to reviews: see over
Copenhagen, November 5th, 2014

On behalf of my colleagues, I would like thank you for the opportunity to re-submit to the Systematic Review journal this manuscript of 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 our comments and responses to the reviewers.

On behalf of the authors

Sincerely,

Jesper Krogh
Design paper for Systematic review on exercise and depression:
Editorial requests:
1) Please include your PROSPERO registration number at the end of your abstract. Alternatively, if you have not registered with PROSPERO then please mention this in your Methods section.
Authors’ response:
The protocol was not accepted at PROSPERO. This is an update of a previously conducted systematic review and a major part of the data had already been collected prior to registration, which was the reason the protocol failed to be registered at PROSPERO. The lack of registration has now been mentioned in the methods section. We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

Please also highlight (with 'tracked changes'/coloured/underlines/highlighted text) all changes made when revising the manuscript to make it easier for the Editors to give you a prompt decision on your manuscript.

Please also ensure that your revised manuscript conforms to the journal style (http://www.systematicreviewsjournal.com/info/instructions/). It is important that your files are correctly formatted.

We look forward to receiving your revised manuscript by 23 October 2014. If you imagine that it will take longer

Reviewer's report
Title: Exercise for patients with depression: a protocol for a systematic review with meta-analysis and trial sequential analysis
Version:1 Date:16 September 2014
Reviewer: Alexander Tsertsvadze
Reviewer’s report:
Abstract – Methods/design
• Authors need to clarify the research question more explicitly but briefly in PICO format. Namely, a reader needs to know what specific benefits and harms (e.g., outcomes such as severity of depression, compliance to antidepressants, etc...) of exercise will be assessed in patients with depression. What will be the intervention of interest, exercise alone or in combination/add-on with an antidepressant or psychotherapy? What will be comparator interventions, antidepressant alone (without exercise), psychotherapy, placebo, or no intervention?

Authors’ response:
We have changed the objective accordingly:
The objective of this systematic review is to investigate the beneficial (e.g., severity of depression; quality of life; suicidality; etc.) and harmful effects of exercise compared with treatment as usual or as add-on treatment in randomized clinical trials including adults with a clinical diagnosis of depression.

Background – Objectives
• Same as above, please formulate your objectives/research question using PICO framework

Authors’ response:
We have changed the objective accordingly:
The objective of this systematic review is to investigate the beneficial (e.g., severity of depression; quality of life; suicidality; etc.) and harmful effects of exercise compared to treatment as usual or as add-on treatment in randomized clinical trials including adults with a clinical diagnosis of depression.

Methods – Eligibility criteria
• Please, delete the first paragraph (e.g., definition of RCT, blinding, etc...) and organize your study eligibility criteria by a) inclusion criteria and b) exclusion criteria. In inclusion criteria, please specify your criteria as bullets by study design (RCTs), language of publication (any language), type of publication (abstract vs. full text), and PICO elements (population, interventions of interest, comparator intervention, outcomes).

Authors’ response
This has been done.

• The inclusion criteria needs to be followed by your list of exclusion criteria preferable using PICO framework by specifying which interventions, populations, outcomes and study designs will be excluded.

Authors’ response
The inclusion criteria have now been listed accordingly to PICO. We also added an exclusion list. We did not include obvious statements in the exclusion list such as trials including children or observational studies.

• Will the authors try to distinguish harms due to medical treatments and exercise?

Authors’ response
In the collection of data we will not try to guess if a harmful effect is due to exercise or medication. We compare groups were exercise is additional to TAU or additional to medical treatment and any additional harm-full effects in these groups is potentially due to exercise.

• Please, move ‘subgroup analysis’ subsection to ‘Data synthesis and analysis’ section on page 8. Rename ‘statistical analysis’ to ‘Data synthesis and analysis’ section.

Authors’ response
This has been done.

• Move the following sentence from ‘outcomes’ subsection (“We expect some trials to have several intervention groups. We will pool data from the
experimental groups and compare to the control group”) to ‘Data synthesis and analysis’ section.

Authors’ response
This has been done

Methods – Search strategy and study selection
• Will the authors search for grey/unpublished literature? If so, please state this and which databases and other sources will be searched.

Authors’ response
The search strategy is as described using bibliographic databases, and reference list from similar studies. We will not exclude any material as long as it satisfies our inclusion criteria.

• Will there be any language restriction applied to the searches?

Authors’ response
As mentioned, there is no language restriction and no such restriction will be applied to our searches.

• Will there be any date restriction applied to the searches? What periods will be searched in major databases?

Authors’ response
There will be no restriction on date to our search.

• Search methods and screening articles (study selection) are merged in one section; will the authors separate them and create a new separate section ‘Study selection’ right after ‘Search strategy’ section?

Authors’ response
This has been done.

• In ‘study selection’ section, will the authors describe two levels of screening? i.e., screening of all identified abstracts/titles and then full text papers of all potentially relevant records passing the title/abstract screening level.

Authors response
The current version already describes these two levels.

• Will the authors use the pre-defined piloted screening form?

Authors’ response
Yes, this is mentioned in Data-extraction.

• How many reviewers will screen? How the conflicts will be resolved?
Authors’ response
The number of reviewers at each level is already and resolution of conflicts is mentioned in the current version. Please see study selection and data extraction.

• Will the authors present PRISMA study flow chart with reasons and numbers for exclusions at the end of ‘Search strategy’ section?

Authors’ response
Good point. We have now inserted the reason for exclusions at the end of the search strategy section.

Methods – Data extraction
• Please, add more specifics, what type of data will be extracted for study (e.g., design, sample size, study author, year of publication, etc...), population (e.g., age, sex, etc...), interventions (type of exercise, dose and duration of exercise, dose/duration of antidepressant medications, etc...), outcomes (e.g., depression mean scores, adverse events, rate of compliance, success rate, etc...).

Authors response
We have now included a specification on type of data that will be extracted.

• Will the authors specify what data will be extracted for study quality/risk of bias (ROB) assessment? Will it be methods of randomization, concealment allocation, or any other ROB domain?

Authors’ response
This is described under data extraction.

• Description of ROB is too long. Please describe briefly what instrument will be used and what major ROB domains will be addressed using such instrument. Indicate which outcomes will be assessed for ROB and what will be the ratings (e.g., low, high, etc...)

Authors response.
In the current manuscript it is mentioned that we will assess bias domains according to Cochrane standards and the specific domains has been mentioned. We have deleted a few sentences. However, we strongly believe that bias assessment is as important as assessment of outcomes etc. Results from trials/meta-analysis should always be interpreted in context of risk of bias. Description of bias assessment should therefore be adequately addressed in both protocols and reports.

• Please create a new separate section ‘Risk of bias assessment’; it should be separate from data extraction section.

Authors’ response
This has been done.

Methods – Data synthesis and analysis
• Please rename ‘Statistical analysis’ to ‘Data synthesis and analysis’ section.

Authors’ response
This has been done.

• Explain how evidence will be synthesized qualitatively? Will there be any comparison groups? Should the studies comparing exercise alone to
antidepressants be analyzed together with studies comparing exercise as add-on to antidepressant vs. antidepressant alone? Will the evidence synthesis be organized by outcome for each comparison?

Authors’ response
As described we will pool data from all the included trials according to the description in the methods section. We plan to distinguish subgroups of trials according to co-interventions, so that trials that compare exercise versus placebo/TAU will be analysed as one subgroup compared to another analyzing exercise plus antidepressants versus antidepressants alone. This has now been clarified. Thank you.

• In which cases the authors will consider meta-analyzing the studies? Please list these conditions precluding the meta-analysis (e.g., presence of clinical heterogeneity in populations, interventions, and outcomes; study design)

Authors’ response
In this particular study we will pool data as described. In case of heterogeneity we will rather investigate this by meta-regression than abstain from pooling data. Meta-regression potentially explains differences in effect size across trials, and therefore increase our understanding of the effect of exercise in patients with depression. Regarding the interpretation of the pooled estimate this will be done in context of I2.

• The authors stated that they will use SMD; will they use MD (change from baseline or difference between end points) using original score units by any chance? Its interpretation is more straightforward than that of SMD.

Authors’ response
We agree that the interpretation of MD is more straightforward than that of SMD. However, we will not use MD. Based on our last report we know that different assessment tools are used (e.g. HAMD, BDI) and by using MD we will restrict our analysis. We will try to translate back any effects into comparable points in, e.g., HAMD.

• The authors stated that would use subgroup analysis to explore the sources of heterogeneity; will they also explore the robustness of pooled estimates via sensitivity analysis across ROB domains, sample size, or intention to treat analysis?

Authors’ response
Heterogeneity analysis could be considered a sensitivity analysis (in case there are no differences). We have carefully selected the domains and groups we would like to compare. While it could be tempting to analyze many domains or trial characteristics this bears a risk of ‘type 1 errors’. Furthermore, we will as described handle missing data by imputing missing data in the three different described scenarios.

• Please inform if there are any a priori selected factors which will be explored for their influence on effect estimates of exercise.

Authors’ response
We are not sure we understand this question. The exploration of heterogeneity is a priori defined.

• Will the authors state anything about how they will assess publication bias?

Authors response
We will assess publication by funnel plot and Egger’s test. This is now mentioned in the ‘Risk of bias’ section.

• Are the authors planning to assess an overall quality of evidence (‘strength of evidence’) for their primary outcome (i.e., association between childhood socioeconomic status and LTPI) using the GRADE system?

Authors response
We will present our findings in a summary of findings table according to the GRADE system. We have added a sentence on this in the data synthesis section.

Discussion
• Will the authors highlight strengths/limitations in identified evidence (e.g., amount, validity, applicability, etc…)?

Authors response
Yes, we will highlight identified strengths/limitations of identified evidence in the discussion. This has now been clarified.

• Will the authors highlight strengths/limitations of their review (any limitations in the review methods)?

Authors response
Yes, we will highlight identified strengths/limitations of our review in the discussion. This has now been clarified.

• Will the authors compare their findings with those from other systematic reviews that explored the same or similar question?

Authors’ response
The results will be compared to previously published reviews. This has now been clarified.

• Will the authors highlight future research and policy implications of this review?

Authors’ response
Based on our results we will highlight the implications for health authorities as well as future research. This has now been clarified.

Reviewer’s report
Title: Exercise for patients with depression: a protocol for a systematic review with meta-analysis and trial sequential analysis
Version: 1 Date: 20 September 2014
Reviewer: Robert Stanton
Reviewer’s report:
General comments:
This is a timely and useful topic. The investigation of harmful effects will be an important inclusion.
Minor essential revisions
1. There are some grammatical errors and the use of both past, present and future tense. I would expect the methods would all be future tense since this is a protocol for a study yet to be conducted.

Authors’ response
We have corrected into future tense.

2. The authors should define the use of ‘light exercise’ as an attention control, eg stretching, yoga or Tai Chi, since that latter 2 have been found to reduce depressive symptoms.

Authors’ response
We have now added in the methods section:
Light exercise would be equivalent to stretching or light aerobic exercise. Some evidence suggests that Tai-chi and Yoga could be effective in treatment of depression and would not be considered a valid control group.

Discretionary revisions
1. Background: Second last line. What are ‘health authorities’ and is this a comparison group in your review?

Authors’ response
Agree. ‘Health authorities’ does not make sense in that context. It has been deleted.

2. You name the 2 investigators who will likely perform data extraction but not those who will perform trial identification

Authors’ response
This has now been added.

3. There are no language restrictions therefore I assume the research team has, or has access to the requisite language skills.

Authors’ response
We have in our network access to relevant language skills. In case we do not the relevant skills in our network we will use foreign students living in Copenhagen.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
There are no competing interests