Author's response to reviews

Title: Yoga for schizophrenia: A systematic review and meta-analysis

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Author's response to reviews: see over
Response to the Editor’s and the Reviewer’s comments:

Dear editor, dear reviewers,

Thank you very much indeed for your valuable comments and efforts while reviewing this manuscript. We have found your comments helpful and addressed them accordingly. Changes are highlighted in grey.

Reply to reviewer 1:

1. This is a well-written and comprehensive meta-analysis on a clinically important topic. The authors conducted a systematic review and meta-analysis to clarify the effects of yoga on symptoms of schizophrenia, well-being, function, and hospitalization in patients with schizophrenia.

HC: Thanks a lot for your kind comments.

2. The introduction is well written and builds upon the current knowledge base. The rationale for this study is clearly outlined. I only have one minor comment. I do believe that in daily clinical practice not all therapists do perceive breathing exercises and meditation as psycho-spiritual techniques but rather as body awareness related exercises. A minor discretionary revision could be to delete “psycho-spiritual techniques” in the text.

HC: I have replaced "psycho-spiritual" with "body awareness".

Reply to reviewer 2:

1. The methods and statistics used in the meta-analysis needs confirmation from a statistician familiar with meta-analytic methods. This is especially so as more than one of the studies has used non-parametric statistics to compute results as the data were not normally distributed. I am not sure how this can be managed in a meta-analysis; the current study has used only means and SD's.

HC: I agree, including skewed data in meta-analyses is difficult. One study that was included in the meta-analysis reported that baseline values were not normally distributed. However, only post-intervention data were used in our meta-analysis. We have run a formal statistical test on the data (according to the recommendations of the Cochrane Collaboration) and this test clearly indicated that the data were not likely to be skewed. We therefore decided to leave the respective data in the analysis. This has been added in the methods and results sections.

2. It will be difficult for a clinician to understand how the meta-analysis found no effects on symptoms when all the 4 studies included have reported positive results, particularly in negative symptoms and socio-occupational functioning.

HC: There were actually no significant group differences in the study by Visceglia. The study by Behere did not report any group comparisons. While within-group comparisons are no valid outcomes for randomized trials, both studies reported positive within-group comparisons in their abstracts. Therefore, they might mislead clinicians to believe that there were significant group differences. The study of Xie only assessed quality of life. Thus, the study by Varambally is the only one that reported significant group comparisons on symptoms or functioning and these were based on differences in proportions of patients who
obtained improvement rather than group differences in means. It might therefore appear to the clinician that the results of this meta-analysis contradict those of individual studies. This is, however, an artifact of different statistics used (within-group vs. between group statistics; parametrical vs. non-parametrical tests).

3. The study refers to ‘well-being’ when the actual scales being measured are those of ‘quality of life’. I am not sure that these terms are interchangeable and that they refer to the same construct.

HC: I agree that while the terms are often used interchangeable, they might not be totally identical. I have therefore changed the inclusion criteria to “quality of life or well-being”. As all studies in the meta-analysis actually assessed quality of life, this term is used throughout results and discussion.

4. The authors make these comments/ conclusions in the discussion –
   - “The primary limitation of this review is the small total number of eligible RCTs (page 15, para 3) - “As this review could not find any effects of yoga for schizophrenia patients that were robust against bias, it seems questionable whether further research on this topic is warranted (page 15, para 4). - “Future studies should ensure rigorous methodology and reporting, mainly adequate sample size, adequate randomization, allocation concealment, intention-to treat analysis, and blinding of at least outcome assessors' (page 15, para 4). The above comments seem contradictory to each other. I disagree with these second comment/ conclusion as it seems to me that the implication of the first comment is precisely that more research is needed on this topic!

HC: The paragraph has been changed to improve congruency.

Reply to reviewer 3:

1. The authors provide an interesting overview of the literature on yoga in schizophrenia. They provide systematic review and meta-analytic evidence to suggest that there is insufficient evidence to recommend yoga as a routine intervention in schizophrenia. This runs contrary to Vancampfort et al's (2012) findings.

HC: Thanks a lot for your kind comments.

2. The major limitation of the paper as it stands is the application of meta-analysis to the data set. Individual meta-analyses are conducted on at most 3 studies, and in one occasion (Cognitive function) on only one study of n=119. The small number of studies, small samples and substantial heterogeneity of methodologies, measures, diagnostics etc. makes the resulting estimates derived from the meta-analysis highly unstable. Therefore, it is difficult to meaningfully draw any conclusions from the meta-analysis, thus the advantage of including meta-analysis in addition to a systematic review is lost. Similarly, sub-group and sensitivity analyses are compromised by the small number of studies.

HC: I agree that the meta-analyses are based on a small amount of studies. However, as only 2 studies reported parametrical tests of group differences, the evidence for positive effects might be overestimated when the studies are analyzed in a more qualitative manner. Two studies reported positive within-group results that are interesting but do not substitute for missing or insignificant between-group differences. Using a meta-analytic approach, we tried to compensate for the inconclusive results that were presented in the individual studies.
3. The authors could also use a systematic review format to discuss theoretical links between yoga and other non-pharmacological interventions that are under evaluation for schizophrenia. For instance, mindfulness based techniques would be relevant here.

4. HC: Thank you for this valuable suggestion. While a systematic review on mindfulness-based interventions seems beyond the scope of this work (and might be premature), we have added references regarding mindfulness-based interventions in the discussion section.

Reply to reviewer 4:

1. Authors have included at least three studies which were included in earlier review by Vancampfort et al.2012. The earlier reviewers have concluded that yoga may be beneficial. How the new results of this review have questioned the effect of yoga? Is it only statistical twist?

HC: Summarizing results in a qualitative systematic review relies on the original reports. As I have pointed out above and in the article, only 2 out of 3 studies that were included in the review of Vancampfort et al. reported group comparisons. Therefore, using a meta-analytic approach can lead to different results. Moreover, different systematic reviews often use different inclusion criteria and different outcomes of interest that might also explain differences in results. Furthermore, additional data from Varambally and the totally new study by Xie have added additional information.

2. Yoga duration is a very important variable. Was it controlled or taken as covariate.

HC: We have now included an additional subgroup analysis to compare studies that used interventions that were shorter than 12 weeks (a usual length of yoga interventions in the USA or Europe) with those with longer yoga interventions.

3. Cognitive outcome is measured by PANSS which is not a robust measure of cognition.

HC: The PANSS has a cognitive factor in some factor analyses and does not have one in others. Therefore, we have followed your advice and deleted the PANSS cognitive factor from possible outcome measures. No study actually used the PANSS for cognitive outcomes.

Reply to reviewer 5:

1. The manuscript titled “Yoga for Schizophrenia: A Systematic Review and Meta-Analysis” by Cramer, Lauche ,Klose, Langhorst, and Dobos offers a meta-analysis of the effectiveness of yoga practice for persons with schizophrenia. This appears to be a well planned and rigorous analysis. There are several noteworthy strengths evident in the study. The authors clearly defined the inclusionary criteria for studies to be included in the meta-analysis and also focused on identifying biases in the studies that were under review. The result however was that only 4 studies met the author’s guidelines for inclusion in the analysis. This provides a rather small sample of studies from which to determine the effectiveness and safety of yoga as an intervention for psychosis. The authors acknowledge this as a limitation of the study and despite finding only moderate evidence for short term effects of yoga on wellbeing resist making recommendations for or against the use of yoga as an intervention. The manuscript is scientifically sound and appears ready for publication.
HC: Thanks a lot. We really appreciated your kind comments.

Reply to reviewer 6:

1. I was wondering if the authors included this article that is attached in their meta-analysis.

HC: I apologize but I did not receive any article. We have conducted a systematic review and hope that we have located all available randomized trials that meet our inclusion criteria.

2. I am unclear that I understand their methods that they used to re-analyze the data they culled from a number of studies.

HC: Standard procedures for meta-analyses were used according to PRISMA guidelines and the recommendations of the Cochrane Collaboration.

3. I am personally disappointed that their conclusions are not more positive, because exercise of any type is proven to be helpful for schizophrenia.

HC: Unfortunately, we had no influence on the available evidence.

4. I wonder if the variety of yoga practices offered was one of the reasons that the results in the meta-analysis may not be valid as there is a bit of comparing apples to oranges when yoga practices have such variability.

HC: I don’t think that the yoga programs were overly heterogeneous. As can be seen in table 1, all included studies used postures, breathing techniques, and relaxation. No study used meditation. The studies differed in length but we now included a subgroup analysis to compare programs with different lengths (8 weeks vs. 4 months). Two programs actually seemed to be totally identical (the studies by Behere and Duraiswamy).

5. The interpretation should discuss the relevance of all the results in an unbiased manner. Are the interpretations overly positive or negative? Interpretation seems overly negative.

HC: The available evidence unfortunately does not allow drawing more positive conclusions. We have changed the “Implications for future research” section so that it does sound a bit less negative.

Once again, we would like to thank the editor and the reviewers for their efforts, encouraging comments and constructive criticism.

Sincerely yours,

Holger Cramer

(on behalf of the authors)