Author's response to reviews

Title: Effects of Exercise on Depressive Symptoms in Adults with Arthritis and Other Rheumatic Disease: A Systematic Review of Meta-analyses

Authors:

George A Kelley (gkelley@hsc.wvu.edu)
Kristi S Kelley (kskelley@hsc.wvu.edu)

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Author's response to reviews: see over
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Dr. Rachael Gooberman-Hill  
Associate Editor  
BMC Musculoskeletal Disorders  

Dear Dr. Gooberman-Hill:

Please find uploaded revised manuscript #9754916631127425 titled "Effects of Exercise on Depressive Symptoms in Adults with Arthritis and Other Rheumatic Disease: A Systematic Review of Meta-analyses" for publication consideration in BMC Musculoskeletal Disorders. We believe that we have addressed both reviewers’ helpful and important comments and that the study is now suitable for publication in BMC Musculoskeletal Disorders because of its quality, broad interest and special importance. Specifically, the nationally and internationally recognized research team addresses a critical problem, that is, the importance of exercise for reducing depressive symptoms in adults with arthritis and other rheumatic disease. Specifically, this National Institutes of Health (NIH) R01 funded study provides both statistically significant and practically important information showing that exercise reduces depressive symptoms in adults. We accomplish this by providing a first-ever systematic review of previous meta-analyses on this topic, an emerging and critical approach for addressing important health issues. Immediately following this cover letter you will find our point-by-point responses to each of the reviewer’s comments. Per journal recommendations, changes appear using the track changes function in Microsoft Word.

We acknowledge that (1) the manuscript is being submitted only to BMC Musculoskeletal Disorders and will not be submitted elsewhere while under consideration, (2) that it has not been published elsewhere, (3) should it be published in BMC Musculoskeletal Disorders it will not be published elsewhere, either in similar form or verbatim, (4) that all authors are responsible for the reported research, (5) that all authors have participated in the concept and design; analysis and interpretation of data; drafting or revising of the manuscript, and that they have approved the manuscript as submitted, and (6) that none of the authors have any affiliation, financial agreement, or other involvement with any company whose product figures prominently in the submitted manuscript.

Thank you and we look forward to your prompt handling of this manuscript.

Sincerely yours,

George A. Kelley, DA, FACSM  
Professor/Director, Meta-Analytic Research Group  
School of Public Health  
Department of Biostatistics  
PO Box 9190  
Robert C. Byrd Health Sciences Center  
West Virginia University  
Morgantown, WV 26506-9190  
Office Phone: 304-293-6279  
Lab Phone: 304-293-6280  
Fax: 304-293-5891  
E-mail: gkelley@hsc.wvu.edu  

Phone: 304-293-2502  
Fax: 304-293-6685
Responses to Reviewer One Comments (Dr. Moncada-Jimenez)

Thanks so much for the time and effort you devoted to reviewing our work. You provided both editorial and content comments that we believe has improved this manuscript. We also want to apologize for the editorial errors we made and of which you appropriately identified.

In order to make it easier for you to review, we have copied your comments below, boldfaced, with our responses after each one, including the location of our revisions, also boldfaced, in the revised document. Prior to converting to pdf format, changes in the revised manuscript were accomplished using the track changes function in Microsoft Word 2010.

Minor Essential Revisions:

C1. Page 5, line 95 to 98: While somewhat arbitrary...

Can you provide evidence to support this sentence showing that 4 weeks of exercise can change depressive symptoms?

R1. Great observation. Both you and the other reviewer commented on this. Unfortunately, we know of no research to support a definitive cut point here for this outcome. Thus, in the absence of research, we did what is typically done, make an educated guess.

The major thing that we were trying to avoid was acute studies, defined as those in which participants would participate in an exercise session or two and then immediately after the session be assessed for depressive symptoms. We also didn’t want to simply use a term such as ‘chronic exercise’ without including some type of cut point. However, based on you and the other reviewer’s similar concern, we have gone back and removed the 4 week cut point and now include a brief statement about excluding acute studies as described above. Please see page 5, lines 97-102 for these changes.

C2. Page 8, line 161 and 162: This is a minor mistake in the citation format. Please correct accordingly.

R2. Thank you. There is no excuse for the mistake we made here. However, this reference is now omitted since we have left out the information about citations based on the concerns of the other reviewer.

C3. Page 13, line 293: ...meeting the American College of Sports Medicine (ACSM)
The abbreviation was previously used in page 9 (line 188) and page 12 (lines 269 and 271). I think you do not need to spell all the name out. Use abbreviation again.

R3. Thank you again. We have now corrected this. Please see page 14, line 308 for this correction.

C4. Page 14, line 303: ...as well eight studies... ...as well as eight studies...

R4. Good. Thanks. Please see page 14, line 318 for this correction.

C5. Page 14, line 304 to 306: The authors reported no statistically significant differences...

It seems to me that in line 306 a significant difference is reported (p = 0.05). Please verify.
R3. Good observation. However, this is actually accurate as we have written it here. The original authors reported that the difference was not statistically significant because the p value was 0.05. There are probably one or two reasons that they did this. First, they were using a p value of less than 0.05 versus less than or equal to 0.05 for statistical significance. A second and more appropriate reason may have been because the 95% confidence intervals included zero (0).

**Discretionary Revisions:**

C1. Based on your results, it seems to me that your findings are only true for female patients and not for adults (in general) with fibromyalgia. In other words, exercise reduces depression symptoms in female adults with fibromyalgia. Would you agree with me?

R1. Excellent point. Given that we were approaching this from a public health perspective, we felt comfortable generalizing our results to males since some were included and we could think of no reason(s) why the responses to exercise would be different between males and females. Regardless, you raised an important point and we now include information about our decision and how it may not have been the correct one, as you have suggested here. Please see page 19, lines 422-427 as well as page 22, lines 490-492 for these additions.

**END OF RESPONSES TO REVIEWER ONE COMMENTS**
Responses to Reviewer Two Comments (Dr. Herring)

Thank you for taking the time to review this manuscript. Based on your comments, we believe that the manuscript has been improved substantially.

In order to make it easier for you to review, we have copied your comments below, boldfaced, with our responses after each one, including the location of our revisions, also boldfaced, in the revised document. Prior to converting to pdf format, changes in the revised manuscript were accomplished using the track changes function in Microsoft Word 2010. References appear at the end of our responses to your comments.

General Comments:

This article detailed the results of a systematic review of previous meta-analyses of exercise effects on depressive symptoms among individuals with arthritis and/or other rheumatic disease(s). The authors described their evaluation and summarization of three previous meta-analyses of exercise effects on depressive symptoms among adults with fibromyalgia, concluding that exercise improves depressive symptoms in adults with fibromyalgia and that there is a continued need to meta-analytic work in this area. The purpose of this research is well-defined, the methods are well-articulated and appropriate, and the research is of interest to the field. However, there limitations regarding design and rationale that should be addressed prior to publication. Specific comments are provided below.

Thank you for the positive feedback. It is greatly appreciated. Below we address your concerns and are hopeful that our responses are acceptable to you.

Major Compulsory Revisions:

C1. There are potential design and rationale issues that need clarification and revision, particularly justification regarding the included meta-analyses. The individual reviews appear to inherently differ with regard to inclusion criteria for trials included in the individual reviews. It appears that the Hauser et al., 2010 review did not entirely focus on randomized controlled trials, detailing on page 6 of the published manuscript that control groups in more than 10 studies received another active therapy. Clarification is needed regarding the selection and inclusion of these data.

R1a. Great observation with respect to Hauser et al. meta-analysis [1]. Let’s discuss.

A review of additional file 2, a table of study characteristics, and additional file 6, a forest plot of results for the depressive symptoms outcome, shows 18 [2-19] studies representing 19 comparisons in the Hauser et al. meta-analysis [1]. There were 19 comparisons because one study included more than one exercise intervention group [15]. Of the 18 studies, seven included what the authors described in their additional file 6 as an ‘active control’ and in their manuscript on page 6, column 2, paragraph 3, lines 2-5 as an ‘active therapy’ group [3,4,7,11,13,14,18]. A closer ‘look under the hood’ reveals that groups described by the authors as ‘active therapy’ or ‘active control’ included (1) unsupervised participation in a therapeutic pool with no exercise [3], (2) muscle strengthening [4], (3) three educational meetings [7], (4) hot packs 2 times per week for 30 minutes [11] (5) cognitive behavioral therapy 1 time per week for 2.5 hours [13], (6) an education program delivered 7 times for 120 minutes and (7) supervised stretching 3 times per week for 45 minutes. Our initial thinking was that with the exception of muscle strengthening [4] all other interventions could have just as easily...
been justified as an attention control and/or sham intervention. For example, the Valim et al study that included stretching considered it as a form of exercise and was comparing it against walking exercise [18]. In contrast and while not included in the Hauser et al meta-analysis [1], a randomized controlled exercise intervention study of tai chi by Wang et al, in the New England Journal of Medicine and in which depressive symptoms was an outcome considered stretching as a control group [20]. The major point here is that different researchers will often define what constitutes a control group differently, akin to how different researchers will have very different definitions of what constitutes physically inactive subjects. So, how did we handle all of this? Since all of the data were available in additional file 6, we made a post hoc decision, prior to your review, to examine the results of our originally reported influence analysis when the muscle strengthening 'active control group' was deleted from the overall model [4]. Specifically, the standardized mean difference was -0.24, 95% confidence interval, -0.39 to -0.09, z = 3.13, p = 0.003. As can be seen, these results are similar to our overall findings that we report in Table 2 of our manuscript (-0.32, 95% confidence interval, -0.53 to -0.12, z = 3.13, p = 0.002). However, your concern about the active control groups in general is warranted. Therefore, we went back and conducted a two-group, post hoc, mixed-effects comparison of depressive symptoms results when data were partitioned according to ‘active control’ versus ‘other’ (usual care and attention control/placebo) groups. No statistically significant difference was observed between the two groups (Qb = 1.13, p = 0.29). Given these findings, we believe that the inclusion of the results as originally reported by Hauser et al. [1] is warranted. We now include this post hoc analysis in our revised manuscript. Please see page 10, lines 227-228 and page 11, lines 229-231 for a description of the test as well as page 14, lines 303-305 for a description of the results.

Given the goals for conducting a systematic review of previous systematic reviews, with or without meta-analysis, it has been suggested by others that one should expect to be broader in one’s inclusion criteria [21].

More importantly, the inclusion of Herring et al., 2012 in the current review seems inappropriate and potentially misleading to the readership. The Herring et al., 2012 systematic review was not focused on exercise effects on depressive symptoms among only adults with fibromyalgia. Although the authors of the current review provide a brief statement to this point in the first paragraph of page 11 (i.e., “A third meta-analysis included exercise training (aerobic, strength or both) in adults with a variety of chronic illnesses but of which fibromyalgia results were reported separately [41].”) and a footnote of Table 2, the inclusion of and focus on an aggregated mean effect (#) and 95% confidence interval for effects (k=32) derived from exercise studies of patients with fibromyalgia taken from a large systematic review that included many disease categories, not simply fibromyalgia, seems inappropriate, inherently different from the other two full meta-analyses included, and could mislead readers to believe that the meta-analysis conducted by Herring and colleagues was a small analysis of effects among fibromyalgia patients that was of questionable study quality.

For example, the authors make numerous criticisms of the included meta-analyses which would not apply to the full review by Herring and colleagues. In the first paragraph of page 13, the authors state that “insufficient data were reported or available to calculate small-study effects for the Herring et al. [41] study”, but the overall review by Herring and colleagues did include measures of publication bias (i.e., fail-safe number of effects, funnel plot). In the first paragraph of page 18 (7th implication for research), the authors state that none of the meta-analyses reported NNT with respect to depressive symptoms, though a NNT of 6 was reported for the full sample of chronically-ill patients examined in the full Herring et al. review. In the second paragraph of page 18 (8th implication for research) the authors also state that future meta-analyses should try to identify sources of heterogeneity, but a meta-regression analysis was conducted to examine moderators of exercise effects on depressive
symptoms among patients in the full meta-analysis conducted by Herring and colleagues. Additional rationale regarding the inclusion of the Herring et al. review and more explicit information regarding the nature of the included effects being but one disease category in a larger review need to be provided.

In addition, in the first paragraph of the Discussion on page 14 and again in the third paragraph on page 17 (6th implication for research), the authors highlight that no meta-analysis on exercise and depressive symptoms in adults with osteoarthritis, rheumatoid arthritis, or systemic lupus erythematos had been conducted. However, 8 additional studies included in the pain conditions category of the review by Herring and colleagues focused on patients with arthritis or other rheumatic diseases. Is there a strong rationale for the inclusion of effects from the Herring et al. review that were derived from studies of fibromyalgia patients but not from patients with other rheumatic diseases?

R1b. Good points. Based on these important observations, we have deleted the Herring et al. [22] meta-analysis from our revised manuscript. Our original thought was to include the results from this nice meta-analysis and we thought we had done an adequate job of pointing out that the fibromyalgia results were part of a much larger study. However, we agree that the inclusion of this meta-analysis, including our evaluation of such, is probably not appropriate and could be potentially misleading. Please see the entire manuscript for this change as it has been deleted from all relevant areas. In particular, we report this post hoc decision on page 11, lines 239-242. Also, with respect to your query above, we initially included the fibromyalgia results in the study by Herring at al. [22] but did not consider the additional arthritis-related studies included in the pain condition category because they were not reported specific to disease type (rheumatoid arthritis, osteoarthritis, etc.).

C2. Though well-written, the manuscript can be shortened and streamlined. The methods, particularly the Data Synthesis section, seem potentially laborious to the reader. There is a need to describe the methodology employed, but the detail, especially regarding theoretical underpinnings of certain methodology, seems unnecessary.

R2. As suggested, we have deleted selected information from the Data Synthesis section. However, in order to address your first comment above (see previous section C1) regarding the Hauser et al. meta-analysis [1], a small amount of information needed to be added. Please see page 8, lines 178-183, page 9, line 184, as well as page 9, lines 201 to 205 for these deletions.

C3. The third criterion for study eligibility (page 4) states that exercise interventions lasting an average of at least 4 weeks were required for inclusion. As a rationale for this, the authors state in the first paragraph of page 5 that “while somewhat arbitrary, 4 weeks was chosen as the minimum length of exercise since one should expect some type of change in depressive symptoms during this period of time if the intervention truly has an effect.” Although the effects of pharmacotherapy are most often realized between 4-12 weeks, the rationale for the minimum exercise duration does not seem sufficient. Was a minimum of 4 weeks chosen a priori? Were any interventions excluded because of exercise interventions less than 4 weeks? Given the growing body of evidence regarding the importance of exercise dose and volume, it seems particularly arbitrary to select on length in weeks alone without additional clarification. For example, is there a strong rationale for including a 4-week exercise intervention in which participants exercise three times per week for 30 minutes per session at 65% HRR but excluding a 3-week exercise intervention in which participants exercise three times per week for 40 minutes per session at 65% HRR?
R3. Excellent. Both you and the other reviewer commented on this. Unfortunately, we know of no research to support a definitive cut point here for this outcome. Thus, in the absence of research, we did what is typically done, make an educated guess.

The major thing that we were trying to avoid was acute studies, defined as those in which participants would participate in an exercise session or two and then immediately after the session be assessed for depressive symptoms. We also didn’t want to simply use a term such as ‘chronic exercise’ without including some type of cut point. However, based on your comment we have gone back and removed our a priori 4 week cut point and now include a brief statement about excluding acute studies as described above. **Please see page 5, lines 97-102 for these changes.** Also, no exercise interventions were excluded because they were less than 4 weeks.

We appreciate your comment about dose-response as this was a major area of focus when the first author served as a consultant on the 2008 Physical Activity Guidelines for Americans. As you know, six years later, this continues to be a hot area. Unfortunately, it has been challenging for us to look at this with our own original meta-analytic work given missing data for different variables from different studies as well as other issues surrounding such.

**Minor Essential Revisions:**

C1. Using total citations and average number of citations per year seems arbitrary and biased toward more recent meta-analyses, particularly since the Busch et al. review was the first Cochrane collaboration review in the area of exercise and fibromyalgia.

C2. If the citation indices are retained, the total number of citations for each meta-analysis should be updated in the first paragraph on page 12.

R1. For both C1 and C2 comments above, we have deleted all information regarding citations in our revised manuscript. **Please see page 8, lines 162-166 as well as page 17, lines 375-379 for these deletions.**

One note – We agree that simply listing the total number of citations could be biased. This is why we adjusted these findings by year. We know of no better way to present this information other than to adjust results by year.

Reference List


END OF RESPONSES TO REVIEWER TWO COMMENTS