PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Community-Deliverable Exercise and Anxiety in Adults with Arthritis and other Rheumatic Diseases: A Systematic Review with Meta-Analysis of Randomized Controlled Trials
AUTHORS	Kelley, George; Kelley, Kristi; Callahan, Leigh F

VERSION 1 – REVIEW

REVIEWER	Suhail Doi Australian National University Australia
REVIEW RETURNED	01-Sep-2017

GENERAL COMMENTS	The authors have conducted a comprehensive review and analysis of community deliverable exercise for reduction of anxiety in AORD. As methods reviewer I have no concerns regarding the methodological approach and indeed the authors are to be commended for selecting the most robust approach to both synthesis and meta-regression. It is quite common for researchers to apply the most commonly available tools for synthesis without considering suitability for purpose. In this paper the authors have considered model selection and have computed effect estimates after adequate consideration of the requirements for variance estimates. The only minor comment is that the Forest plot can be rendered better by truncating the CI's, increasing spacing between studies and increasing the font size

REVIEWER	Charles F. Reynolds III, M.D. University of Pittsburgh School of Medicine and School of Public Health
REVIEW RETURNED	03-Sep-2017

GENERAL COMMENTS	Thank you for a well-written manuscript of considerable methodological interest. I found the paper interesting to read as a rigorous exercise in meta-analysis and systematic review. I am less confident, however, about its implications and utility for clinical practice. It is this lack of certainty about true clinical relevance (and confidence in clinical implications) that my comments are intended to address.

	Study quality appears to have been quite variable over all and with unclear risk of bias in many studies, arising from lack of clarity about randomization, allocation concealment, selective reporting, and high dropout rates. As well, effect size estimates were influenced by year of publication, with higher estimates in reduction of anxiety appearing in earlier, less rigorously conducted studies. The clinical heterogeneity of AORD's studied also gives rise to uncertainty about how truly applicable your inferences are to different disorder groups and at the level of the individual patient. For example, are there specific patient characteristics that might moderate effects of exercise intervention. Your rationale for focusing on anxiety as your primary outcome is not convincing. Why is it important in the context of AORD to study anxiety specifically, as opposed to pain, depression, sleep quality or functional impairment? Granted that rates of anxiety are high in AORD, but why does this matter? Does anxiety effect treatment adherence or lifestyle choices? Anxiety interacts with other sources of suffering in AORD, such as pain and depression. It is difficult to interpret changes in anxiety severity without also understanding how other facets of suffering change. In addition, did the studies in question examine exposure to psychotropic and analgesic medications before and during the clinical trials? Did they address the issue of pharmacological parity between study arms? Anxiety as a construct is heterogeneous (generalized, panic, social, etc): there are many clinical manifestations expressed variously as psychological and somatic symptoms, as well as at a syndromal (disorder-specific) level. It is not clear how and at one level anxiety was measured across studies. The overall effect size and NNT for anxiety appeared small to modest. How can we know that this was a difference that truly made a difference or one that should inform clinical practice? It wasn't clear how you got to specific recommendations re: dose and type of exercise, especially given the clinical heterogeneity of types of AORD addressed in the 14 studies and the lack of clarity concerning risk of bias. Can you really be confident about your recommendations as having a solid empirical basis? In your discussion of recommendations for future research, which I liked, would you consider group exercise formats, which provide further opportunity for social contact and learning? This facet of exercise could be particularly relevant to racial and ethnic minorities. I would also have liked a discussion of what a truly strong clinically useful study would look like, based upon what you learned from conducting a thorough-going methodologic review of extant studies Thank you.

REVIEWER	Cornelia van den Ende Sint Maartenskliniek, Nijmegen, The Netherlands
REVIEW RETURNED	15-Sep-2017

GENERAL COMMENTS	The paper is well written and well structured. The main purpose of this meta-analysis was to examine the effects of exercise on anxiety in patients with various rheumatic disorders. Secondary outcomes were, amongst others, measures of pain and functioning. I would like to compliment authors with the novel and in-depth approach of analyzing results and the clarity of presentation. I have the following comments Introduction: The relevance of this work should be better explained. For their argumentation authors refer multiple times to their own previous work, but a statement as “the effects are not known” is not sufficient to justify research. Please make clear why you hypothesize that exercise for rheumatic diseases could have positive effect on anxiety? Are there any literature findings on other chronic diseases with regard of this topic? In line with this: please, justify why this meta-analysis was restricted to community delivered exercise? The patient populations in this meta-analysis consisted of three different groups: patients with osteoarthritis, rheumatoid arthritis and fibromyalgia. A clear argumentation why it is justifiable to combine the effects of exercise of these three groups is lacking. On the other hand, why are data of exercise interventions for patients with low back pain not included? Discussion: I do not agree with the authors that significant statistical findings are a strength of this study (or any other study).

REVIEWER	Robert Boyce University of North Carolina Wilmington
REVIEW RETURNED	18-Sep-2017

GENERAL COMMENTS	Expertly done with one question. Your writing is clear and the documentation is exceptional. Just one small item for clarity. Re look at wording in abstract of sentence starting at line 41 with Overall.....See if moving "exercise minus control to end of sentence makes it more clear. Outstanding work. There is no doubt that this manuscript is well written and should be published in your journal. I will be positive in my review as this is one of the most complete works of its kind and brings a major message to the readers through a comprehensive assessment of exercise on anxiety. This is in the light that arthritis and other rheumatic diseases are prevalent and are expected to increase, thus bring with it higher medical cost and suffering. The authors expressed the strength of this paper and I fully agree. I found the literature analysis to be comprehensive with nearly 400 studies from numerous countries. Each study was taken through a rigorous quality process of selection that still left 14 substantial studies with over 30 groups and 926 enrollees.

	The meta-analytical procedure was followed in detail and explanations were given at each step. The tables, figures and supplemental materials were clear and well developed and enhanced the understanding of the research. The authors are to be commended on their use of the new and innovative inverse-heterogeneity techniques in the pooling of the data. They creatively expanded the review into secondary findings that enhanced the scope of the outcomes such as inference that exercise could have the potential to improve multiple physiological and psychological outcomes. The completeness of this work and the review has set this paper in a class that will allow others to more precisely target needed areas for future research. The paper is clear, comprehensive, well documented, and most definitely is a work where the outcomes can be put into practice. Publish this paper!

VERSION 1 – AUTHOR RESPONSE

Responses to Reviewer 1 (Dr. Suhail Doi)
Institution and Country: Australian National University, Australia
Thank you for taking the time and effort to review our work. To make it easier for you, we have copied your comments below, designated as “C”, with our responses after each one, designated as “R”. Line numbers refer to those that we have inserted into the manuscript and which correspond exactly with each line. Additions are highlighted in red font, although I’m not sure you’ll be able to see this.

C1. The authors have conducted a comprehensive review and analysis of community deliverable exercise for reduction of anxiety in AORD. As methods reviewer I have no concerns regarding the methodological approach and indeed the authors are to be commended for selecting the most robust approach to both synthesis and meta-regression. It is quite common for researchers to apply the most commonly available tools for synthesis without considering suitability for purpose. In this paper the authors have considered model selection and have computed effect estimates after adequate consideration of the requirements for variance estimates.

R1. Thank you very much for the positive feedback. It is greatly appreciated.

C2. The only minor comment is that the Forest plot can be rendered better by truncating the CI’s, increasing spacing between studies and increasing the font size.

R2. Agreed. Thank you. Please see the revised forest plot (Figure 3).

Responses to Reviewer 2 (Dr. Charles F. Reynolds III)
Institution and Country: University of Pittsburgh School of Medicine and School of Public Health

Thank you for taking the time and effort to conduct a thorough review, especially the clinical aspects, of our NIH funded study (2 RO1AR061346) that was scored at the second percentile. We appreciate the time and effort you took to provide this non-compensatory service and believe the clinical aspects of this work are greatly improved because of your constructive criticism. To make it easier for you to locate, we have copied your comments below, designated as “C”, with our responses after each one, designated as “R”. Line numbers refer to those that we have inserted into the manuscript and which correspond exactly with each line. Additions are highlighted in red font, although I’m not sure you’ll be able to see this.

Finally, we would like to let you know that the published protocol for this study referenced on line 129 is the same protocol that was published in BMJ Open (see: Kelley GA, Kelley KS, Callahan LF. Community-deliverable exercise and anxiety in adults with arthritis and other rheumatic diseases: a protocol for a systematic review and meta-analysis of randomised controlled trials. BMJ Open 2017;7(3):e014957). However, we understood that the publication of a protocol does not ensure the publication of the actual study.

C1. Thank you for a well-written manuscript of considerable methodological interest. I found the paper interesting to read as a rigorous exercise in meta-analysis and systematic review. I am less confident, however, about its implications and utility for clinical practice. It is this lack of certainty about true clinical relevance (and confidence in clinical implications) that my comments are intended to address.

R1. Thank you for the positive feedback regarding the methodological aspects of our work. It is greatly appreciated. We believe that our responses to your comments below adequately address your concerns about the utility for clinical practice and note that the focus of this work was on exercise programs conducted in any environment but adapted for use in the community. However, we do understand that the division between clinic and community is not as straight-forward as it sounds.

C2. Study quality appears to have been quite variable overall and with unclear risk of bias in many studies, arising from lack of clarity about randomization, allocation concealment, selective reporting, and high dropout rates. As well, effect size estimates were influenced by year of publication, with higher estimates in reduction of anxiety appearing in earlier, less rigorously conducted studies. The clinical heterogeneity of AORD's studied also gives rise to uncertainty about how truly applicable your inferences are to different disorder groups and at the level of the individual patient. For example, are there specific patient characteristics that might moderate effects of exercise intervention?

R2. Great comments. Thank you. Like any study, especially a systematic review with meta-analysis, subjective decisions need to be made. Broadly, a primary purpose of meta-analysis is to reach general conclusions about a body of research and to combine studies that are not exactly the same (see: Glass GV, McGaw B, Smith ML. Meta-analysis in social research. Newbury Park, California: Sage, 1981.) Using this as the basis for decision-making as well as our overall results and the minimum risks associated with exercise, we believe that our inferences are acceptable but obviously not perfect as you appropriately point out. For example, if a group were developing guidelines for the treatment of anxiety in adults with AORD, it would seem plausible to us that a broad recommendation in favor of exercise for reducing anxiety in adults with AORD based on our findings would be appropriate given the numerous other benefits that can be derived from exercise as well as the low risk for adverse events. As you know, we wouldn’t want to withhold treatment if there is potential benefit and the risks are minimal. As for the clinical heterogeneity of AORD's, we have now included our justification for combining these different groups on lines 180-189 and 331-333. Also, if you look at Supplementary file 4 as well as lines 490-492, you will see that there was no statistically significant association between type of AORD and changes in anxiety. Regardless, and to help address your query, we now also report effect size data for each type of AORD. Please see lines 491-494. Finally, and with respect to effects at the participant level, we point out the potential limitation of ecological fallacy now on lines 765 to 767. Ideally, we would have liked to have conducted an individual participant data (IPD) meta-analysis so that we could look at patient and intervention characteristics at the level of the individual. Unfortunately, and probably of no surprise to you, we have had little success in obtaining de-identified IPD from investigators. As an example, please see the following article related to the topic of the current study (Kelley GA, Kelley KS. Retrieval of individual participant data for exercise meta-analyses may not be worth the time and effort. Biomed Research International 2016;2016(5059041):1-5). Ironically, there is actually a method to combine aggregate and IPD but we couldn’t retrieve the example IPD used by the very authors that created the model to verify their statistical method (see: Riley RD, Lambert PC, Staessen JA, et al.

Meta-analysis of continuous outcomes combining individual patient data and aggregate data. Stat Med 2008;27(11):1870-93). Finally, potential group-level patient characteristics that we studied, in which sufficient data were available, and in which we felt may moderate the effects of the exercise intervention, are shown in Supplementary file 4. Importantly, these are considered exploratory when conducting a meta-analysis.

C3. Your rationale for focusing on anxiety as your primary outcome is not convincing. Why is it important in the context of AORD to study anxiety specifically, as opposed to pain, depression, sleep quality or functional impairment? Granted that rates of anxiety are high in AORD, but why does this matter? Does anxiety effect treatment adherence or lifestyle choices? Anxiety interacts with other sources of suffering in AORD, such as pain and depression. It is difficult to interpret changes in anxiety severity without also understanding how other facets of suffering change. In addition, did the studies in question examine exposure to psychotropic and analgesic medications before and during the clinical trials? Did they address the issue of pharmacological parity between study arms?

R3. Based on your comments, it appears that we could have done a better job with these issues. While we agree that the other outcomes you mention are very important and may interact with anxiety, we included pain, physical function, etc. as secondary outcomes, but not primary outcomes because they have previously been examined as primary outcomes by ourselves as well as others (see for example: Kelley GA, Kelley KS, Hootman JM, et al. Effects of community-deliverable exercise on pain and physical function in adults with arthritis and other rheumatic diseases: A meta-analysis. Arthritis Care Res 2011;63(1):79-93; Conn VS, Hafdahl AR, Minor MA, et al. Physical activity interventions among adults with arthritis: meta-analysis of outcomes. Semin Arthritis Rheum 2008;37(5):307-16).) Thus, including these as primary outcomes, from our perspective, would be redundant, something that has recently been criticized by Ioannidis (see: Ioannidis JPA. The mass production of redundant, misleading, and conflicted systematic reviews and meta-analyses. Milbank Q 2016;94(5):485-514). In addition, to go back and treat these as primary outcomes would entail redoing the entire study since we limited our search to those studies that examined anxiety. This is not something we are in the position to do. Furthermore, we believe that anxiety is an important outcome to focus on in adults with AORD given that it has been recommended, as now described on lines 90-91, that health care providers screen people with AORD for anxiety. The former notwithstanding, and with respect to your comment about treatment adherence, we now provide additional rationale for why we think it's important to focus on anxiety as a primary outcome in the manner we have chosen (lines 87-90, 93-99,111-117). Based on your comments about potential interactions, we also went back and conducted meta-regression on changes in anxiety and our secondary outcomes, i.e., pain, depression, quality of life, VO2max (ml.kg-1.min-1) and muscular strength (see Supplementary file 4 and Table 5), modified our multiple regression model (Table 5) and have added text about this in the Discussion (see lines 654-658). Again however, these are considered exploratory analyses.

With respect to your comments about exposure to psychotropic and analgesic medications before and during the clinical trials as well as pharmacological parity between study arms - As pointed out in the original manuscript and now on lines 409-413 of the revised manuscript, nine of the 14 studies reported that one or more participants were taking some type of medication for their condition. However, you make a good point here as there was actually a lack of specific data on exposure to psychotropic and analgesic medications before and during the trial, including any changes, as well as data on pharmacological parity between study arms. Based on your comments, we have had added this information as well as a recommendation for the conduct and reporting of future research (see lines 413-416 and lines 692-695).

C4. Anxiety as a construct is heterogeneous (generalized, panic, social, etc): there are many clinical manifestations expressed variously as psychological and somatic symptoms, as well as at a syndromal (disorder-specific) level. It is not clear how and at one level anxiety was measured across studies.

R4. Thank you for the specificity here. Based on your comment, we now briefly address this with a focus on types of anxiety as defined by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders. Please see lines 695-702.

C5. The overall effect size and NNT for anxiety appeared small to modest. How can we know that this was a difference that truly made a difference or one that should inform clinical practice?

R5. While certainty is always difficult to establish, we now include specific information on how our results, i.e., magnitude of effect, NNT and percentile improvement, compare to a previous meta-analysis on the pharmacological treatment of generalized anxiety disorder (please see lines 736-740).

C6. It wasn't clear how you got to specific recommendations re: dose and type of exercise, especially given the clinical heterogeneity of types of AORD addressed in the 14 studies and the lack of clarity concerning risk of bias. Can you really be confident about your recommendations as having a solid empirical basis?

R6. Based on your comments, and as previously mentioned, we more clearly clarify our rationale (see lines 331-333), point out that there was no statistically significant relationship between changes in anxiety and types of AORD (see lines 490-492 and Supplementary file 4). In addition, we now caution our reader with respect to our suggestions (see lines 743-744 and lines 749-751).

C7. In your discussion of recommendations for future research, which I liked, would you consider group exercise formats, which provide further opportunity for social contact and learning? This facet of exercise could be particularly relevant to racial and ethnic minorities. I would also have liked a discussion of what a truly strong clinically useful study would look like, based upon what you learned from conducting a thorough-going methodologic review of extant studies.

R7. Thank you for the positive feedback regarding our recommendations for future research in the Discussion section of the manuscript. Per your other suggestions, we now include information about group exercise while being cognizant of the length of this manuscript (see lines 702-704). In addition, we now include additional information on what a strong clinically useful study might look like but try to do so with the understanding again that this is already a very long manuscript (see lines 705-728). In addition, and with a focus on clinical utility, we also include a suggestion regarding the conduct of a network meta-analysis (see lines 728-731).

Responses to Reviewer 3: Cornelia van den Ende
Institution and Country: Sint Maartenskliniek, Nijmegen, The Netherlands

Thank you Dr. van den Ende for taking the time and effort to review our work again. We understand that reviewing manuscripts takes considerable time and effort. As a reminder, the published protocol for this study that is referenced on line 129 is the same protocol that you accepted and was subsequently published in BMJ Open (see: Kelley GA, Kelley KS, Callahan LF. Community-deliverable exercise and anxiety in adults with arthritis and other rheumatic diseases: a protocol for a systematic review and meta-analysis of randomised controlled trials. BMJ Open 2017;7(3):e014957).

We have copied your comments below, designated as “C”, with our responses after each one, designated as “R”. Line numbers refer to those that we have inserted into the manuscript and which correspond exactly with each line. Additions are highlighted in red font, although I’m not sure you’ll be able to see this.

C1. The paper is well written and well structured. The main purpose of this meta-analysis was to examine the effects of exercise on anxiety in patients with various rheumatic disorders. Secondary outcomes were, amongst others, measures of pain and functioning. I would like to compliment authors with the novel and in-depth approach of analyzing results and the clarity of presentation.

R1. Thank you very much for the positive feedback regarding our work. It is always encouraging to receive positive affirmation from national and international experts in their field.

C2. Introduction: The relevance of this work should be better explained. For their argumentation authors refer multiple times to their own previous work, but a statement as “the effects are not known” is not sufficient to justify research. Please make clear why you hypothesize that exercise for rheumatic diseases could have positive effect on anxiety? Are there any literature findings on other chronic diseases with regard of this topic? In line with this: please, justify why this meta-analysis was restricted to community delivered exercise?

R2. Great suggestions. It appears that we did not do a good job of justifying the relevance of this work. We address all of your comments now. Please see lines 87-91, 93-99, and 111-117. In addition, if you look at our eligibility criteria on lines 154-155 you’ll see that we also included studies that may not have been community-based but could be adapted for use in the community. Interestingly, the nine studies in which data were available took place in other various settings, something that we now report on lines 658-663 of the Discussion. Finally, we did indeed cite our previous work because we felt it was relevant to the issue(s) being discussed. Along those lines, we would like to let you know that according to Research Gate, and as of October 12, 2017, the corresponding author’s h-index is the same whether self-citations are included in the calculation or not. To the best of our knowledge, that is not common.

C3. The patient populations in this meta-analysis consisted of three different groups: patients with osteoarthritis, rheumatoid arthritis and fibromyalgia. A clear argumentation why it is justifiable to combine the effects of exercise of these three groups is lacking. On the other hand, why are data of exercise interventions for patients with low back pain not included?

R3. Based on your comment, it again appears that we needed to do a better job explaining our rationale for combining all three types of AORD in the same systematic review with meta-analysis. We now provide an expanded rationale for such on lines 331-333. Also, if you look at Supplementary file 4 as well as lines 490-492 now, you will see that there was no statistically significant association between type of AORD and changes in anxiety as well as the overall effect sizes by type of AORD. We also report the effects sizes on lines 492 through 494. Finally, we did not include low back pain because it is not classified as a type of arthritis or other rheumatic disease (AORD) in the United States.

C4. Discussion: I do not agree with the authors that significant statistical findings are a strength of this study (or any other study).

R4. Yes, looking at this again, this makes sense to us. Per your comment, we have deleted this information from the Discussion. Please see lines 753-764.

Responses to Reviewer 4 (Dr. Robert Boyce)
Institution and Country: University of North Carolina Wilmington

Thank you for taking the time and effort to review our work. To make it easier for you, we have copied all your comments below, designated as “C”, with our responses after each one, designated as “R”. Line numbers refer to those that we have inserted into the manuscript and which correspond exactly with each line. Additions are highlighted in red font, although I’m not sure you’ll be able to see this.

C1. Expertly done with one question. Your writing is clear and the documentation is exceptional. Just one small item for clarity. Re look at wording in abstract of sentence starting at line 41 with Overall.....See if moving "exercise minus control to end of sentence makes it more clear. Outstanding work.

R1. Thank you for the positive feedback. As suggested, we have moved this information. Please see lines 41-42.

C2. There is no doubt that this manuscript is well written and should be published in your journal. I will be positive in my review as this is one of the most complete works of its kind and brings a major message to the readers through a comprehensive assessment of exercise on anxiety. This is in the light that arthritis and other rheumatic diseases are prevalent and are expected to increase, thus bring with it higher medical cost and suffering.

The authors expressed the strength of this paper and I fully agree. I found the literature analysis to be comprehensive with nearly 400 studies from numerous countries. Each study was taken through a rigorous quality process of selection that still left 14 substantial studies with over 30 groups and 926 enrollees.

The meta-analytical procedure was followed in detail and explanations were given at each step. The tables, figures and supplemental materials were clear and well developed and enhanced the understanding of the research. The authors are to be commended on their use of the new and innovative inverse-heterogeneity techniques in the pooling of the data. They creatively expanded the review into secondary findings that enhanced the scope of the outcomes such as inference that exercise could have the potential to improve multiple physiological and psychological outcomes. The completeness of this work and the review has set this paper in a class that will allow others to more precisely target needed areas for future research. The paper is clear, comprehensive, well documented, and most definitely is a work where the outcomes can be put into practice.

Publish this paper!

R2. Thank you again for the very positive feedback. We GREATLY appreciate your affirmation of our work.

VERSION 2 – REVIEW

REVIEWER	Suhail Doi Qatar University, Qatar
REVIEW RETURNED	11-Nov-2017

GENERAL COMMENTS	Thank you - I have no further comments

REVIEWER	Cornelia van den Ende Sint Maartenskliniek, the Netherlands
REVIEW RETURNED	20-Nov-2017

GENERAL COMMENTS	The authors responded thoroughly and satisfactorily to all comments; I have no additional comments.

REVIEWER	Robert Boyce University of North Carolina Wilmington
REVIEW RETURNED	06-Nov-2017

GENERAL COMMENTS	This is an excellent paper and the authors are to be commended for the detailed and state-of-the-art techniques. The review process was comprehensive and the suggestions by others have been most helpful. The author thoroughly and systematically addressed the reviewer suggestions making this even a better paper. This work needs to be published as it greatly moves our understanding forward in the field.