

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

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Abstract

Background: Anxiety is a major public health problem among adults with arthritis and other rheumatic disease (AORD). The purpose of this study was to conduct a systematic review of previous meta-analyses addressing the effects of exercise on anxiety in adults with osteoarthritis, rheumatoid arthritis, fibromyalgia or systemic lupus erythematosus.

Methods: The a priori inclusion criteria for this study were as follows: (1) previous systematic reviews that included a meta-analysis of randomized controlled trials or data reported separately for randomized controlled trials if the meta-analysis included other study designs, (2) adults 18 years of age and older with osteoarthritis, rheumatoid arthritis, fibromyalgia or systemic lupus erythematosus, as defined by the inclusion criteria of the authors of the original meta-analyses (3) aerobic and/or strength training intervention(s) lasting an average of at least 4 weeks, (4) studies published in any language and from any source, (5) anxiety as a primary outcome in the original meta-analysis. Potential studies to be included were identified by searching nine electronic databases and cross-referencing. Methodological quality was to be assessed using the AMSTAR Instrument. Random-effects models that included the standardized mean difference and 95% confidence intervals were planned, with non-overlapping 95% confidence intervals considered statistically significant. In addition, 95% prediction intervals, U3 index, number needed to treat and number of US people who could benefit were also planned.

Results: Of the 46 articles identified, none met the criteria for inclusion. Major reasons for exclusion included (1) inappropriate study design (32.9%), (2) inappropriate intervention (30.4%), (3) inappropriate population (25.3%), (4) inappropriate outcome (8.9%) and (5) inappropriate comparison (2.5%).

Conclusions: Given the prevalence of anxiety in adults with AORD and apparent plethora of randomized controlled trials on this topic, a need exists for a meta-analysis addressing the effects of exercise on anxiety in adults with AORD.

Keywords: Exercise; Physical activity; Physiotherapy; Systematic review; Meta-analysis; Arthritis; Osteoarthritis; Rheumatoid arthritis; Fibromyalgia; Lupus

Introduction

Arthritis is a major public health problem in the United States, with recent estimates placing the prevalence of doctor-diagnosed arthritis at 52.5 million or 22.7% of adults aged 18 years and older [1]. Of these, 22.7 million or 43.2% of adults with arthritis will experience an arthritis-attributable activity limitation during their lifetime. By 2030, the prevalence of doctor-diagnosed arthritis is expected to increase to 67.7 million (25% of the adult US population) while arthritis-attributable activity limitations will increase to 25 million adults [2]. Not surprisingly, the costs associated with arthritis are substantial, increasing from 86.2 to 128 billion dollars between 1997 and 2003 in the US [3]. Given the increasing prevalence of arthritis as well as increasing healthcare costs in general, a concomitant increase in the economic costs for those with arthritis is expected [2].

While fibromyalgia is a disease of soft tissue, not joint disease, the US Centers for Disease Control and Prevention consider

osteoarthritis, rheumatoid arthritis, fibromyalgia and systemic lupus erythematosus as four common types of arthritis [1]. Estimates regarding the prevalence of osteoarthritis, rheumatoid arthritis, fibromyalgia and systemic lupus erythematosus have been reported to be 27 million [4], 1.5 million [5] 5 million [4], and 161,000 [4], respectively.

A common problem among adults with arthritis is anxiety. For example, while it is well-recognized that depression is a common comorbidity among adults with arthritis, recent research suggests that anxiety is a much greater problem [6]. Murphy et al. found that the prevalence of anxiety among US adults was approximately twice as high as depression (30.5% versus 17.5%), with US population estimates of 11.5 million for anxiety versus 6.6 million for depression [6]. One potential treatment option for adults with arthritis and anxiety is exercise, a low-cost nonpharmacologic intervention that is available to the vast majority of the general population. Systematic reviews with meta-analysis, a quantitative approach for combining the results of different studies on the same topic [7], are considered by many to be the most relevant form of evidence for determining the efficacy and effectiveness of various treatments on selected outcomes [8,9]. However, with the proliferation of systematic reviews on the same

subject, it becomes difficult to make evidence-based decisions regarding the effects of various interventions such as exercise on selected outcomes. To illustrate, a recent systematic review identified 33 previous meta-analyses examining the effects of exercise on blood pressure [10]. Given the increasing number of systematic reviews, with or without meta-analysis on the same topic [7], there is now a need to systematically review these previous reviews for the purpose of providing decision makers and practitioners with the necessary information for making evidence-based decisions regarding the efficacy and effectiveness of various interventions such as exercise on selected outcomes, for example, anxiety, as well as provide researchers with direction for future research [8,11]. In addition, searching for systematic reviews of previous meta-analyses is important for identifying whether a new or first-time meta-analysis is necessary in a given topic area. Given the previous, the purpose of the current study was to conduct a systematic review of previous meta-analyses addressing the effects of exercise (aerobic, strength training, or both) on anxiety in adults with osteoarthritis, rheumatoid arthritis, fibromyalgia or systemic lupus erythematosus.

Methods

Study eligibility

The *a priori* inclusion criteria for this study were as follows: (1) previous systematic reviews that included a meta-analysis of randomized controlled trials or data reported separately for randomized controlled trials if the meta-analysis included other study designs, (2) adults 18 years of age and older with osteoarthritis, rheumatoid arthritis, fibromyalgia or systemic lupus erythematosus, as defined by the inclusion criteria of the authors of the original meta-analyses (3) aerobic and/or strength training intervention(s) lasting an average of at least 4 weeks, (4) studies published in any language and from any source, (5) anxiety as a primary outcome in the original meta-analysis and reported or calculable as the standardized mean difference (SMD). Studies were limited to meta-analyses of randomized controlled trials because they are the only way to control for unknown confounders [12,13]. Additionally, nonrandomized controlled trials tend towards overestimating the effects of treatment in healthcare interventions [12,13]. Studies were limited to those with osteoarthritis, rheumatoid arthritis, fibromyalgia or systemic lupus erythematosus given not only their prevalence, but also that these are the most common types of rheumatic diseases in which randomized controlled exercise intervention studies have been conducted. Since the purpose of the current study was to examine the chronic versus acute effects of exercise on anxiety, 4 weeks was chosen as the minimum length of exercise since one should expect some type of change in symptoms of anxiety during this period of time, assuming the exercise intervention had an effect. Given the different instruments used to assess anxiety, the inclusion of meta-analyses were limited to those in which the SMD was reported. Meta-analyses were limited to those in which anxiety was a primary outcome because secondary outcomes may be biased given that they are usually only included if the primary outcome of interest is available. Any studies not meeting all of the criteria above were excluded. Studies were excluded based on at least one of the following: (1) inappropriate population (for example, adults without arthritis), (2) inappropriate intervention (for example, diet), (3) inappropriate comparison (for example, exercise versus diet), (4) inappropriate outcome (for example, depression), (5) inappropriate study type (for example, systematic review without meta-analysis).

Data sources

Using the graphical-user interface for each database, the following electronic sources were searched from their inception forward: (1) PubMed (1966 to January 3, 2014), (2) Sport Discus (1975 to January 6, 2014), (3) Web of Science (1955 to January 6, 2014), (4) Scopus (1823 to January 5, 2014), (5) Proquest (1861 to January 6, 2014), (6) Cochrane Database of Systematic Reviews (1996 to January 6, 2014), (7) Physiotherapy Evidence Database (PEDRO) (1929 to January 12, 2014), (8) Database of Abstract of Reviews of Effects (DARE) (1991 to January 15, 2014), (9) Health Evidence Canada (HEC) (1985 to January 15, 2014). Scopus was included because it has been reported to provide coverage of Embase, a database that was not available to the authors [14]. While specific search strategies varied depending on the database searched, key terms or forms of key terms included exercise, physical activity, physical fitness, arthritis, osteoarthritis, rheumatoid arthritis, fibromyalgia, lupus, randomized, anxiety, systematic review and meta-analysis. Search strategies for each database can be found in Supplementary File 1. *A priori*, the plan was to determine the overall precision of the searches by dividing the number of studies included by the total number of studies screened [15]. It was then planned to calculate the number needed to read (NNR) as the inverse of the precision [15]. In addition to electronic database searches, cross-referencing for potentially eligible meta-analyses from any retrieved reviews was also conducted. All studies were stored in Reference Manager, version 12.0 [16].

Study selection

All studies were examined for potential inclusion by both authors, independent of each other. They then met and reviewed their selections for agreement. Any disagreements were resolved by consensus.

Data Abstraction

Prior to data abstraction, coding sheets were developed in Microsoft Excel 2010 [17]. The coding sheets could hold up to 201 items from each included meta-analysis. The *a priori* plan was to have both authors code all studies independent of each other. Upon completion of coding, all coding sheets were to be merged into one common codebook and reviewed by both authors for correctness. Disagreements would be resolved by consensus.

Methodological quality

The *a priori* plan was to use the Assessment of Multiple Systematic Reviews (AMSTAR) Instrument to determine the methodological quality of each included meta-analysis [18-21]. AMSTAR was chosen over other instruments [22,23] because of its reported inter-rater reliability ($k=0.70$), construct validity (intra-class correlation coefficient=0.84) and feasibility (average of 15 minutes per study to complete) [20]. The 11-item questionnaire is designed to elicit responses of "Yes", "No", "Can't Answer", or "Not Applicable". The response "Can't Answer" is chosen when an item is relevant but not described. The response "Not Applicable" is chosen when an item is not relevant (for example, meta-analysis of data not possible) [18-21]. For consistency when summing responses, the following question was modified from "Was the status of publication (i.e. grey literature) used as an inclusion criterion?" to "Was the status of publication (i.e. grey literature) as an inclusion criterion avoided?" In addition, the question regarding conflict of interest was considered to be adequately met if the authors of the systematic review provided a statement on conflict of interest versus the reporting of conflict of interest by both the

authors of the systematic review and all the original studies included in the meta-analysis. Both authors planned to assess methodological quality independent of each other and then meet to review every item for agreement. Disagreements were to be resolved by consensus. In addition to AMSTAR, impact was to be assessed by identifying the total number of times that each included meta-analysis was cited as well as the average number of citations per year. This was accomplished using version 4.4.6 of Publish or Perish (Google Scholar Citation, mechanism) [24].

Data synthesis

The *a priori* plan was to extract the main results from each meta-analysis [7] with a focus on random-effects models because they incorporate between-study heterogeneity into the model [25,26]. The SMD, 95% Confidence Intervals (CIs) and associated *z* and alpha value for *z* were also to be abstracted or calculated if sufficient data were available to do so. Standardized mean differences were to be classified as trivial (<0.20), small (0.20 to 0.49), medium (0.50 to 0.79) or large (≥ 0.80) [27]. Non-overlapping 95% CIs were considered to be statistically significant. The *Q* statistic, a measure of heterogeneity, was also planned to be extracted for each outcome with an alpha value ≤ 0.10 considered representing statistically significant heterogeneity [28].

Because of issues surrounding the power of the *Q* statistic, it was also planned to calculate the I^2 statistic if it was provided in the meta-analysis. If I^2 was not provided, it was to be calculated if sufficient data existed to do so [28]. Negative values of I^2 are set to zero (0) so that I^2 falls between 0% and 100% [28]. A value of 0% indicates no observed inconsistency while larger values indicate increasing inconsistency [28]. Values were considered to be representative of low (0 to 25%), moderate (25 to 50%), large (50 to 75%) or very large (>75%) inconsistency [28]. In addition to *Q* and I^2 , tau-squared (τ^2) was to be reported or calculated if sufficient data were available to do so. An *a priori* decision was made to not pool results from the different meta-analyses because of the expectation that many of the same studies would be included in the different meta-analyses, thus violating the assumption of independence.

Since it was assumed that none of the eligible meta-analyses would include 95% prediction intervals (PIs), these were to be calculated if the findings were statistically significant and the results from each study included in each meta-analysis were provided [29-31]. Prediction intervals are used to estimate the treatment effect in a new trial [29-31] and may be more appropriate in decision analysis [32].

To enhance practical application, it was planned to calculate the number-needed-to treat (NNT) for any overall findings that were statistically significant. This was to be accomplished using the approach suggested by the Cochrane Collaboration and was based on control group risk of 30% [8]. In addition, it was planned to calculate Cohen's *U3* index to determine the percentile gain in the intervention group [33].

If not already provided and if sufficient data were available to do so, it was planned to examine for small-study effects (for example, publication bias) using the regression-intercept approach of Egger et al. [34]. One-tailed alpha values <0.05 for *t* were considered to be representative of statistically significant small-study effects. To examine the sensitivity of each SMD on the pooled results, influence analysis was planned with each SMD deleted from the model once. Cumulative meta-analysis, ranked by year, was also planned in order to examine results over time [35]. Negative SMDs were to be

considered as indicative of benefit, i.e., decreases, i.e., improvements, in anxiety. Analyses were to be conducted using Comprehensive Meta-Analysis (version 2.2) [36] and Microsoft Excel 2010 [17].

Results

Characteristics of included meta-analyses

Of the 52 citations initially identified, 46 (88.5%) remained after removing duplicates. Of the 46 articles that were screened, none met the criteria for inclusion. The major reasons for exclusion of ineligible studies were an inappropriate study design (32.9%) followed by an inappropriate intervention (30.4%), population (25.3%), outcome (8.9%) and comparison (2.5%). No meta-analysis was excluded because they did not report their results as a SMD. A flow diagram that depicts the search process can be found in Figure 1 while a list of the excluded studies, including the reasons for exclusion, is shown in Supplementary File 2.

Discussion

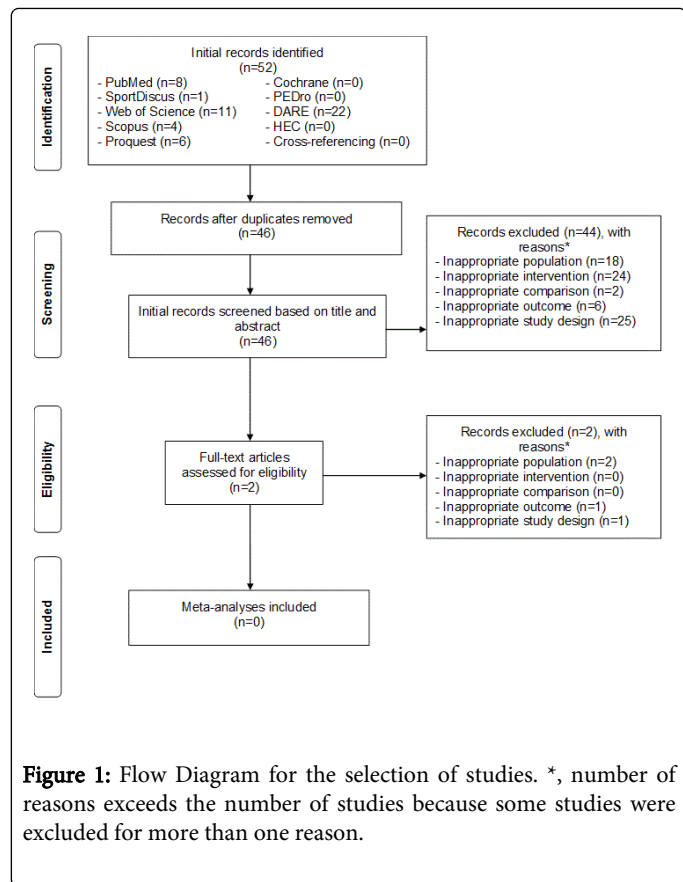
Findings

The purpose of the present study was to conduct a systematic review of previous meta-analyses addressing the effects of exercise (aerobic, strength training, or both) in the treatment of anxiety in adults with osteoarthritis, rheumatoid arthritis, fibromyalgia or systemic lupus erythematosus. The results indicate that no meta-analysis currently exists which met the inclusion criteria. While an important finding, the authors were surprised that no previous meta-analysis on this topic was identified given (1) the prevalence of arthritis in adults, (2) the prevalence of anxiety in adults with arthritis and (3) the potential benefit of exercise in the treatment of anxiety in adults. One potential reason may have to do with the lack of randomized controlled trials on this topic. However, this does not appear to be a valid rationale given that the authors are aware, without any formal searching, of at least 11 randomized controlled trials on this topic [37-47]. A brief qualitative review of these 11 studies that included 14 intervention groups indicate inconsistency in findings with nine of 14 results (64%) reported as statistically significant and five (36%) reported as not statistically significant. While this may lead one to question the relevance of exercise for improving anxiety in adults with osteoarthritis, rheumatoid arthritis, fibromyalgia or systemic lupus erythematosus, this assertion would be based on the vote-counting approach, an approach that has been shown to be less valid than the meta-analytic approach [26]. Given the former, the authors believe that it is both scientifically and clinically important to conduct a systematic review with meta-analysis on this topic.

Implications for research

The results of the current systematic review of previous meta-analyses suggest that a need exists for a meta-analysis of randomized controlled trials that addresses the effects of exercise (aerobic, strength training, or both) on anxiety in adults with osteoarthritis, rheumatoid arthritis, fibromyalgia and systemic lupus erythematosus. Given the interest in dose-response [48], an attempt should be made to try and identify the volume of exercise necessary for achieving improvements, if any, in anxiety. In addition, any differences between training types as well as different types of arthritis should be explored if sufficient data are available to do so. This includes any potential differences

between traditional movement therapies such as walking and meditative movement therapies such as tai chi. Furthermore, estimates such as number-needed-to-treat should be provided in order to enhance practical application and interpretation.



Implications for practice

Given the absence of any systematic review with meta-analysis that was identified, no definitive recommendation can be made regarding the use of exercise for improving anxiety in adults with osteoarthritis, rheumatoid arthritis, fibromyalgia and systemic lupus erythematosus. However, given the numerous other benefits that can be derived from exercise, including those with exercise [49], it would appear plausible to suggest that practitioners follow the general guidelines for exercise recommended by the Centers for Disease Control and Prevention [50]. This includes 150 minutes of moderate- intensity aerobic activity, for example, brisk walking, per week, or 75 minutes of vigorous-intensity aerobic activity, for example, water aerobics, per week, or an equivalent combination of both, following a general rule that 1 minute of vigorous-intensity exercise is equivalent to 2 minutes of moderate-intensity exercise. In addition to aerobic activity, muscle strengthening exercises should be performed at least 2 days per week as well as balance exercises at least 3 days week. The exercise programs should (1) minimize any increase in pain, fatigue or other symptoms, (2) begin at a low level and progress gradually, (3) allow for day to day variations based on how the participant feels, (4) improve the physiological and psychological functioning of the participant and (5) promote long-term adherence [51].

Strengths and potential limitations of current study

The primary strength of the current study was the identification of the need for a meta-analysis of randomized controlled trials addressing the effects of exercise on anxiety in adults with osteoarthritis, rheumatoid arthritis, fibromyalgia or systemic lupus erythematosus. This is important given the public health importance of arthritis as well as the fact that meta-analyses are considered by some to be the gold standard with respect to making evidence-based decisions regarding the effects of an intervention such as exercise on an outcome such as anxiety [52-54].

A potential limitation of the current study may have been the limitation of anxiety as the only outcome. While more focused and potentially applicable, other relevant outcomes (quality of life, quality of sleep, pain, fatigue, stiffness, physical function) were not captured. If this were the case, it would appear plausible to suggest that one or more meta-analyses would have been identified. Second, some may consider the value of the current study given that no meta-analyses met the inclusion criteria. However, it's important to understand that meta-analyses, including systematic reviews of meta-analyses, should not be conducted based on some a priori estimate of the number of studies available given [8]. For example, the Cochrane Collaboration routinely publishes systematic reviews that yield no studies that meet the intended inclusion criteria [8].

Conclusions

Given the absence of systematic review with meta-analysis that met the authors' inclusion criteria, a need exists for a systematic review with meta-analysis addressing the effects of exercise on anxiety in adults with osteoarthritis, rheumatoid arthritis, fibromyalgia and systemic lupus erythematosus.

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