Exercise improves global well-being in adults with fibromyalgia: confirmation of previous meta-analytic results using a recently developed and novel varying coefficient model

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ABSTRACT

Objective. *To determine the effects of exercise (aerobic, strength training or both) on global well-being in adults with fibromyalgia (FM).*

Methods. *The meta-analytic approach and recently developed varying coefficient model were used to pool the results of previous randomised controlled trials of exercise (aerobic, strength training or both) on global well-being in adults with FM. The standardised effect size (ES) for global well-being from each study was pooled using a recently developed and novel varying coefficient (VC) model and partitioned according to per-protocol and intention-to-treat analyses. Results were also compared to the traditionally used random effects (RE) model. Non-overlapping 95% confidence intervals were considered statistically significant with negative ESs indicative of improvements in global well-being.*

Results. *Five ESs representing 377 participants were included in the per-protocol analysis and 5 ESs representing 252 participants were included in the intention-to-treat analysis. Using the VC model, statistically significant improvements in global-well being were found for both per-protocol ($\bar{X}$, -0.39, 95% CI, -0.62, -0.15) and intention-to-treat analysis ($\bar{X}$, -0.40, 95% CI, -0.68, -0.13). Results were similar to those from the RE model.*

Conclusion. *Using the recently developed and more valid varying coefficient model, these findings confirm that exercise improves global-well being in adults with FM.*

Introduction

Fibromyalgia syndrome (FM) is a disorder characterised by widespread muscular pain and fatigue. In 2005, it was estimated that approximately 5 million adults in the United States had FM, with a greater prevalence among women than men (1). When compared to those with other chronic diseases, individuals with FM have been shown to score lower on scales related to well-being (2). One potential non-pharmacologic approach for improving global well-being is exercise. Using the aggregate data meta-analytic approach and commonly recommended random effects (RE) model (3-5), we previously reported statistically significant and clinically important improvements in global well-being as a result of exercise (aerobic, strength training or both) in adults with FM (6). While RE models are almost always preferred over fixed effects (FE) models given that the latter assume that all results from different studies share the same common effect size (ES) while the former does not, RE models also assume that all studies included in a meta-analysis have been randomly sampled from a defined super-population that follows a normal distribution, which is almost never the case (7). Recently, a novel, varying-coefficient (VC) model has been proposed that makes no assumptions with respect to a common ES or random sampling from a normally distributed population of studies (7, 8). Given the potential benefit of exercise on global well-being in those with FM as well as the importance of reaching accurate conclusions regarding a body of research based on the most valid models available, the purpose of this *Brief paper* was to compare the results of our previous meta-analysis with those derived from the more recently developed VC model.

Materials and methods

Data source

We used data from our previous meta-analytic research dealing with the effects of exercise (aerobic, strength

training or both) on global well-being in adults with FM, details of which have been described elsewhere (6). Briefly, studies were limited to randomised controlled trials ≥4 weeks in adults ≥18 years of age.

Calculation and pooling of effect sizes from each study

For each study, standardised mean difference (exercise minus control) ESs and ES variances for global well-being, adjusted for small-sample bias, were previously calculated using the approach of Hedges' (9). The results were then pooled using a RE model, an approach that incorporates heterogeneity into the model and assumes that all included studies have been randomly sampled from a defined population that follows a normal distribution (4). Separate results for global well-being were reported according to type of analysis (per-protocol versus intention-to-treat) and with multiple ESs from the same study pooled so that only one ES represented each study (6). A more detailed description regarding this process can be found in our original work (6).

For the current analysis, we continue to use the same standardised ES data, adjusted for small sample bias, but now calculate our variance statistics for each ES and pool our results using the recently developed VC model for standardised mean differences, a model that makes no assumptions with respect to a common ES or random sampling from a normally distributed super-population of studies (7, 8). The only assumption is that a random sample is obtained from each study population (7).

The mean unweighted estimate of the population standardised mean difference ES is calculated as follows:

$$\bar{\delta} = m^{-1}\sum_{i=1}^{m} b_i \hat{\delta}_i$$

where $\bar{\delta}$ is the pooled mean standardised ES, m represents the number of studies, $\hat{\delta}_i$, is the standardised ES estimate from each study, and b_i is Hedges' small sample-size adjustment for ESs from each study, calculated as $3/[4(/n_1 + n_2)-9]$, where n_1 represents the number of subjects in the exercise group from each study and n_2 represents the number of control group subjects from each study (10). In the formula above, $_i$ represents each study for all indicators. To simplify, the formula above reads as the pooled mean standardised ES, derived from the sum of the estimated standardised ESs from each study, with each ES from each study adjusted for small sample bias prior to pooling.

The independent samples variance for each study is calculated as:

$$\text{var}\,(\hat{\delta}_i) = [\hat{\delta}_i^2\,(\hat{\sigma}_{i1}^4 / df_{i1} + \hat{\sigma}_{i2}^4 / df_{i2}) / 8\,\hat{\sigma}_i^4 + (\hat{\sigma}_{i1}^2 / df_{i1} + \hat{\sigma}_{i2}^2 / df_{i2})\,\hat{\sigma}_j^2]$$

where $\hat{\delta}_i$ is the estimated variance from each study, $\hat{\sigma}_i$ the estimated standard deviation from each study, subscripts $_1$ and $_2$ identifiers for the exercise and control groups in each study, df_i the degrees of freedom from each study, and $_i$ representing each study for all indicators. In the formula above, $df_{ij} = n_{ij} - 1$, where df_{ij} represents the degrees of freedom for each study within each group (exercise = $_1$ and control = $_2$) and n_{ij} the number of subjects for each study within each group (exercise = $_1$ and control = $_2$). Additionally, $\hat{\sigma}_i = [(\hat{\sigma}_{i1}^2) + \hat{\sigma}_{j2}^2)/2]^{1/2}$ with all notation previously described above.

The 95% confidence interval around the pooled standardised mean ES is calculated as:

$$\bar{\delta} \pm z_{\alpha/2}[m^{-2}\textstyle\sum_{i=1}^{m} b_i^2\ \text{var}\,(\hat{\delta}_i)]^{1/2}$$

where $_{z\alpha/2}$ represents z alpha. All other notation is previously described above.

The VC model has been shown to have coverage probabilities for standardised ESs that are superior to those from both RE and FE models (7). Generally speaking, standardised ESs of 0.20, 0.50 and 0.80 are considered to represent small, medium and large effects (11). Results were considered statistically significant if the 95% confidence intervals did not include zero (0), with negative results indicative of improvements in global well-being. All data were analysed using the standardised ES module in Synthesizer 1.0 (8), a meta-analytic software tool that employs the VC models proposed by Bonett (7, 12, 13).

Results

The results are shown in Table I. As can be seen, both RE and VC models resulted in small, statistically significant improvements in global well-being as a result of exercise in adults with FM. Improvements in global well-being for intention-to-treat analyses were greater when the VC *versus* RE model was used.

Discussion

Using a recently developed and novel VC model (7), this *brief report* helps to confirm that exercise is both efficacious (per-protocol analysis) and effective (intention-to-treat analysis) for improving global well-being in adults with FM (14). Confirmation of these findings is important given that participants with FM tend to score lower than other populations on scores related to well-being (2). While the results for both RE and VC models were similar, the use of the VC model may be preferable given the greater coverage probabilities reported as well as the fact that the assumptions underlying the VC model are more realistic in the meta-analytic setting (7). Given the former, we would encourage those who conduct meta-analytic research in rheumatology to consider using the VC model in the analysis of their data. However, it is important to understand that the external validity of a meta-analysis depends not only on the statistical models used but also on the quality and representativeness of

Table I. ES Changes in global well-being.

Variable	Participants (n.)	ES (n.)	RE $\bar{X}$ (95% CI)	VC $\bar{X}$ (95% CI)	Difference (%)
Per-protocol	377	5	-0.39 (-0.69, -0.08)*	-0.39 (-0.62, -0.15)*	0
Intention-to-treat	252	5	-0.34 (-0.53, -0.14)*	-0.40 (-0.68, -0.13)*	6%

n.: number; ES: effect size; $\bar{X}$ (95% CI): mean and 95% confidence interval; RE: random-effects model; VC: varying coefficient model; %: percent change; Negative ESs: indicate improvements in global well-being; *: statistically significant.

the individual studies included (8). In conclusion this brief report confirms that exercise improves global well-being in adults with FM.

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