Archives of Physical Medicine and Rehabilitation
journal homepage: www.archives-pmr.org
Archives of Physical Medicine and Rehabilitation 2021;102:752-61

SYSTEMATIC REVIEW

Effectiveness of Exercise on Fatigue and Sleep Quality in Fibromyalgia: A Systematic Review and Meta-analysis of Randomized Trials

Fernando Estévez-López, PhD,[a,*] Cristina Maestre-Cascales, PhD,[b,*] Deborrah Russell, MSc,[c] Inmaculada C. Álvarez-Gallardo, PhD,[d] María Rodriguez-Ayllon, PhD,[e] Ciara M. Hughes, PhD,[c] Gareth W. Davison, PhD,[f] Borja Sañudo, PhD,[g] Joseph G. McVeigh, PhD[h]

From the [a]Department of Child and Adolescent Psychiatry/Psychology, Erasmus MC University Medical Center, Rotterdam, The Netherlands; [b]LFE Research Group, Department of Health and Human Performance, Universidad Politécnica de Madrid, Madrid, Spain; [c]Institute of Nursing and Health Research, School of Health Sciences, Ulster University, Belfast, Northern Ireland, United Kingdom; [d]Department of Physical Education, Faculty of Education Sciences, University of Cádiz, Cádiz, Spain; [e]PROmoting FITness and Health Through Physical Activity (PROFITH) Research Group, Department of Physical Education and Sport, Faculty of Sport Sciences, University of Granada, Granada, Spain; [f]Sport and Exercise Science Research Institute, Ulster University, Belfast, Northern Ireland, United Kingdom; [g]Department of Physical Education and Sport, University of Seville, Seville, Spain; and [h]Physiotherapy, School of Clinical Therapies, College of Medicine and Health, University College Cork, Cork, Ireland.
[*]Estévez-López and Maestre-Cascales contributed equally to this work.

Abstract
Objectives: To determine the effects of exercise on fatigue and sleep quality in fibromyalgia (primary aim) and to identify which type of exercise is the most effective in achieving these outcomes (secondary aim).
Data Sources: PubMed and Web of Science were searched from inception until October 18, 2018.
Study Selection: Eligible studies contained information on population (fibromyalgia), intervention (exercise), and outcomes (fatigue or sleep). Randomized controlled trials (RCT) testing the effectiveness of exercise compared with usual care and randomized trials (RT) comparing the effectiveness of 2 different exercise interventions were included for the primary and secondary aims of the present review, respectively. Two independent researchers performed the search, screening, and final eligibility of the articles. Of 696 studies identified, 17 RCTs (n=1003) were included for fatigue and 12 RCTs (n=731) for sleep. Furthermore, 21 RTs compared the effectiveness of different exercise interventions (n=1254).
Data Extraction: Two independent researchers extracted the key information from each eligible study.
Data Synthesis: Separate random-effect meta-analyses were performed to examine the effects from RCTs and from RTs (primary and secondary aims). Standardized mean differences (SMD) effect sizes were calculated using Hedges' adjusted g. Effect sizes of 0.2, 0.4, and 0.8 were considered small, moderate, and large. Compared with usual care, exercise had moderate effects on fatigue and a small effect on sleep quality (SMD, −0.47; 95% confidence interval [CI], −0.67 to −0.27; $P<.001$ and SMD, −0.17; 95% CI, −0.32 to −0.01; $P=.04$). RTs in which fatigue was the primary outcome were the most beneficial for lowering fatigue. Additionally, meditative exercise programs were the most effective for improving sleep quality.
Conclusions: Exercise is moderately effective for lowering fatigue and has small effects on enhancing sleep quality in fibromyalgia. Meditative exercise programs may be considered for improving sleep quality in fibromyalgia.
Archives of Physical Medicine and Rehabilitation 2021;102:752-61

Supported by the Health and Social Care Public Health Agency, Northern Ireland (STL/5268/16 to C.H. and J.G.M.). F.E.-L. received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant (agreement no. 707404). The funders of the present study did not have any role in the study design, data collection and analyses, decision to publish, or preparation of the manuscript. F.E.-L. is the guarantor of the review.
Disclosures: none.

https://doi.org/10.1016/j.apmr.2020.06.019

More than 80% of people with fibromyalgia experience severe fatigue[1] or poor sleep quality,[2] both of which are identified by people with fibromyalgia and health care providers as priority targets for treatment. Increased fatigue and poor sleep quality are therefore acknowledged as core symptoms in the updated fibromyalgia diagnostic criteria.[3] Despite the importance of fatigue and sleep quality, most of the research to date has traditionally focused on pain-related outcomes. For instance, the European League Against Rheumatism highlights that exercise is the only therapy supported by "strong" evidence for the management of fibromyalgia.[4] However, the recommendations were based on previous reviews that provided evidence of the benefits of exercise for pain but were unclear for other symptoms[5-9]

In their earliest works, Busch et al performed comprehensive reviews including all types of exercise (eg, aerobic, resistance, and flexibility training).[5,9] These reviews concluded that the effects of exercise on fatigue or sleep were unknown owing to the paucity of research at that time. A number of subsequent systematic reviews focused on specific types of exercise have been published (ie, flexibility,[10] aerobic,[6] resistance,[8] and vibration[7] training), which have explored the effects of exercise on fatigue and sleep quality, among other outcomes. Although the contribution of these reviews to the evidence base is acknowledged, the decision to narrow the scope of each review resulted in the inclusion of a restricted number of studies. For instance, for fatigue, only 4 and 2 studies were included in the reviews by Bidonde et al[6] and by Busch et al,[8] respectively. Consequently, it is difficult to make robust conclusions about the effects of exercise interventions on fatigue and sleep in fibromyalgia. Compared with previous reviews, a recent systematic review has focused on mixed exercise training (ie, 2 or more types of exercise combined).[11] This review included a larger number of studies (ie, 11 studies conducted with a total sample of 493 adults with fibromyalgia) and concluded that the effect of mixed exercise resulted in improvements in fatigue, but omitted study of sleep quality.[11] To date, no review has summarized all relevant literature on the effectiveness of exercise interventions (of any type) on fatigue and sleep quality in fibromyalgia. In doing so, the current review will include a large sample size and accurately estimate, for the first time, the effects of physical exercise on these 2 outcomes.

The aims of this systematic review were to determine the effectiveness of exercise for reducing fatigue and improving sleep quality in people with fibromyalgia (primary aim) and to identify which type of exercise interventions might be the most effective in achieving these outcomes (secondary aim).

Methods

A multidisciplinary international task force was established to conduct this review. The PRISMA guidelines were used to guide this systematic review and meta-analysis.[12] The protocol of the present review was specified in advance and registered in the PROSPERO database (registration number: CRD42018118005).

List of abbreviations:

CI	**confidence interval**
RCT	**randomized controlled trial**
RT	**randomized trial**
SMD	**standardized mean difference**

Data sources and searches

PubMed and Web of Science were searched from inception until October 18, 2018. Search terms used in PubMed were "Fibromyalgia"[MeSH] AND ("Exercise"[MeSH]) OR "Training"[All Fields]) OR "Yoga"[MeSH]) OR "Tai Ji"[MeSH]) OR "Qigong" [MeSH]) OR "Hydrotherapy"[MeSH]) OR "body awareness"[Title/Abstract]) OR danc*[Title/Abstract]). For Web of Science, the search terms were TI=(fibromyalgia) AND TI=("exercise" OR "training" OR "yoga" OR "tai chi" OR "tai ji" OR qigong OR hydrotherapy OR "physical activity" OR "body awareness" OR danc*).

Study selection

Two independent researchers (F.E.-L. and C.M.-C.) performed the search, screened the titles and abstracts of all retrieved articles, and examined the final eligibility of the full-text articles. When a study did not report data on fatigue or sleep quality but used questionnaires including these outcomes, the authors were contacted for further information. No restrictions were applied for language. This review followed the PICOS framework.

Population

Adults with fibromyalgia who were diagnosed using 1 of the recognized American College of Rheumatology criteria (1990, 2010, 2011, or 2016) were included in this study.

Intervention (exposure)

Intervention was based on exercise. Mixed interventions that consisted of exercise combined with other interventions (ie, cointerventions) were considered, as long as exercise comprised at least 50% of the intervention.

Comparison

Studies should have either an intervention group with exercise and a non-intervention control group (eg, treatment as usual) or 2 exercise groups. Therefore, the primary subset of studies included randomized controlled trials (RCT) and the second subset of studies included randomized trials (RT).

Outcome

Outcomes measured were fatigue and sleep quality. When a study included more than 1 assessment per outcome, all the figures were extracted but only the most common assessment among the included studies was meta-analyzed.

Study design

RCTs and RTs were included for the primary and secondary aims, respectively.

Data extraction and quality assessment

Two independent researchers (C.M.-C. and D.R.) extracted the key information from each eligible study. When the information to be extracted was unavailable, authors were contacted. Disagreements were solved in a consensus meeting between the independent reviewers with a third reviewer (C.M.H.).

The Grading of Recommendations Assessment, Development and Evaluation framework was used to assess the quality of the evidence across studies for fatigue and sleep quality separately. Risk of bias of individual studies was assessed using the Cochrane Risk of Bias tool. Studies with a score of at least 5 points were considered as having high risk of bias. Inconsistency across studies was considered serious when heterogeneity was high ($I^2 \geq 50\%$). Indirectness was considered serious when interventions included both exercise and additional components (ie, cointerventions). Imprecision was considered serious when the 95% confidence interval (CI) was wide and crossed the line of no effect, and as such the interpretation of the data would be different if the true effect were at 1 end of the CI or the other. Finally, publication bias was assessed via funnel plots.

Two researchers independently assessed risk of bias (I.C.A.-G. and M.R.-A.) and the inconsistency, indirectness, imprecision, and publication bias (F.E.-L. and J.G.M.) of each eligible study. Disagreements on these assessments were solved in a consensus meeting between the independent reviewers with a third reviewer (C.M.H.).

Data synthesis and analysis

For the primary aim, quantitative synthesis of RCTs (ie, meta-analyses) were performed using Review Manager version 5.3.[a] Statistical significance was set at a *P* value less than .05. Standardized mean differences (SMD) between the exercise and control groups were computed for both outcomes separately. When a control group was used as a comparator twice in the same study, we halved the sample size of the control group. Weighted mean differences were calculated using a random effects model. Heterogeneity was measured using the I^2 statistic (the percentage of total variability attributed to between-study heterogeneity). When heterogeneity was high ($I^2 \geq 50\%$), further explorations based on subgroups analyses were computed. SMD effect sizes were calculated using Hedges' adjusted g (similar to Cohen's d). Effect sizes of 0.2, 0.4, and 0.8 were considered small, moderate, and large, respectively.

For the secondary aim, a narrative synthesis structured around each outcome was conducted. When at least 3 of the included studies presented similar comparisons, we performed meta-analyses using the same methods that have been described for the primary aim.

Results

Study selection and characteristics

Thirty-seven unique studies were included in this review.[13-49] Of them, 4 studies included 3 arms (ie, control group and 2 exercise intervention groups, each with a different exercise training such as aerobic in 1 group and flexibility in another group) and therefore they were included for addressing both aims of the present review.[40-43] Thus, a total 20 RCTs[13-20,25,36,40-49] and 21 RTs[21-24,26-35,37-43] were included in the review. Figure 1 shows a PRISMA diagram.

Of the 20 RCTs that compared the effectiveness of exercise versus usual care, 9 included both outcomes of interest,[14,16,17,19,20,41,43,44,46] 8 included only fatigue,[13,15,18,25,36,40,42,50] and 3 included only sleep quality.[45,47,49] Of the 21 RTs that compared the effectiveness of different exercise interventions, 12 included both outcomes of interest,[21-23,27,28,30,31,33,37,39,41,43] 7 included only fatigue,[24,26,29,32,35,40,42] and 2 included only sleep quality.[34,38] A summary of the characteristics of the RCTs and RTs included in the present review is presented in supplemental tables S1 and S2 (available online only at http://www.archives-pmr.org/), respectively.

A moderate risk of bias was present in most of the included RCTs and RTs (see supplemental figs S1 and S2 for overall summaries and supplemental figs S3 and S4 [available online only at http://www.archives-pmr.org/] for specific information on each individual included work per study design). No study reported having conflicts of interest.

Synthesis of the data

Figure 2 presents a meta-analysis conducted in 1003 people with fibromyalgia (61% randomly allocated into exercise interventions). In comparison with usual care, exercise interventions were effective for reducing fatigue in fibromyalgia (pooled SMD, −0.47; 95% CI, −0.67 to −0.27). This finding was robust across 2 sensitivity analyses, as shown in supplemental figures S5 and S6 (available online only at http://www.archives-pmr.org/): (1) when a study with high risk of bias[40] was not included in the meta-analysis (pooled SMD, −0.49; 95% CI, −0.71 to −0.27) and (2) when fixed effects models were computed (pooled SMD, −0.40; 95% CI, −0.53 to −0.26). Supplemental figure S7 (available online only at http://www.archives-pmr.org/) demonstrates the funnel plot, which did not indicate publication bias.

Owing to the high heterogeneity (ie, $I^2 = 51\%$) observed across RCTs testing the effects of exercise on fatigue, we explored several post hoc analyses. Most of them were not significant, as the effects on fatigue were similar between levels of adherence: (1) studies in which participants had to attend to at least 80% of the training sessions (ie, adherence) to be included in the analyses and those studies with a lower or no adherence criterion, (2) sex of participants: studies in which only women participated versus those in which both sexes were included, (3) type of intervention: only exercise versus cointerventions, (4) type of exercise: meditative exercise programs (ie, tai chi, yoga, qigong) versus others (ie, aerobic, muscular resistance, flexibility), (5) sample size: those with at least 20 participants in each group versus others, (6) type of setting in which exercise was performed: land-based versus water-based, and (7) training intensity: low-to-moderate versus moderate-to-high. Supplemental figures S8 to S14 (available online only at http://www.archives-pmr.org/) show these nonsignificant findings. Interestingly, those studies in which fatigue was the primary outcome (fig 3) and used a shorter (<24wk) nonaerobic exercise intervention resulted in greater effect on fatigue (greater effect sizes) than comparative studies (supplemental figs S15 and S16; available online only at http://www.archives-pmr.org/).

Figure 4 depicts a meta-analysis conducted in 731 people with fibromyalgia (59% randomly allocated into exercise interventions). In comparison with usual care, exercise interventions had a small effect on enhancing sleep quality in fibromyalgia (pooled SMD, −0.17; 95% CI, −0.32 to −0.01). This finding was robust across 2 sensitivity analyses, as shown in supplemental figures S17 and S18 (available online only at http://www.archives-pmr.org/): (1) when a study with high risk of bias[45] was not included in the meta-analysis (pooled SMD, −0.19; 95% CI, −0.35 to −0.02), and (2) when fixed effects model were computed (pooled SMD, −0.17; 95% CI, −0.32 to −0.02). Owing to the small heterogeneity (ie, $I^2 = 5\%$), post hoc analyses were not needed. Supplemental figure S19 (available online only at http://www.archives-pmr.org/) depicts the funnel plot, which did not indicate publication bias.

Table 1 shows that when comparing exercise versus usual care, there was low to moderate quality evidence for the beneficial

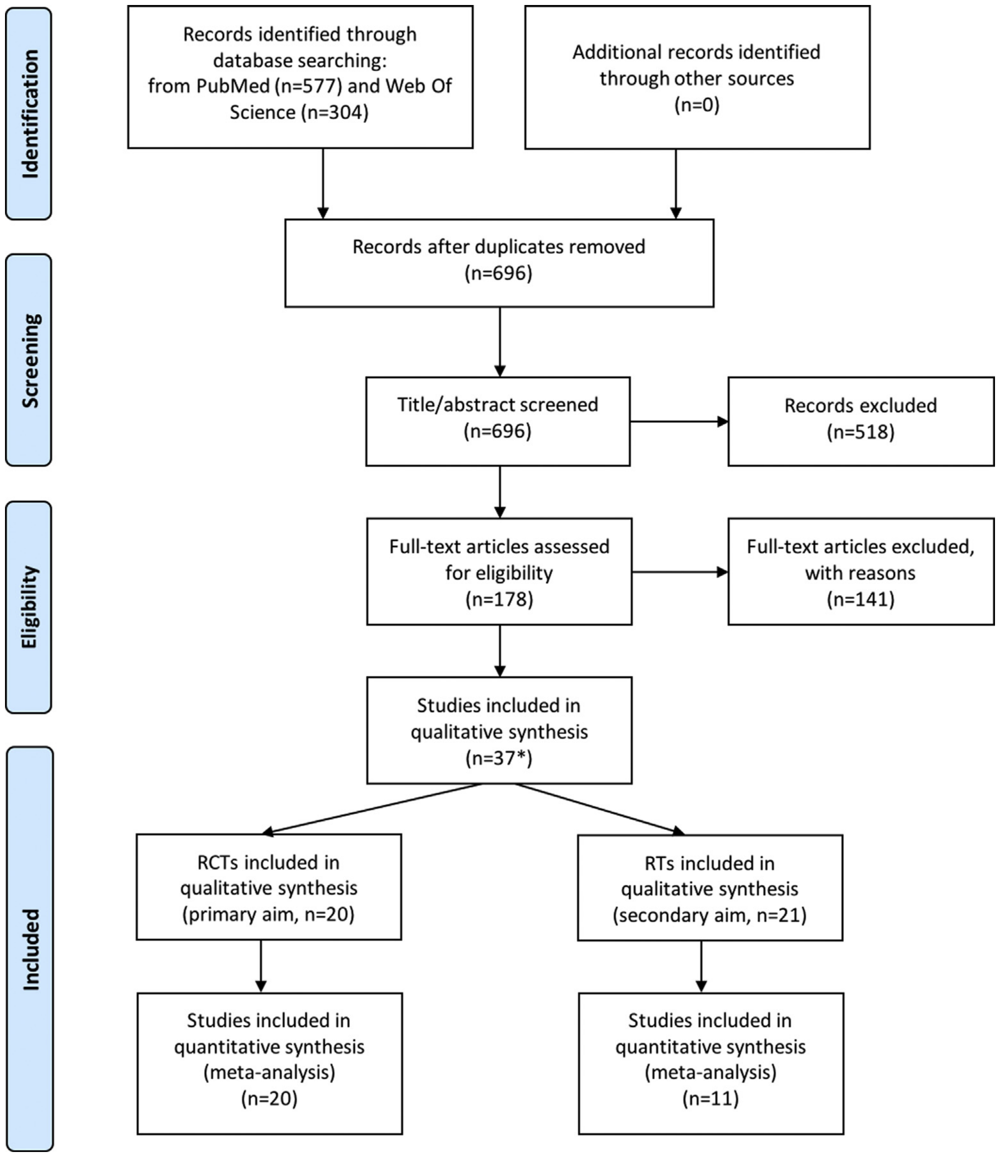

Fig 1 Flow chart showing the results of the selection process. *Four studies included a usual care (control) group and 2 different exercise interventions. Thus, they were included in the analyses related to the primary and second aims of the present review.

effects of exercise on fatigue, whereas the evidence was moderate for benefits on sleep quality.

In the 21 RTs included in the present review, a wide range of exercise interventions were implemented and compared in a total of 1254 individuals with fibromyalgia who were randomly allocated into different interventions. Thus, it was difficult to perform robust comparisons. However, we were able to quantify 1 comparison for sleep quality and 3 for fatigue. First, when comparing different types of exercise, meditative exercise programs were more effective for improving sleep quality but not for lowering fatigue (fig 5; [pooled SMD, −0.80; 95% CI, −1.57 to −0.02] and supplemental fig S20, available online only at http://www.archives-pmr.org/ [pooled SMD, −0.39; 95% CI, −0.88 to 0.11]). Second, the effectiveness of resistance versus flexibility training was similar for fatigue (supplemental fig S21, available online only at http://www.archives-pmr.org/ [pooled SMD, −1.64; 95% CI, −4.31 to 1.02]). Third, the effectiveness of water- versus land-based exercise was also similar for fatigue (supplemental figure S22, available online only at http://www.archives-pmr.org/ [pooled SMD, 0.00; 95% CI, −0.42 to 0.43]).

Discussion

This systematic review aimed to determine the effectiveness of exercise on fatigue and sleep quality in those with fibromyalgia and to identify which type of exercise interventions might be the most effective in achieving these outcomes. In the current review, we found that, compared with usual care, exercise has moderate effects for lowering fatigue and small effects for improving sleep quality. We also observed that, compared with other types of exercise, meditative exercise programs were more effective for improving sleep quality but not for lowering fatigue. In interpreting the findings of this review, several

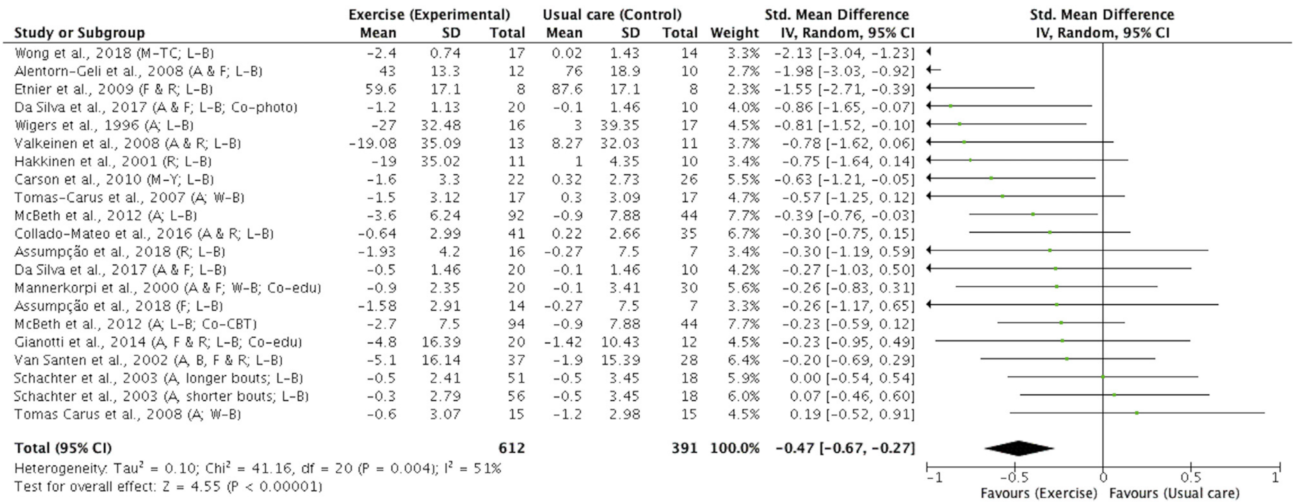

Fig 2 Pooled effects of randomized controlled trials analyzing the effectiveness of exercise in reducing fatigue in people with fibromyalgia. Analyses were conducted using a random effects model. A, aerobic exercise; CI, confidence interval; Co-edu, cointervention-education; Co-photo, cointervention-phototherapy; df, degrees of freedom; F, flexibility exercise; IV, inverse variance; L-B, land-based exercise; M, meditative exercise; R, resistance exercise; Std, standardized; TC, tai chi; W-B, water-based exercise; Y, yoga.

factors must be noted. First, most of the studies were based on aerobic exercise. Thus, the effect sizes of the present meta-analyses may more accurately reflect the effectiveness of aerobic training on fatigue and sleep quality than the effects of other types of exercise. Indeed, we observed that those exercise interventions that did not include aerobic exercise appeared to be more effective at reducing fatigue. Second, the effects of exercise on fatigue were highly variable across studies ($I^2 = 51\%$) and remarkably higher when fatigue was the main outcome. Third, there was a lack of high-quality studies in the field and, consequently, the quality of evidence provided in the present review is low to moderate for the effectiveness of exercise in reducing fatigue (the evidence is in favor of exercise but the effect size is unclear and likely to be moderate) and moderate for small effects of exercise (of any type) on enhancing sleep quality.

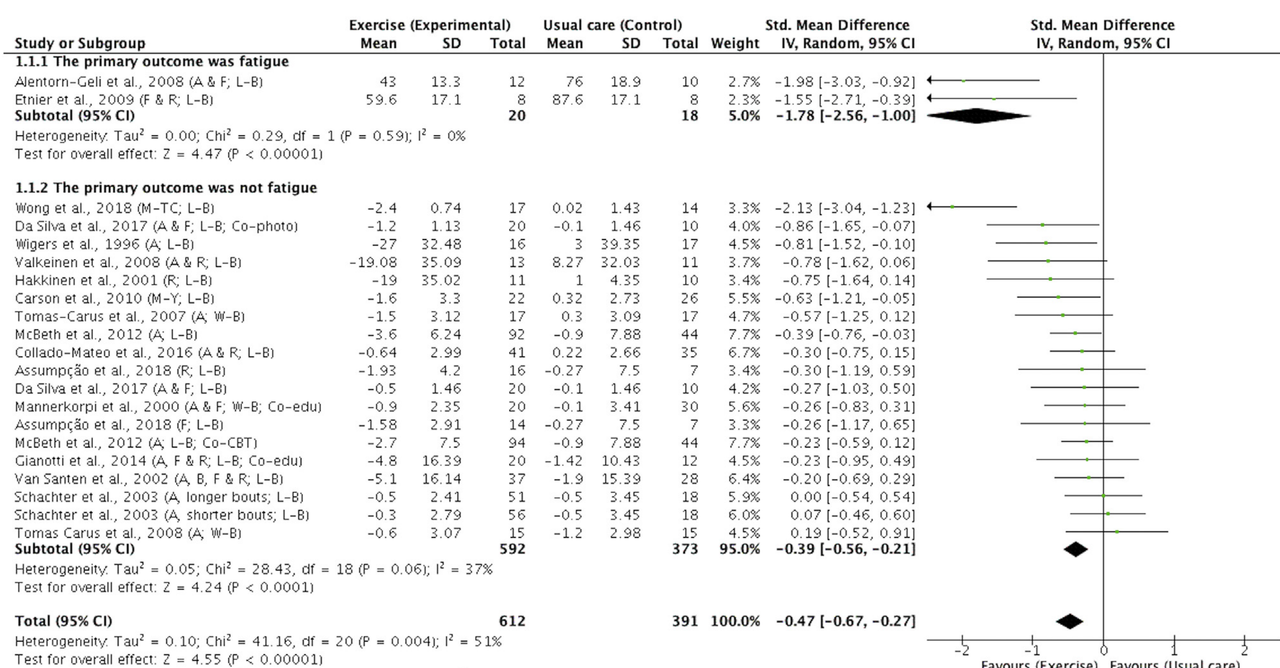

Fig 3 Post hoc analysis showing the pooled effects of randomized trials analyzing the effectiveness of studies in which fatigue was the primary outcome versus the remaining studies for lowering fatigue in people with fibromyalgia. Analyses were conducted using a random effects model.

Study or Subgroup	Exercise (Experimental) Mean	SD	Total	Usual care (Control) Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Da Silva et al., 2017 (A & F; L-B; Co-photo)	−1.2	1.13	20	−0.1	1.46	10	3.8%	−0.86 [−1.65, −0.07]
Lynch et al., 2012 (M-QG; L-B)	-3.04	3.75	44	-0.62	3.02	45	12.2%	-0.71 [-1.13, -0.28]
Da Silva et al., 2017 (A & F; L-B)	−0.6	1.46	20	0	2.46	10	4.1%	−0.32 [−1.08, 0.45]
Carson et al., 2010 (M-Y; L-B)	−1.44	3.89	22	0.28	7.08	26	7.1%	−0.29 [−0.86, 0.28]
Hakkinen et al., 2001 (R; L-B)	−10	28.66	11	−3	39.02	10	3.2%	−0.20 [−1.06, 0.66]
McBeth et al., 2012 (A; L-B; Co-CBT)	−1.3	7.94	94	0.3	9.4	44	16.8%	−0.19 [−0.55, 0.17]
Valkeinen et al., 2008 (A & R; L-B)	−4.23	22.25	13	−1.18	22.25	11	3.7%	−0.13 [−0.94, 0.67]
Wong et al., 2018 (M-TC; L-B)	−0.2	2	17	−0.2	2.1	14	4.7%	0.00 [−0.71, 0.71]
McBeth et al., 2012 (A; L-B)	0.4	6.07	92	0.3	7.75	44	16.7%	0.01 [−0.34, 0.37]
Tomas-Carus et al., 2007 (A; W-B)	0.43	1.57	17	0.34	1.57	17	5.2%	0.06 [−0.62, 0.73]
Haak et al., 2007 (M-QG; L-B)	0.43	1.18	29	0.34	1.54	28	8.5%	0.06 [−0.45, 0.58]
Gianotti et al., 2014 (A, F & R; L-B; Co-edu)	−0.5	4.07	20	−0.84	4.6	12	4.6%	0.08 [−0.64, 0.79]
Sañudo et al., 2015 (A; L-B)	0.2	3.24	16	−0.3	4.21	12	4.2%	0.13 [−0.62, 0.88]
Wigers et al., 1996 (A; L-B)	10	44.37	16	2	50	17	5.0%	0.16 [−0.52, 0.85]
Total (95% CI)			**431**			**300**	**100.0%**	**−0.17 [−0.32, −0.01]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 13.68$, df = 13 (P = 0.40); $I^2 = 5\%$
Test for overall effect: Z = 2.09 (P = 0.04)

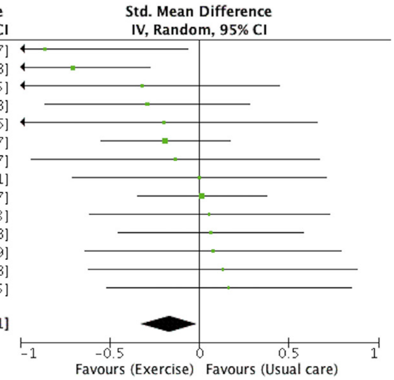

Fig 4 Pooled effects of randomized controlled trials analyzing the effectiveness of exercise in enhancing sleep quality in people with fibromyalgia. Analyses were conducted using a random effects model.

Effectiveness of exercise for reducing fatigue in fibromyalgia

Owing to the limited number of studies included in previous meta-analyses, their findings were inconclusive and inconsistent. For example, Busch et al meta-analyzed 2 resistance training studies (n = 81) showing significant pooled reductions on fatigue (*P*<.001).[8] However, Bidonde et al recently meta-analyzed 4 aerobic exercise studies (n = 286)[6] in which the *P* value of the pooled effects for the exercise group was 0.06. Recently, Bidonde et al meta-analyzed a sample size of 493 adults with fibromyalgia, estimating that the effects of mixed exercise training (ie, 2 or more types of exercise combined) on fatigue were significant (*P*<.001).[11] Using similar statistical methods to previous meta-analyses but in a larger sample size (n = 1003), our pooled estimation showed that exercise produces significant and probably meaningful (moderate effect size) reduction in fatigue in fibromyalgia. Thus, the comprehensive approach followed in the present meta-analysis allowed us to robustly determine, for the first time, the overall effects of exercise on fatigue in large sample of individuals with fibromyalgia.

Effectiveness of exercise for improving sleep quality in fibromyalgia

Previous meta-analyses were unable to determine the effectiveness of exercise on sleep quality in fibromyalgia owing to the paucity of research. Indeed, most failed to find RCTs on this topic. Given the extent of sleep dysfunction in individuals with fibromyalgia, it is important to determine the effectiveness of exercise for improving sleep quality in this population. The most comprehensive review to date included only 2 studies examining sleep and reported moderate effects of exercise for enhancing sleep quality (n = 104).[51] The number of included studies in the present work was considerably higher (13 RCTs, n = 806), allowing us to better estimate the effectiveness of exercise for improving sleep quality in fibromyalgia. The effectiveness of exercise (of any type) in enhancing sleep quality in fibromyalgia was limited (small effect). However, meditative exercise programs (ie, tai chi, yoga, qigong) may offer a promising approach. Although there are potential mechanisms that can provide a rationale to support the effectiveness of meditative exercise on improving sleep quality, our finding is based on an imprecise estimation (SMD, −0.80; 95% CI, −1.57 to −0.02) from a relatively small sample size (141 participants in meditative exercise vs 177 participants in other types of exercise). Thus, further high-quality experimental research is required to confirm or refute our findings.

Exercise mechanisms for fatigue and sleep quality in fibromyalgia

Aberrations in the central nervous system are well-known in fibromyalgia.[52-54] For example, compared with nonfibromyalgia controls, abnormal levels of metabolites (eg, reductions in the ratio of N-acetylaspartate to creatine) have been observed in the hippocampus of people with fibromyalgia,[52] as well as structural abnormalities (eg, lower volume)[53] and functional changes (eg, increased activation).[54] Another system that might be altered in fibromyalgia is the hypothalamic-pituitary-adrenal axis, as well as a sympathetic hyperactivity mediated by a dysfunction in the autonomic nervous system.[55] These alterations may be related to increased levels of fatigue.[52] Interestingly, exercise may revert these aberrations by regulating the levels of metabolites and promoting angiogenesis, neurogenesis, and connectivity of the hippocampus.[56,57]

The present meta-analyses demonstrated that exercise had a small beneficial effect on sleep quality in fibromyalgia. In this disease, hyperactivity of the sympathetic nervous system is well-documented and, thus, stress levels are considerably high.[58,59] Physiological responses to exercise often include a decrease in this sympathetic tone and a shift toward parasympathetic activity, which may be related to muscular and nervous relaxation, leading to reductions in stress levels and, finally, to improvement in sleep quality.[60-62] In this respect, our review showed that meditative exercise programs were more effective in improving sleep quality than other types of exercise. Although meditative exercise is safe in fibromyalgia, little is known about their mechanisms of action. It is likely that this type of exercise can enhance the parasympathetic activity and reduce sympathetic tone by decreasing activation of the hypothalamic-pituitary-adrenal axis. Moreover, meditative exercise may facilitate enhanced rapid eye movement sleep by increasing central nervous system inhibitory c-aminobutyric acid and serotonin levels.[63]

Clinical applications

The recent European League Against Rheumatism recommendations for the management of fibromyalgia highlight exercise as the

Table 1 Level of quality evidence for the effectiveness of exercise for reducing fatigue and enhancing sleep quality in fibromyalgia

		Certainty Assessment					No. of Participants		Effect			
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Exercise	Usual Care	SMD (95% CI)	Size	Certainty	Direction
Outcome: fatigue												
17	Randomized controlled trials	Not serious	Serious	Not serious	Unclear	Not serious	612/1003 (62%)	391/1003 (39%)	−0.47 (−0.67 to −0.27)	Moderate	⊕⊕◯◯ to ⊕⊕⊕◯ Low to moderate	In favor of exercise
Outcome: sleep quality												
12	Randomized controlled trials	Not serious	Not serious	Not serious	Serious	Not serious	431/731 (59%)	300/731 (41%)	−0.17 (−0.32 to −0.01)	Small	⊕⊕⊕◯ Moderate	In favor of exercise

only therapy with a strong level of evidence.[4] These recommendations were based on the findings provided by systematic review of previous reviews. As we have discussed, although previous systematic reviews showed reliable findings for pain management, they have provided limited evidence on the effectiveness of exercise for reducing fatigue and increasing sleep quality in fibromyalgia.[6,8] The present meta-analyses suggest that the effectiveness of exercise may differ for different outcomes. This means that it cannot be assumed that the benefits of exercise for pain automatically extend to other symptoms of the condition. An interesting finding for health care providers has emerged from our review in that fatigue reductions were higher when the main outcome of the study was fatigue. Therefore, instead of designing a "fix-all" exercise protocol for fibromyalgia, exercise programs should be designed as outcome-specific by considering how fibromyalgia manifests in the person who is going to engage in the program. For example, meditative exercise programs (eg, tai chi or qigong) may be more advisable for people with fibromyalgia who experience difficulty sleeping.

The studies included in the present systematic review investigated a wide range of exercise programs, including different types of exercise, intensities, frequencies, and program durations. Although we explored several post hoc analyses, we were unable to determine the most effective exercise intervention for reducing fatigue. From our approach to subgrouping the effects of different exercise interventions compared with usual care, we observed that the ideal intervention for reducing fatigue in fibromyalgia appears to be specifically designed for such an outcome, lasts less than 24 weeks, and does not involve aerobic exercise. Collectively, the high heterogeneity that emerged from the effects of exercise on fatigue limits the establishment of evidence-based guidelines. Although the American College of Sports Medicine has released specific recommendations to consider when conducting exercise interventions in fibromyalgia,[64] a recent review has reported poor therapeutic validity of studies that accomplish these American College of Sports Medicine exercise recommendations.[65]

Standard exercise interventions for the average or most common profile of people with fibromyalgia appears misjudged as people with fibromyalgia are heterogeneous.[66] Thus, personalized exercise programs are warranted. In this context, some people with fibromyalgia may experience fears related to engaging in exercise[67] or a discordance of being more capable to engage in exercise than is self-perceived.[68] Individuals with these characteristics may be more likely to experience exercise as stressful. Therefore, exercise interventions should not only be tailored to how fibromyalgia manifests in each person but also to (more) general characteristics of the person.

Implications for research agenda

Findings of the present study provide evidence indicating that exercise is effective for reducing fatigue in fibromyalgia. However, future research is needed to determine what type of exercise is most beneficial for people with fibromyalgia, which intensity is best, the optimal length of the training, and the most beneficial delivery method. Our findings indicate that exercise appears to promote only small benefits on sleep quality in fibromyalgia. Although relaxation is a potential mechanism by which exercise might improve sleep quality, not all types of exercise promote relaxation. Thus, meditative exercise programs that suppose a lower physical load than other types of exercises could be more effective for enhancing sleep quality in fibromyalgia. Therefore, large, high-quality experimental studies testing the effectiveness

	Meditative exercise			Other types of exercise				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Lopez-Rodriguez et al., 2013 (AqBD vs F)	-7.51	2.38	29	-0.3	3.28	30	19.6%	-2.48 [-3.16, -1.79]
Wang et al., 2010 (TC vs F)	-3.6	3.5	33	-0.7	2	33	21.1%	-1.01 [-1.52, -0.49]
Calandre et al., 2009 (AC vs F)	-0.91	2.62	32	-0.29	2.43	34	21.3%	-0.24 [-0.73, 0.24]
Wang et al., 2018 (TC vs A)	-2.1	5.1	36	-1.1	4.09	75	21.9%	-0.22 [-0.62, 0.17]
Norregaard et al., 1997 (BA vs A)	0	2.3	11	0	2	5	16.2%	0.00 [-1.06, 1.06]
Total (95% CI)			**141**			**177**	**100.0%**	**-0.80 [-1.57, -0.02]**

Heterogeneity: $Tau^2 = 0.67$; $Chi^2 = 37.39$, $df = 4$ ($P < 0.00001$); $I^2 = 89\%$
Test for overall effect: $Z = 2.02$ ($P = 0.04$)

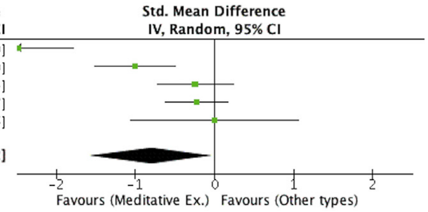

Fig 5 Post hoc analysis showing the pooled effects of randomized trials analyzing the effectiveness of meditative exercise vs the remaining types of exercise for enhancing sleep quality in people with fibromyalgia. Analyses were conducted using a random effects model.

of very gentle exercise specifically designed for enhancing sleep quality in fibromyalgia are warranted in the future. In addition, further research testing the effectiveness of exercise in objectively measured fatigue or sleep quality is warranted.

Study limitations

The most common limitations among the included studies were as follows: (1) the long-term effects of the interventions were not reported; (2) results were not stratified by sex, and most of the participants were women. Moreover, we did not include conference proceedings and other types of gray literature owing to the often low quality of reporting in conference abstracts.

Conclusions

We provided low-to-moderate quality evidence that exercise is moderately effective for lowering fatigue and demonstrated that there is moderate evidence of small effects of exercise for enhancing sleep quality in fibromyalgia. Although speculative, meditative exercise programs may be a promising approach for improving sleep quality in fibromyalgia. As most of the interventions involved aerobic exercise, research using other types of exercise is warranted. Instead of designing "fix-all" and "one size fits all" protocols, exercise programs should be specifically designed for the outcome that is targeted and tailored to the characteristics of the person who is going to engage in the exercise in order to be as effective as possible.

Supplier

a. Review Manager version 5.3; Cochrane Collaboration.

Keywords

Chronic pain; Management; Physical exercise; Rehabilitation; Training; Vitality

Corresponding author

Fernando Estévez-López, PhD, Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands. *E-mail address:* fer@estevez-lopez.com.

References

1. Overman CL, Kool MB, Da Silva JaP, Geenen R. The prevalence of severe fatigue in rheumatic diseases: an international study. Clin Rheumatol 2016;35:409-15.
2. Bigatti SM, Hernandez AM, Cronan TA, Rand KL. Sleep disturbances in fibromyalgia syndrome: relationship to pain and depression. Arthritis Rheum 2008;59:961-7.
3. Wolfe F, Clauw DJ, Fitzcharles M-A, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken) 2010;62:600-10.
4. Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis 2017;76:318-28.
5. Busch AJ, Schachter CL, Overend TJ, Peloso PM, Barber KAR. Exercise for fibromyalgia: a systematic review. J Rheumatol 2008;35:1130-44.
6. Bidonde J, Busch AJ, Schachter CL, et al. Aerobic exercise training for adults with fibromyalgia. Cochrane Database Syst Rev 2017;6(6):CD012700.
7. Bidonde J, Busch AJ, van der Spuy I, Tupper S, Kim SY, Boden C. Whole body vibration exercise training for fibromyalgia. Cochrane Database Syst Rev 2017;9:CD011755.
8. Busch AJ, Webber SC, Richards RS, et al. Resistance exercise training for fibromyalgia. Cochrane Database Syst Rev 2013;12:CD010884.
9. Busch A, Schachter CL, Peloso PM, Bombardier C. Exercise for treating fibromyalgia syndrome. Cochrane Database Syst Rev 2002:CD003786.
10. Kim SY, Busch AJ, Overend TJ, et al. Flexibility exercise training for adults with fibromyalgia. Cochrane Database Syst Rev 2019;9:CD013419.
11. Bidonde J, Busch AJ, Schachter CL, et al. Mixed exercise training for adults with fibromyalgia. Cochrane Database Syst Rev 2019.
12. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
13. Alentorn-Geli E, Padilla J, Moras G, Lazaro Haro C, Fernandez-Sola J. Six weeks of whole-body vibration exercise improves pain and fatigue in women with fibromyalgia. J Altern Complement Med 2008;14:975-81.
14. Carson JW, Carson KM, Jones KD, Bennett RM, Wright CL, Mist SD. A pilot randomized controlled trial of the Yoga of Awareness program in the management of fibromyalgia. Pain 2010;151:530-9.
15. Tomas-Carus P, Gusi N, Hakkinen A, Hakkinen K, Leal A, Ortega-Alonso A. Eight months of physical training in warm water improves physical and mental health in women with fibromyalgia: a randomized controlled trial. J Rehabil Med 2008;40:248-52.
16. Tomas-Carus P, Hakkinen A, Gusi N, Leal A, Hakkinen K, Ortega-Alonso A. Aquatic training and detraining on fitness and quality of life in fibromyalgia. Med Sci Sports Exerc 2007;39:1044-50.
17. Valkeinen H, Alen M, Hakkinen A, Hannonen P, Kukkonen-Harjula K, Hakkinen K. Effects of concurrent strength and endurance training on physical fitness and symptoms in postmenopausal women with fibromyalgia: a randomized controlled trial. Arch Phys Med Rehabil 2008;89:1660-6.

18. van Santen M, Bolwijn P, Verstappen F, et al. A randomized clinical trial comparing fitness and biofeedback training versus basic treatment in patients with fibromyalgia. J Rheumatol 2002;29:575-81.
19. Wigers SH, Stiles TC, Vogel PA. Effects of aerobic exercise versus stress management treatment in fibromyalgia. A 4.5 year prospective study. Scand J Rheumatol 1996;25:77-86.
20. Wong A, Figueroa A, Sanchez-Gonzalez MA, Son W-M, Chernykh O, Park S-Y. Effectiveness of tai chi on cardiac autonomic function and symptomatology in women with fibromyalgia: a randomized controlled trial. J Aging Phys Act 2018;26:214-21.
21. Bircan C, Karasel SA, Akgun B, El O, Alper S. Effects of muscle strengthening versus aerobic exercise program in fibromyalgia. Rheumatol Int 2008;28:527-32.
22. Calandre EP, Rodriguez-Claro ML, Rico-Villademoros F, Vilchez JS, Hidalgo J, Delgado-Rodriguez A. Effects of pool-based exercise in fibromyalgia symptomatology and sleep quality: a prospective randomised comparison between stretching and Ai Chi. Clin Exp Rheumatol 2009;27:S21-8.
23. Demir-Gocmen D, Altan L, Korkmaz N, Arabaci R. Effect of supervised exercise program including balance exercises on the balance status and clinical signs in patients with fibromyalgia. Rheumatol Int 2013;33:743-50.
24. Fernandes G, Jennings F, Nery Cabral MV, Pirozzi Buosi AL, Natour J. Swimming improves pain and functional capacity of patients with fibromyalgia: a randomized controlled trial. Arch Phys Med Rehabil 2016;97:1269-75.
25. Collado-Mateo D, Dominguez-Munoz FJ, Adsuar JC, Garcia-Gordillo MA, Gusi N. Effects of exergames on quality of life, pain, and disease effect in women with fibromyalgia: a randomized controlled trial. Arch Phys Med Rehabil 2017;98:1725-31.
26. Gavi MBRO, Vassalo DV, Amaral FT, et al. Strengthening exercises improve symptoms and quality of life but do not change autonomic modulation in fibromyalgia: a randomized clinical trial. PLoS One 2014;9:e90767.
27. Jentoft ES, Kvalvik AG, Mengshoel M. Effects of pool-based and land-based aerobic exercise on women with fibromyalgia/chronic widespread muscle pain. Arthritis Rheum 2001;45:42-7.
28. Jones KD, Burckhardt CS, Clark SR, Bennett RM, Potempa KM. A randomized controlled trial of muscle strengthening versus flexibility training in fibromyalgia. J Rheumatol 2002;29:1041-8.
29. Kendall SA, Brolin-Magnusson K, Soren B, Gerdle B, Henriksson KG. A pilot study of body awareness programs in the treatment of fibromyalgia syndrome. Arthritis Care Res 2000;13:304-11.
30. López-Pousa S, Bassets Pagès G, Monserrat-Vila S, de Gracia Blanco M, Hidalgo Colomé J, Garre-Olmo J. Sense of well-being in patients with fibromyalgia: aerobic exercise program in a mature forest-a pilot study. Evid Based Complement Alternat Med 2015;2015:614783.
31. Lopez-Rodriguez MM, Fernandez-Martinez M, Mataran-Penarrocha GA, Rodriguez-Ferrer ME, Granados Gamez G, Aguilar Ferrandiz E. [Effectiveness of aquatic biodance on sleep quality, anxiety and other symptoms in patients with fibromyalgia] [Spanish]. Med Clin (Barc) 2013;141:471-8.
32. Mannerkorpi K, Nordeman L, Cider Å, Jonsson G. Does moderate-to-high intensity Nordic walking improve functional capacity and pain in fibromyalgia? A prospective randomized controlled trial. Arthritis Res Ther 2010;12:R189.
33. Norregaard J, Lykkegaard JJ, Mehlsen J, DanneskioldSamsoe B. Exercise training in treatment of fibromyalgia. J Musculoskelet Pain 1997;5:71-9.
34. van Santen M, Bolwijn P, Landewe R, Verstappen F, Bakker C, Hidding A, et al. High or low intensity aerobic fitness training in fibromyalgia: does it matter? J Rheumatol 2002;29:582-7.
35. Vitorino DFD, Carvalho LBC, do Prado GF. Hydrotherapy and conventional physiotherapy improve total sleep time and quality of life of fibromyalgia patients: randomized clinical trial. Sleep Med 2006;7:293-6.
36. Etnier JL, Karper WB, Gapin JI, Barella LA, Chang YK, Murphy KJ. Exercise, fibromyalgia, and fibrofog: a pilot study. J Phys Act Health 2009;6:239-46.
37. Wang C, Schmid CH, Rones R, et al. A randomized trial of tai chi for fibromyalgia. N Engl J Med 2010;363:743-54.
38. Wang C, Schmid CH, Fielding RA, et al. Effect of tai chi versus aerobic exercise for fibromyalgia: comparative effectiveness randomized controlled trial. BMJ 2018;360:k851.
39. Genc A, Tur BS, Aytur YK, Oztuna D, Erdogan MF. Does aerobic exercise affect the hypothalamic-pituitary-adrenal hormonal response in patients with fibromyalgia syndrome? J Phys Ther Sci 2015;27:2225-31.
40. Assumpcao A, Matsutani LA, Yuan SL, Santo AS, Sauer J, Mango P, et al. Muscle stretching exercises and resistance training in fibromyalgia: which is better? A three-arm randomized controlled trial. Eur J Phys Rehabil Med 2018;54:663-70.
41. McBeth J, Prescott G, Scotland G, Lovell K, Keeley P, Hannaford P, et al. Cognitive behavior therapy, exercise, or both for treating chronic widespread pain. Arch Intern Med 2012;172:48-57.
42. Schachter CL, Busch AJ, Peloso PM, Sheppard MS. Effects of short versus long bouts of aerobic exercise in sedentary women with fibromyalgia: a randomized controlled trial. Phys Ther 2003;83:340-58.
43. da Silva MM, Albertini R, de Tarso Camillo de Carvalho P, et al. Randomized, blinded, controlled trial on effectiveness of photobiomodulation therapy and exercise training in the fibromyalgia treatment. Lasers Med Sci 2018;33:343-51.
44. Giannotti E, Koutsikos K, Pigatto M, Rampudda ME, Doria A, Masiero S. Medium-/long-term effects of a specific exercise protocol combined with patient education on spine mobility, chronic fatigue, pain, aerobic fitness and level of disability in fibromyalgia. Biomed Res Int 2014;2014:474029.
45. Haak T, Scott B. The effect of Qigong on fibromyalgia (FMS): a controlled randomized study. Disabil Rehabil 2008;30:625-33.
46. Hakkinen A, Hakkinen K, Hannonen P, Alen M. Strength training induced adaptations in neuromuscular function of premenopausal women with fibromyalgia: comparison with healthy women. Ann Rheum Dis 2001;60:21-6.
47. Lynch M, Sawynok J, Hiew C, Marcon D. A randomized controlled trial of qigong for fibromyalgia. Arthritis Res Ther 2012;14:R178.
48. Mannerkorpi K, Nyberg B, Ahlmen M, Ekdahl C. Pool exercise combined with an education program for patients with fibromyalgia syndrome. A prospective, randomized study. J Rheumatol 2000;27:2473-81.
49. Sanudo B, Carrasco L, de Hoyo M, Figueroa A, Saxton JM. Vagal modulation and symptomatology following a 6-month aerobic exercise program for women with fibromyalgia. Clin Exp Rheumatol 2015;33:S41-5.
50. Palstam A, Mannerkorpi K. Work ability in fibromyalgia: an update in the 21st century. Curr Rheumatol Rev 2017;13:180-7.
51. Bidonde J, Busch AJ, Webber SC, et al. Aquatic exercise training for fibromyalgia. Cochrane Database Syst Rev 2014;10:CD011336.
52. Wood PB, Ledbetter CR, Glabus MF, Broadwell LK, Patterson JC. Hippocampal metabolite abnormalities in fibromyalgia: correlation with clinical features. J Pain 2009;10:47-52.
53. McCrae C, O'Shea A, Boissoneault J, et al. Fibromyalgia patients have reduced hippocampal volume compared with healthy controls. J Pain Res 2015;8:47.
54. González-Roldán AM, Bomba IC, Diesch E, Montoya P, Flor H, Kamping S. Controllability and hippocampal activation during pain expectation in fibromyalgia syndrome. Biol Psychol 2016;121:39-48.
55. Martinez-Lavin M. Biology and therapy of fibromyalgia. Stress, the stress response system, and fibromyalgia. Arthritis Res Ther 2007;9:216.
56. Valim V, Natour J, Xiao Y, et al. Effects of physical exercise on serum levels of serotonin and its metabolite in fibromyalgia: a randomized pilot study. Rev Bras Reumatol 2013;53:538-41.

57. Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart: exercise effects on brain and cognition. Nat Rev Neurosci 2008;9:58-65.
58. Petzke F, Clauw DJ. Sympathetic nervous system function in fibromyalgia. Curr Rheumatol Rep 2000;2:116-23.
59. Sarzi-Puttini P, Atzeni F, Diana A, Doria A, Furlan R. Increased neural sympathetic activation in fibromyalgia syndrome. Ann N Y Acad Sci 2006;1069:109-17.
60. O'Connor PJ, Youngstedt SD. Influence of exercise on human sleep. Exerc Sport Sci Rev 1995;23:105-34.
61. Kubitz KA, Landers DM, Petruzzello SJ, Han M. The effects of acute and chronic exercise on sleep. A meta-analytic review. Sports Med 1996;21:277-91.
62. Stults-Kolehmainen MA, Sinha R. The effects of stress on physical activity and exercise. Sports Med 2014;44:81-121.
63. Karimi M, Yazdani Noori A. Serotonin and mood state changes in response to a period of yoga training in well-trained wrestlers. Int J Wrestl Sci 2015;5:89-92.
64. Pescatello LS; American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. 9th ed. Philadelphia: Wolters Kluwer; 2014.
65. Álvarez-Gallardo IC, Bidonde J, Busch A, et al. Therapeutic validity of exercise interventions in the management of fibromyalgia. J Sports Med Phys Fitness 2018;59:828-38.
66. Estévez-López F, Segura-Jiménez V, Álvarez-Gallardo IC, et al. Adaptation profiles comprising objective and subjective measures in fibromyalgia: the al-Ándalus project. Rheumatology 2017;56:2015-24.
67. Russell D, Álvarez Gallardo IC, Wilson I, et al. "Exercise to me is a scary word": perceptions of fatigue, sleep dysfunction, and exercise in people with fibromyalgia syndrome-a focus group study. Rheumatol Int 2018;38:507-15.
68. Estévez-López F, Álvarez-Gallardo IC, Segura-Jiménez V, et al. The discordance between subjectively and objectively measured physical function in women with fibromyalgia: association with catastrophizing and self-efficacy cognitions. The al-Ándalus project. Disabil Rehabil 2018;40:329-37.