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REVIEW

Effect of Exercise Programs on Symptoms of Fibromyalgia in Peri-Menopausal Age Women: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Alberto José Cerrillo Urbina, MSc[1], Antonio García-Hermoso, PhD[2], Mairena Sánchez-López, PhD[1,3], and Vicente Martínez-Vizcaíno, MD, PhD[2]

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Abstract

Objectives: The aim of this review and meta-analysis was to summarize evidence regarding the effect of physical exercise programs on fibromyalgia syndrome symptoms in peri-menopausal age women, and the characteristics of these programs.

Findings: Nineteen randomized controlled trials [$N = 1077$ women] satisfied the inclusion criteria. Methodological quality of papers was assessed using the PEDro scores. Data on the study, subject, and exercise program characteristics as well as assessment of changes in depression, fatigue, global well-being [overall feeling of well-being and health-related quality of life], pain, sleep, and stiffness were extracted. The studies were grouped according to the intervention program: land interventions [aerobic, combined [aerobic endurance, strength, and flexibility], vibrations, and alternative programs], and aquatic interventions. Nineteen studies were selected for systematic review, but clinical heterogeneity limited the meta-analysis to two aerobic, three combined, two alternative, and five aquatic studies.

Conclusions: In general, exercise programs have a positive effect on the symptoms of fibromyalgia in women in peri-menopausal age. The meta-analysis indicates that programs based on combined exercise and aquatic exercises have, respectively, a moderate [$d = -0.63$; $I^2 = 0\%$] and small effect [$d = -0.41$; $I^2 = 30\%$] on functional global well-being [assessed using the Fibromyalgia Impact Questionnaire total score]. Short-term interventions [12 weeks], including two to three sessions lasting 30–60 min each per week seem to improve symptoms in peri-menopausal age women with fibromyalgia, although high-quality studies with larger sample sizes are necessary to confirm these results.

Keywords: Menopausal, perimenopause, fibromyalgia, exercise, global well-being, randomized controlled trial, systematic review, meta-analysis

INTRODUCTION

Fibromyalgia syndrome [FMS] is a syndrome characterized by widespread pain, fatigue, sleep disturbance and/or joint stiffness, paresthesia, anxiety, and stress (1,2). In addition, it has been associated with restrictions to participating in daily life activities and, in general, with a worse quality of life (2). The prevalence of FMS in the general population is estimated to be 0.5–5% (3), and it is higher in women [73–95%] than in men (4).

Women with FMS are less active than women without this condition (5). The symptoms characteristic of this syndrome might stop many patients performing sufficient physical activity to gain

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health benefits (6). However, studies have found that programs including aquatic exercises (7), a combination of aerobic exercise and stretching at home (8), pilates (9), yoga (10), giqong (11), or tai chi (12) might relieve the symptoms of FMS and improve the patient's quality of life. Increasing benefits have been reported when combined with exercise self-management education (13,14).

During menopause, women frequently face vasomotor symptoms [hot flashes, night sweats], insomnia, paresthesia, nervousness, dizziness, weakness, joint pain/muscle pain, headache, and palpitations (15). These symptoms are often accompanied by anxiety and stress, which facilitate the occurrence of depression and weight gain (16,17). Around 3% of women with FMS are at an age at which menopause appears (3), and it is assumed that these women not only experience the symptoms of both conditions (15,16) but that the conditions also exacerbate each other (18).

Physical exercise might be an effective strategy to reduce the symptoms of both menopause (19,20) and FMS, but to our knowledge the evidence regarding its effectiveness has not yet been synthesized. The purpose of the present systematic review and meta-analysis was thus to summarize, in peri-menopausal age women with FMS, evidence regarding the ability of physical exercise programs to control FMS symptoms, and the characteristics of these programs.

METHODS

Data sources and searches

Five databases covering the period from 1980 to October 2014 [PubMed, Scopus, Science Direct, EBSCO [E-journal, CINAHL, SportDiscus], and The Cochrane Library] were searched. Manual searches were also conducted, but resulted in the inclusion of no further articles. The search terms used were: [''menopause'' OR ''postmenopausal'' OR ''premenopausal'' OR ''peri-menopause'' OR ''menopause symptoms'' OR ''early menopause'' OR ''elderly woman'' OR ''women'' OR ''female''] AND [''fibromyalgia'' OR ''fibromyalgia syndrome'' OR ''therapy fibromyalgia'' OR ''treatment fibromyalgia''] AND [''exercise'' OR ''physical fitness'' OR ''physical activity'' OR ''mind-body therapies'' OR ''tai chi'' OR ''yoga'' OR ''pilates'' OR ''qigong''].

Study selection

The criteria for inclusion were as follows: [1] Patients: peri-menopausal age women [or mean age 45–60 years] diagnosed with FM syndrome based on American College of Rheumatology criteria (1); [2] Type of study: randomized controlled trial [RCT], in which the control group received no physical exercise intervention; [3] Type of intervention: physical exercise programs, participants that were taking regular medication and could not change the pharmacological treatment during the trials, studies in which exercise was part of a multicomponent therapy involving a combination of exercise and alternative therapy were excluded (21); and also excluding those limited to testing the effect of exercise on improving the components of fitness and/or strength without reporting the effect on the symptoms of FMS and menopause; [4] Main outcome: for the meta-analysis we only selected trials that used the Fibromyalgia Impact Questionnaire [FIQ] as a measure of global well-being, as previous research suggested that the pooling of global well-being instruments might result in biased meta-analyses (22); and [5] in English or Spanish language. Finally, no restrictions on frequency or duration of training were imposed. The search was conducted between the 1st and the 15th of October 2014.

A protocol for data extraction was designed in order to obtain the information from each selected study according to predefined criteria listed below. Verification was performed first by title and abstract, considering the following questions: Is the effect of exercise studied? Does the study include peri-menopausal age women [or mean age 45–60 years] diagnosed with FMS syndrome? Does it include women with FMS? Are symptoms or quality of life in postmenopausal age women and/or FMS reported? Does exercise with menopause and/or FMS? Two negative responses were the criterion for exclusion; therefore, when there was one or no negative response, the evaluators [A.J. and A.G.] proceeded to full text verification. When there were doubts about a study's eligibility from the abstract, the authors examined the full text of the article.

Data collection

A codebook was designed for data extraction including the following major categories: [1] characteristics of trial participants [number, age, year of symptoms, and diagnosis]; [2] intervention features [type, duration, frequency, and intensity of physical exercise]; [3] results of outcomes [before and after the intervention]. The two above-mentioned authors independently extracted the data from each selected article.

Quality assessment [risk of bias]

The quality of the studies was evaluated using Physiotherapy Evidence Database [PEDro] criteria: Trials [but not reviews or guidelines] were rated using the PEDro scale which includes 11 items designed for rating the methodological quality of RCTs. These items evaluate some quality criteria, including random allocation, concealment of allocation, comparability of groups at baseline, blinding of patients, therapists and assessors, analysis by intention to treat and adequacy (23).

Data analysis

For the data analysis, effect sizes [*d* Cohen] and 95% confidence intervals [CI] were calculated using *t* scores, number of subjects, and standard deviation [standardized mean differences]. Cohen's categories were used to evaluate the magnitude of the effect size, calculated according to the standardized mean difference [*d*] statistic and considering scores of $d \geq |0.8|$ as a large effect, scores from $\geq|0.5|$ to $<|0.8|$ as medium, scores from $\geq|0.2|$ to $<|0.5|$ as small, and scores $\geq|0.1|$ to $|0.2|$ as trivial (24). Pooled data were calculated for the studies, which were grouped into three categories: aerobic (8,13), combined (13,25,26), vibration (27), alternative (10,28) and aquatic (7,29–32) programs. Due to the heterogeneity of the outcome measures of the studies, only the changes in global well-being as assessed by the total score from the FIQ were considered for meta-analysis.

Assessment of heterogeneity

The heterogeneity of the studies was assessed using Cochran's Q-statistic applied to the *d* (33). The percentage of total variation across the studies due to heterogeneity was determined using I^2. The magnitude of the inconsistency was assessed as follows: small if $0 \leq I^2 \leq 25\%$, medium if $25\% < I^2 \leq 50\%$, and large if $I^2 > 50\%$ (34).

Sensitivity analysis

In order to analyze the influence of each study on the overall results, each study was deleted from the model once and the pooled analyses were conducted without this study in the model.

Assessment of bias

Given the small number of studies as well as the lack of between-study heterogeneity, bias assessment results were not incorporated into the statistical analysis (35).

RESULTS

Study selection

After screening all 572 studies identified by the literature search strategy, 501 did not meet the inclusion criteria, and thus 71 potentially relevant references were included in the next stage, during which the publication was re-evaluated based on the full text. Fifty-one studies were subsequently rejected, and the remaining 19 RCTs were grouped, according to the content of the intervention, into land interventions [aerobic, combined, vibrations, and alternative programs] and aquatic interventions [Figure 1].

Study characteristics and interventions

The characteristics of the 19 studies included in this review (7,8,10,11,13,25–32,36–41) are detailed in Table 1.

Exercises were supervised in eight studies by an instructor [a physical therapist] (7,10,11,28–30,39,40). The other three were supervised in the first session and then subjects received a prescription for exercise at home (8,13,38). In some cases participants were taught how to monitor their heart rate and adjust their activity to maintain the correct exercise intensity (8). For their part, the studies did not report whether the subjects were unable to perform the exercises. Two studies included educational sessions (29,40). In one study, all the patients were asked not to change their medication during the study period (28). Finally, the studies, with one exception (29), did not take into account whether the subjects took medication.

Aerobic programs

Five studies evaluated the effectiveness of aerobic exercise in women with FM (8,13,36,38,39). The program content was based on aerobic work and stretching. In four of the studies, aerobic exercise consisted of walking (13,36,38,39), sometimes complemented with dance (36); the remaining study involved conducting aerobic exercises at home (8). Exercise intensity began at 60–70% of maximum heart rate [HRmax] and was gradually increased to a maximum of 75–85%.

Combined programs

Four studies evaluated a combined exercise program [aerobic, endurance, strength, and flexibility] in women with FM (13,25,26,37). Aerobic exercise consisted of walking or dancing (37), and began at 60–70% of HRmax and was gradually increased to as

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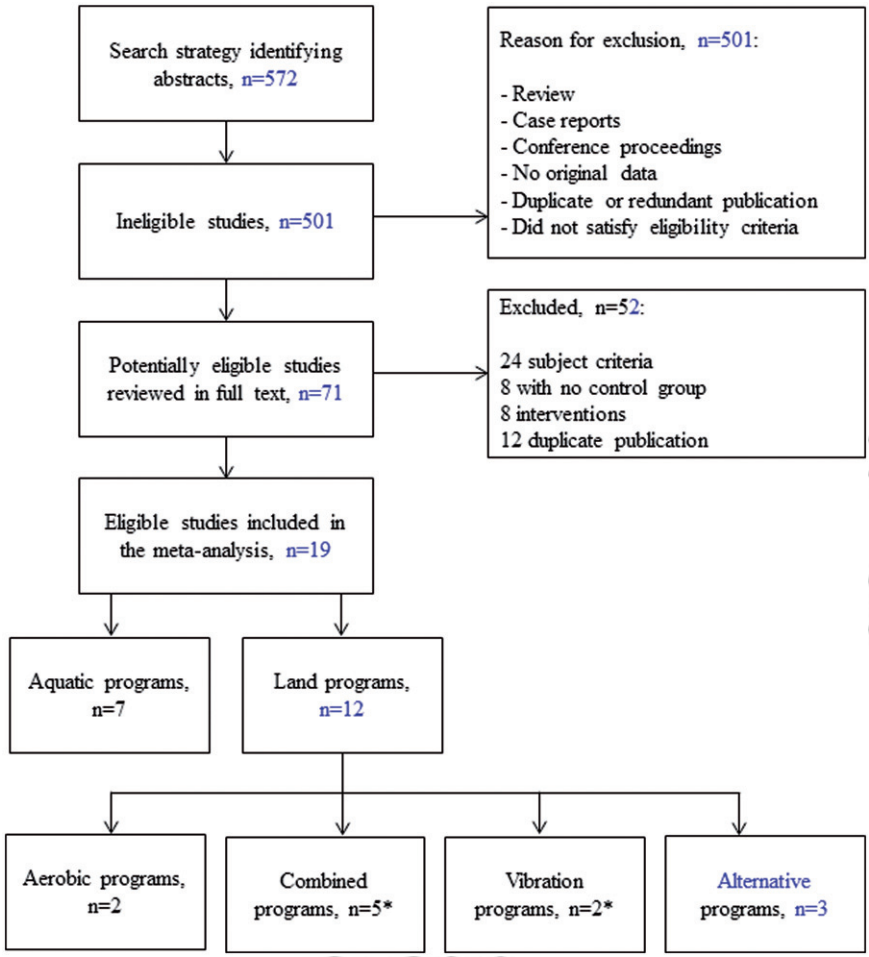

FIGURE 1. Flowchart for the selection of studies. *Three studies (13,36,39) were included in several groups as they had two experimental groups [aerobic and combined program interventions] and a control group.

high as 75–85%, depending on the subjects' adaptation. Muscle strengthening involved performing 12 sets of 8–10 repetitions with several muscle groups, using machines, dumbbells, or the subjects' own weight. Finally, the program included 10 min of flexibility training with eight to nine exercises [one set of three repetitions, maintaining the stretched position for 30 s].

Vibration programs

Two studies evaluated the effect of aerobic exercise combined with a vibration platform in women with FMS (27,39). Vibration programs consisted of a series of six exercises [30 s each] repeated six times with a recovery of 3 min between repetitions. The whole body vibration [WBV] intensity was kept constant at 30 Hz (39), with six repetitions of tilting WBV at a frequency of 12.5 Hz, and a rest interval of 60 s between each repetition; the duration of each repetition was 30–60 s (27).

Alternative programs

Three studies evaluated the effect of yoga (10) or qigong (11,28) exercise in women with FMS. Each yoga class included ~40 min of gentle stretching poses, 25 min of mindfulness meditation, 10 min of breathing techniques, 20 min of didactic presentations on the application of yogic principles to optimal coping, and 25 min of group discussion. Qigong, within Chinese medicine, is one of the four main methods aimed at improving health, vitality, and healing (11). The sessions had a duration of ~90 min, body awareness therapy comprised various breathing and postural techniques and qigong. Relaxation, grounding, breathing, and concentration were performed either in a supine or standing position.

Aquatic programs

Seven studies evaluated the effect of aquatic exercise on women with FMS (7,29–32,40,41). Only two

Table 1. Characteristics of studies included in the systematic review.

Study	Participants (n, years)	Interventions EG	CG (n)	Duration (weeks)	Follow-up (weeks)	Outcomes (symptoms)	Adherence (%)	PEDro score
Da Costa et al. (8)	$n=79$, 49.2	$n=39$. Aerobic: aerobic exercise and stretching at home. Four sessions of 90″ in the first 12 weeks. At home 60–120″ weekly aerobic exercise and stretching	None ($n=40$)	12	12, 24, and 36	- Pain, fatigue, stiffness, anxiety, depression (FIQ) - Psychological symptoms (SCL-90R) - Severity Index (GSI)	77.21	8
Rooks et al. (13)	$n=207$, 48.0	EG1 ($n=51$). Aerobic: aerobic exercise (walking 45′) and flexibility, two times per week in sessions of 60′ EG2 ($n=51$). Combined: aerobic and flexibility both for 20′ and strength training for 25′ (six exercises combination machines)	Edu ($n=50$)	16	–	- Pain, fatigue, sleep, stiffness, anxiety (FIQ) - HRQoL and physical function (SF-36) - Depression (BDI) - Self-efficacy scale pain and other symptoms	65.21	7
Sañudo et al. (36)	$n=64$, 55.9	EG1 ($n=22$). Aerobic: aerobic exercise (walking and aerobic dance), two times per week in sessions of 60′ EG2 (n = 21): Combined: EG1, Strength training (8–10 reps 8 muscle groups) and flexibility, sessions lasted 60′–90′	None ($n=20$)	24	12 and 24	- Pain, fatigue, sleep, stiffness (FIQ) - Depression (BDI) - HRQoL (SF-36).	85.93	6
Sañudo et al. (37)	$n=42$, 55.9	$n=18$. Combined: Aerobic exercise (walking, running or dancing), strength training (8–10 reps 8 muscle groups) and flexibility, two times per week in sessions of 60′	None ($n=20$)	24	–	- HRQoL (SF-36) - Depression (BDI)	90.47	7
Sañudo et al. (25)	$n=42$, 55.5	$n=18$. Combined: Aerobic exercise (walking), strength training (8–10 reps 8 muscle groups) and flexibility, two times per week in sessions of 60′	None ($n=20$)	24	–	- Pain, fatigue, sleep, stiffness, anxiety, depression (FIQ) - Depression (BDI) - HRQoL (SF-36).	90.47	8

(*continued*)

Table 1. Continued

Study	Participants (*n*, years)	Interventions EG	CG (*n*)	Duration (weeks)	Follow-up (weeks)	Outcomes (symptoms)	Adherence (%)	PEDro score
Meyer and Lemley (38)	*n* = 21, 49.5	EG1 (*n* = 8). Aerobic: low-intensity aerobic exercise (walking), three times a week, gradually increasing 12′–30′ EG2 (n = 8). Aerobic: EG1 high intensity	None (*n* = 5)	24	12 and 24	- Pain, fatigue, sleep, stiffness, anxiety, depression, physical function, wellness (FIQ). - Pain (HAQ) - Anxiety (SAI) - Depression (BDI) - Self-report functional ability (HQA-SDI)	38.09	2
García-Martínez et al. (26)	*n* = 28, 59.3	*n* = 14. Combined: Aerobic exercise (walking + progressive intensity movements), stretching and strength exercises, three times per week in sessions of 60′	None (*n* = 14)	12	–	- Pain, fatigue, sleep, stiffness, anxiety, depression (FIQ) - HRQoL (SF-36). - Self-esteem (The Rosenberg Self-Esteem Scale)	89.28	4
Alentorn-Geli et al. (39)	*n* = 36, 55.2	EG1 (*n* = 12). Aerobic: Aerobic activities (dance), stretching and relaxation techniques, two times per week in sessions of 90′ EG2 (*n* = 12). Vibration: EG1 and WBV, six exercises on platform (30 s each). 30 Hz frequency and intensity amplitude 2 mm	None (*n* = 12)	6	–	- Pain, fatigue, sleep, stiffness, anxiety, depression (FIQ)	91.66	6
Olivares et al. (27)	*n* = 41, 53.0	*n* = 21. Vibration: WBV, three times a week, 10′ warm-up (walking slow and slight movements) followed by six reps WBV (intensity 12.5 Hz), 60″ rest interval between each repetition. The time interval between each repetition throughout the treatment varies from 30″ to 60″.	None (*n* = 20)	12	–	- Health and physical function (FIQ) - HRQoL (15D)	87.80	8

Burckhardt et al. (40)	$n = 86$, 46.5	$n = 28$. Pool exercise: two pool therapy sessions, and individual time to ride, walk or swim and Education Program (EG1)	None ($n = 30$)	12	12 and 32	- Pain, fatigue, stiffness, anxiety, depression, wellness (FIQ) - Sense of control over her disease (FAI) - Scale Quality of life (QOLS-S) - Self-Efficacy (Self-Efficacy scale) - Depression (BDI)	89.58	5
Mannerkorpi et al. (29)	$n = 58$, 45.0	$n = 28$. Pool exercise: one time a week for 35′ and Education Program (coping strategies and symptoms) for six sessions of 1 h	None ($n = 30$)	24	–	- Pain, fatigue, sleep, stiffness, anxiety, depression (FIQ) - HRQoL (SF-36). - Self-Efficacy (ASES-S) - Quality of life (QOLS) - Anxiety and depression arthritis impact (AIMS)	84.05	5
Redondo et al. (30)	$n = 40$, 52.5	$n = 21$. Pool exercise: Exercises in hot water pool (one session), strength and flexibility exercises (two sessions), isokinetic exercises with weights (two sessions). Each session once a week with a duration of 45′.	Edu ($n = 19$)	8	8, 24, and 52	- Pain, fatigue, sleep, stiffness, anxiety, depression, wellness (FIQ) - HRQoL (SF-36) - Anxiety (BAI) - Depression (BDI) - Self-Efficacy Scale (CPSS) - Self-Efficacy Pain (The Chronic Pain Coping Inventory) - Pain (scale likert five points)	77.50	6
Tomas-Carus et al. (31)	$n = 34$, 51.0	$n = 17$. Pool exercise: Aerobic exercise and exercise extreme hard water resistance (four sets of 10 repetitions flexion and knee extension at a slow pace, with vertical body) in pool hot water (33 °C), three times per week in sessions of 60′	None ($n = 17$)	12	12 and 24	- HRQoL (SF-36). - Physical and mental health (FIQ)	97.05	5

(*continued*)

Table 1. Continued

Study	Participants (*n*, years)	Interventions EG	CG (*n*)	Duration (weeks)	Follow-up (weeks)	Outcomes (symptoms)	Adherence (%)	PEDro score
Munguia-Izquierdo and Legaz-Arrese (32)	*n* = 60, 50.0	*n* = 21. Pool exercise: Exercises in pool hot water (32 °C) at breast height, slow walking and mobility 10′, slow progressive force exercises 10′–20′, aerobics 20′–30′ and low intensity exercises 10′, three times a week.	None (*n* = 25)	16	–	- Pain (VAS) - Pain, fatigue, stiffness, anxiety, depression, wellness (FIQ) - Cognitive function (PASAT and TMT)	88.33	5
Tomas-Carus et al. (7)	*n* = 33, 50.7	*n* = 17. Pool exercise: Aerobic exercise, lower extremity strength with water resistance to waist (four sets of 10 knee flexion-extension) in hot water pool and upper limb strength exercises without water resistance (four sets of 10 repetition lifting arms over head), three times per week in sessions of 60′.	None (*n* = 16)	32	–	- Pain, fatigue, sleep, stiffness, anxiety, depression (FIQ) - Anxiety and Somatic disorders (STAI)	90.90	6
Munguia-Izquierdo and Legaz-Arrese (41)	*n* = 60, 50	*n* = 35. Pool exercise: aerobic exercise, resistance exercise with slow strength in hot water up to his chest in pool (exercise multiple muscle groups) and relaxation, three times per week in sessions of 60′	None (*n* = 25)	16	16 and 48	- Tender points (Syringe calibrated) - Health (FIQ) - Sleep Quality (PSQI) - Psychological State (SAI) - Cognitive Function (PASAT)	78.33	7
Mannerkorpi et al. (28)	*n* = 36, 45	*n* = 19. Qigong: The qigong movements were performed for 20′ while standing still, focusing on relaxation, grounding and concentration. The sessions were completed with a short discussion about the movements. One time per week in sessions of 90′	None (*n* = 17)	12	–	- Pain, fatigue, anxiety, depression (FIQ)	63.15	5
Haak and Scott (11)	*n* = 57, 53.3	*n* = 29, Qigong: Practice of the Qigong, known as the Lotus method (He Hua Gigong). Nine group sessions, the total amount of time was 11.5 h.	None (*n* = 28)	7	–	- Anxiety (STAI) - Depression (BDI) - Quality of Life (WHOQOL-BREF) - Daily self-recordings,	92.98	5

Carson et al. (10)	$n = 53$, 53.7	$n = 25$. Yoga: stretching, relaxation, and meditation. One time per week in sessions of 75′	None ($n = 28$)	8	–	pain, sleep and psychological health and distress (VNS) - Pain, fatigue, sleep, stiffness, anxiety, depression (FIQ) - Rate overall improvement symptoms (PGIC) - Pain acceptance (CPAQ) - Pain catastrophizing (CSQ) - Pain coping (VMPCI)	90.56	7

Edu = education program; None = no intervention; FIQ = Fibromyalgia Impact Questionnaire; SF-36 = Short-Form health survey with only 36 questions; BDI = Beck Depression Inventory; VAS = Visual Analogue Scale; HAQ = The Pain scale of the health Assessment Questionnaire; SCL-90R = The symptom checklist 90-revised; GSI = The global severity index; WBV = Whole-body vibration; HQA-SDI = Health Assessment Questionnaire Disability Index; SAI = State anxiety Inventory; 15D = The general HRQoL questionnaire was the 15D; FAI = The Fibromyalgia attitudes Index; QOLS-S = The quality of life scale; ASES-S = The Arthritis Self-Efficacy Scales; AIMS = The Arthritis Impact Measurement Scales; CPSS = The Chronic Depression Inventory; BAI = Beck Anxiety Inventory; PASAT = The Paced Auditory Serial Addition Task; TMT = Trail Making Test; STAI = State-Trait Anxiety Inventory; PSQI = Pittsburgh Sleep Quality Index; PGIC = Patient Global Impression of change; CPAQ = The Chronic pain acceptance questionnaire; VMPCI = Vanderbilt Multidimensional Coping Inventory; WHOQOL-BREF = The World Health Organization Quality of Life BREF; VNS = Visual Numerological Scale

studies reported the water temperature. The exercises were conducted in shallow pools with water temperatures of 32–33 °C (31,32). Aerobic exercises were performed at an intensity of 65–75% HRmax for 45–50 min, and were combined with exercises for strength in the lower extremities [four sets of ten repetitions of knee flexion and extension] and flexibility (7,31). The session ended with 10 min of cool-down with low intensity exercises and relaxation (7,41).

Methodological quality of studies

A total of 89.47% of the studies fulfilled at least 50% [5/10] of the PEDro criteria (23) [Table 1].

Participants

The 1077 women included were recruited mostly from general inquiries Associations of Rheumatology and FMS, and ranged in age from 45 to 60 years [mean 51.53 years; SD 7.94 years]. Of these, 200 participated in aerobic activities, 50 participated in combined activities, 45 in vibration programs, 73 in alternative activities, and 167 in aquatic exercise programs. The average sample size of all groups was 28.16 subjects. The mean duration of symptoms was 13.43 ± 8.34 years (7,8,11,26–29,31,32,40,41), the mean number of years after diagnosis was 7.63 ± 4.1 (8,10,13,39), and the mean number of tender points was 14.69 ± 2.85 (7,8,10,11,27–29,31,32,40,41). However, five of the studies included in this systematic review did not provide information about these issues (25,30,36–38).

Adherence, dropouts and adverse effect

The adherence rate was high in all studies [greater than 65%], although in one study subjects abandoned the program due to illness and refusal to participate in a regular walking program [38.09%] (38). One study reported increased pain after the first 3–4 d due to the initial exercise intensity, requiring a reduction in the latter (29). A study presented low adherence, the reasons were time restrictions, surgery, feeling depressed, muscle inflammation, and high pain intensity (28). Another patient experienced an anxiety attack during the first session of WBV (39). To calculate the compliance of home-based exercise (8), following each exercise session, participants completed exercise logs which included information regarding the type of exercise performed; this methodology has previously been validated (42). Average weekly adherence rates were calculated as the ratio of the number of exercise sessions reported to the number

Table 2. Effects of physical exercise on the different parameters evaluated.

	Aerobic ($n=4$)	Combined ($n=3$)	Vibration ($n=2$)	Alternative ($n=3$)	Aquatic ($n=7$)	Total ($n=19$)
Pain	100	66.7	100	100	100	94.74%
Fatigue	100	66.7	100	66.7	100	89.47%
Sleep	75	66.7	100	100	100	89.47%
Stiffness	100	66.7	100	66.7	100	89.47%
Anxiety	50	100	100	100	100	89.47%
Depression	100	100	100	66.7	100	94.74%
Wellness	25	–	–	–	14.3	10.53%
Quality of life	50	100	50	33.3	57.1	57.89%
Physical function	50	33.3	–	–	14.3	21.05%
Self-esteem	–	25	–	–	–	5.26%
Self-Efficacy	25	–	–	–	28.6	15.79%
Cognitive function	–	–	–	33.3	28.6	15.79%
Somatic disorders	–	–	–	–	14.3	5.26%

The values indicate the number of studies (%) that observe improvements between EG versus CG ($p<0.05$)

of sessions prescribed. In general, dropouts were mainly for reasons unrelated to the study [work problems, family, and FMS-unrelated diseases].

Outcomes measures

There was much variability in outcomes measures [Table 1]. The most commonly evaluated symptoms were functional global well-being and pain.

Synthesis of results

Table 2 describes the effect of physical exercise on each of the symptoms evaluated in women with FMS. Pain, fatigue, sleep, stiffness, and anxiety improved with all types of exercise. Depression and quality of life were also positively influenced by all types of program, with the exception of yoga exercises. Finally, self-esteem was only assessed in combined programs, which also had a positive effect. Finally, somatic disorders improved only with aquatic exercises, which had a positive influence on all symptoms.

Meta-analysis [findings for global well-being using the FIQ]

Figure 2 shows the d [95% CI] for each study and each pooled subgroup. Overall, combined [$d=-0.63$, 95% CI, -0.99 to 0.27] and aquatic programs [$d=-0.41$, 95% CI, -0.68 to -0.14] improved the global well-being of women with FM [$p<0.05$] using fixed effect models. No statistically significant within-group heterogeneity was found [combined, $Q=1.61$, $p=0.43$, $I^2=0\%$; aquatic, $Q=5.73$, $p=0.22$, $I^2=30\%$]. There were not enough vibration studies with controlled comparison groups to carry out a meta-analysis.

Sensitivity analysis

With each outcome deleted from the model once, the results remained statistically significant across all deletions for both combined and aquatic programs. The results were also the same after removing studies including peri-menopausal age women (8,13,29,38,40).

DISCUSSION

To the best of our knowledge, this manuscript is the first systematic review and meta-analysis examining the evidence for the effect of physical exercise programs in peri-menopausal age women with FMS. In view of the results of the meta-analysis, the pooled analysis of the evaluated studies reveals that the effectiveness of exercise on controlling FMS symptoms is: [1] moderate for combined programs including aerobic endurance, strength, and flexibility exercises; [2] low for aquatic programs; and [3] not sufficiently proven to be able to recommend aerobic programs and yoga, although it should be noted that yoga is a promising alternative. Therefore, our findings are in accordance with previous reviews and recommendations for FMS management in other less specific populations (21,35,43–45).

Aerobic programs

Two meta-analyses (21,35) have reported a beneficial effect on global well-being in FMS patients. Our results, although showing a positive effect on some symptoms such as pain, stiffness, and depression, even after 9 months follow-up (8), did not confirm an improvement in global well-being [$d=-0.10$, 95% CI, -0.43 to 0.24; $p>0.05$] [Figure 2]. It should be noted that some studies evaluating the

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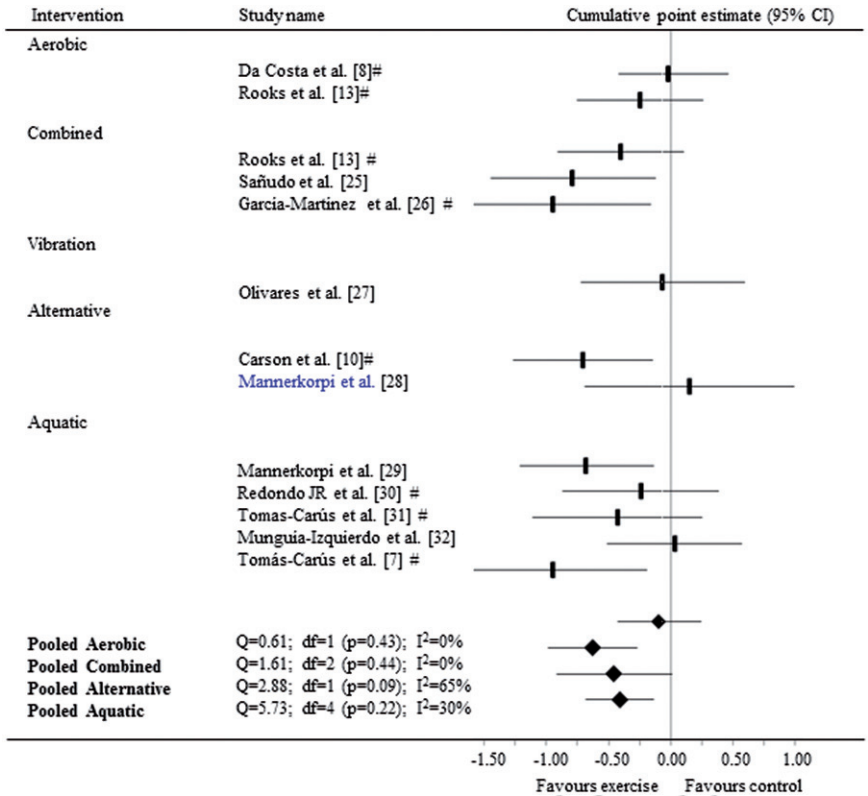

Q6 FIGURE 2. Effect sizes [*d*] and 95% CI of difference for each study and intervention type. #The change in the FIQ total score was clinically relevant [≥14%] (46). Three studies (36,38–40) were not included in the figure because it was impossible to calculate effect sizes due to insufficient data being presented.

effectiveness of aerobic exercise did not meet our inclusion criteria (36,38), and that those studies revealed changes in the FIQ total score that were clinically relevant [≥14%] (46). In general, analysis of the available studies indicates that low-intensity exercise might mitigate FMS symptoms in the medium-to-long term [24 weeks]; however, vigorous physical activity might increase pain in these patients (38).

Combined programs

The effectiveness of combined programs in the control of FMS symptoms has been reported in previous reviews (47). Our meta-analysis revealed an improvement [moderate effect] in global well-being [$d = -0.63$, 95% CI, −0.99 to 0.27] [Figure 2]. In addition, combined programs result in clinically relevant improvements in pain, health-related quality of life [HRQoL] and social well-being (25,48). Finally, it is noteworthy that this type of training does not exacerbate the symptoms of these women, and conversely diminishes their fatigue (48). For this purpose, it is essential to prescribe recovery times between workouts, and to plan the progression of both aerobic and strength exercises carefully. In summary, our results highlight the importance of including endurance and flexibility exercises with aerobic work in physical exercise programs aimed at this population of patients (36) in order to maximize their physical function and well-being (49).

Vibration programs

The WBV vibration is a mode of exercise that has recently been utilized to improve muscle strength, bone density, and balance in healthy adults (50) and aging populations (51). The results of the current systematic review show that women who attended programs including WBV showed improvements in pain and fatigue (39), avoiding deterioration, and maintaining their HRQoL (27) to a greater extent than women in the control group. It is noteworthy that this type of exercise improves symptoms, especially pain and fatigue, from the start of the intervention, and that this improvement is maintained over time (39). A daily walking activity in addition to using WBV improves balance and prevents falls in this group of women (52). The two included studies that evaluated WBV (27,39) concluded that these programs mitigate symptoms and increase HRQoL.

Alternative programs

Several systematic reviews and meta-analyses have reported that alternative and meditative movement therapies [tai chi, yoga, and qigong] constitute a safe and effective strategy to improve FMS symptoms (53,54), although all also noted the need for high-quality studies with larger sample sizes to confirm these results. In accordance with these findings, the only study included yoga exercise in the current review testing the effectiveness of yoga in women with FMS showed that this intervention modality is moderately effective at controlling FMS symptoms in perimenopausal age women, although this requires further study. The qigong exercise showed mixed results, since one study reported that long-term programs do not appear to be generally recommendable for patients with FM with long-term symptoms due to the reported adverse effects (28), another study reported that the obtained results are merely placebo effects, even though authors concluded that their study supports that short qigong intervention has beneficial and long-lasting effects (11).

Aquatic programs

Studies that assessed aquatic training programs for patients with FMS indicated improvements in walking ability, well-being, and fatigue (29,49). The follow-up studies also indicated improvements in anxiety, depression, self-efficacy, and insight into the disease (43,55). Our meta-analysis showed that aquatic programs slightly improved global well-being [$d = -0.41$, 95% CI, −0.68 to −0.14] [Figure 2]. Overall, studies have shown improvements in pain threshold and a reduction in the number of tender points (32). These improvements seem to persist even in the long term (7), even in the case of anxiety and depression (43). Hot pools set at 32–33 °C [a common water temperature for pool studies cited in this review] are well tolerated by people with FMS [they are more sensitive to cold] (32), generating a positive feeling of well-being and a reduction in pain and stiffness (29,49). The buoyancy of water facilitates the performance of movements, and thus also enhances the learning of relaxation and body awareness (49). Movements and exercise load can be easily adjusted to the limitations of each patient, which allows the duration of treatments in this medium to be lengthened (7). Therefore, aquatic exercise can be an effective intervention for women with FMS (43) and menopause.

Outcomes measures [assessments]

The outcome measure chosen [FIQ] has been one of the most frequently used assessment tools in the evaluation of FMS, and has been particularly useful as an outcome measure in FMS clinical trials. The FIQ has been translated from English into 12 languages, and is a valid 10-item instrument that assesses physical function, common symptoms, and general well-being (38). A total score may be obtained after normalization of some items and summing of all visual analog scales [pain, sleep, fatigue, morning stiffness, anxiety, and depression]. The questionnaire is scored from 0 to 100 [0–80 without job-related items], in which a higher score indicates a greater impact of the syndrome on the person.

The two most commonly used instruments in this systematic review were the Short-Form Health Survey [SF-36] and the Beck Depression Inventory [BDI]. These questionnaires cover the symptoms of both FMS and menopause. Studies often included other instruments for assessing parameters such as physical function, self-esteem, self-efficacy, cognitive function, and somatic disorders. The heterogeneity of these questionnaires makes it difficult to reach global conclusions regarding the results of these studies [Table 1].

Regarding the symptoms examined, aquatic programs evaluated all symptoms other than self-esteem [Table 2]. Meanwhile, the number of evaluated symptoms decreased gradually in aerobic, combined, vibration, and alternative programs. Studies evaluating alternative and vibration programs in perimenopausal age women with FMS syndrome are scarce, but have shown a positive effect on the few symptoms assessed. Symptoms less frequently included as outcomes of studies are self-esteem, self-efficacy, cognitive function, and somatic disorders and, in our opinion, all should be considered in future trials.

Approach of interventions

Most of the studies included in this systematic review and meta-analysis included group activities (7,10,11,13,25,27–32,36,37,39,41). Individual sessions are less expensive, although group exercise has a greater impact on health in this population (56). Individual strategies do not seem to produce psychological improvements, require more effort and perseverance, and the dropout rate is much higher (8). Thus, it seems reasonable to suggest that, in order to increase compliance, group strategies should be adopted in the implementation of physical

exercise programs in peri-menopausal age women with FMS, and that these programs might be reinforced by including individual exercises at home (8).

The lack of compliance to physical exercise in this population at the beginning of a program often depends on the appearance of pain after exercise; two sources have been suggested: sometimes interrupting the exercise causes pain (57), but sometimes pain appears as the intensity of exercise decreases (29). This problem seems to be reduced or avoided when implementing continued and progressive exercise (44). In this respect, several reports have shown improvements at 12 months (30), with relief of pain and alleviation of several emotional problems (31). The analgesic effect of physical exercise by breaking the vicious cycle of pain–immobility–pain might favor adherence (9). So, in our opinion, the intensity of exercise must be individually adjusted depending on the perception of pain (29). On the other hand, there is no evidence that high-intensity exercise produces more benefits than moderate exercise, and therefore it seems more appropriate to recommend physical exercise at low–moderate intensity for this population, and to tailor the prescription depending on the perception of pain (29,38).

Finally, some studies included educational programs in their designs (13,29,30,40). Educational programs appear to be complementary and beneficial for this population of patients (13,29). In general, these programs aim to develop self-control strategies to perform daily activities, to control symptoms, and to integrate physical activity into daily routines. Therefore, treatment programs combining education and exercise have been shown to improve function, symptoms, well-being and self-efficacy, and they may be more effective than either treatment alone (49).

Limitations

First, the search strategy was not conducted according to the Cochrane Collaboration procedures (58), although we employed exhaustive search methods. Second, due to heterogeneity between studies [there were numerous outcomes measures assessing the same constructs], it was only possible to perform a meta-analysis of global well-being measured using the FIQ (21). Similarly, some studies could not be included in the meta-analysis due to the lack of data for calculating the effect size [we repeatedly contacted primary authors for clarification and additional information, although responses were not always obtained]. Third, we limited the age range of the participants to the peri-menopause, since after this stage the characteristic symptoms of menopause often disappear, and therefore, do not overlap with the symptoms of FMS. Fourth, we have tried to contact with authors to request the age of the subjects and PEDro scale information, but have had no response from authors. Five, due to studies did not confirm the presence of peri-menopause, we decided to include all studies whose women mean age was from 45 to 60 years.

CONCLUSIONS

In our opinion, our results have clinical relevance and show that combined exercise programs [aerobic endurance, strength, and flexibility] and aquatic programs improve various symptoms in peri-menopausal age women with FMS [pain, fatigue, sleep disorders, anxiety, depression, somatic symptoms, quality of life, well-being, and self-esteem]. Thus, the results of the meta-analysis reinforce findings showing moderate and small change in global well-being through these programs. On the other hand, there is less evidence regarding the benefits of aerobic exercise, vibration, and alternative programs [yoga and qigong]. In general, short-term interventions [12 weeks] including two to three sessions lasting 30–60 min each per week seem to mitigate FMS symptoms in peri-menopausal age women. However, due to the small number of studies on each type of intervention, the results need to be interpreted with caution.

Directions for future research

Suggestions for future research follow the EPICOT structure for formulating research recommendations (59). The main elements are: [E] Evidence [current]: physical exercise provides benefits for health-related fitness (60) and may decrease bone loss in menopausal women (61); [P] Population: studies in women with FMS syndrome and peri-menopause; [I] Intervention: aquatic exercise programs combined with educational programs; [C] Comparison: no active treatment (treatment as usual control) or education treatment group; [O] Outcomes: to evaluate the long-term effects on health in this population; [T] Time stamp: December 2015. The optional elements were: [d] Disease burden: the prevalence of FMS plus menopause is three percent (3); [t] Timeliness: long-term interventions [at least 24 weeks, two sessions a week, each lasting 60 min]; [s] Study type: randomized controlled trial.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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