Systematic Review and Meta-Analysis

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Efficacy of nonpharmacological interventions for individual features of fibromyalgia: a systematic review and meta-analysis of randomised controlled trials

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Abstract

Fibromyalgia is a highly heterogeneous condition, but the most common symptoms are widespread pain, fatigue, poor sleep, and low mood. Nonpharmacological interventions are recommended as first-line treatment of fibromyalgia. However which interventions are effective for the different symptoms is not well understood. The objective of this study was to assess the efficacy of nonpharmacological interventions on symptoms and disease-specific quality of life. Seven databases were searched from their inception until June 1, 2020. Randomised controlled trials comparing any nonpharmacological intervention to usual care, waiting list, or placebo in people with fibromyalgia aged >16 years were included without language restriction. Fibromyalgia Impact Questionnaire (FIQ) was the primary outcome measure. Standardised mean difference and 95% confidence interval were calculated using random effects model. The risk of bias was evaluated using the modified Cochrane tool. Of the 16,251 studies identified, 167 randomised controlled trials (n = 11,012) assessing 22 nonpharmacological interventions were included. Exercise, psychological treatments, multidisciplinary modality, balneotherapy, and massage improved FIQ. Subgroup analysis of different exercise interventions found that all forms of exercise improved pain (effect size [ES] −0.72 to −0.96) and depression (ES −0.35 to −1.22) except for flexibility exercise. Mind–body and strengthening exercises improved fatigue (ES −0.77 to −1.00), whereas aerobic and strengthening exercises improved sleep (ES −0.74 to −1.33). Psychological treatments including cognitive behavioural therapy and mindfulness improved FIQ, pain, sleep, and depression (ES −0.35 to −0.55) but not fatigue. The findings of this study suggest that nonpharmacological interventions for fibromyalgia should be individualised according to the predominant symptom.

Keywords: Fibromyalgia, Nonpharmacological intervention, Meta-analysis

1. Introduction

Fibromyalgia is a common condition affecting 2% to 8% of the general population.[45] It manifests with multiple regional pain and other symptoms such as fatigue, low mood, nonrestorative sleep, and cognitive dysfunction.[201,202] It has a substantial impact on quality of life (QoL)[87] and results in a 5-fold higher health-care expenditure.[23] Its diagnosis and management are often challenging because of heterogeneous manifestations and differences between individuals with respect to dominant symptoms.[113,194]

Nonpharmacological interventions are recommended as the first-line treatment for fibromyalgia in multinational recommendations.[61,114] However, a comprehensive systematic review (SR) of all nonpharmacological interventions has not been conducted to-date and the recommendations about the use of nonpharmacological interventions in the EULAR evidence-based recommendations were based on a review of SRs published between 2008 and 2015.[114] Since then, a number of randomised controlled trials (RCTs) have been published, and the evidence needs updating to better inform clinical practice. Moreover, the disease characteristics that predict response to different nonpharmacologic therapies are poorly understood, and further research in this field is needed.[114] Lack of knowledge about these factors limits the ability to personalise nonpharmacological management of fibromyalgia.

Thus, the objectives of this study were to assess the efficacy of all nonpharmacological interventions, including different types of exercise and psychological therapies on disease-specific QoL, and 4 common manifestations of fibromyalgia, pain, fatigue,

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sleep, and depression that were ranked as key symptom domains for fibromyalgia by an Outcome Measures in Rheumatology Clinical Trials (OMERACT) working group.[125]

2. Methods

This SR with meta-analysis (MA) followed the guidelines for Preferred Reporting Items for Systematic reviews and Meta-Analyses and was registered in the PROSPERO database (CRD42017074982).[132]

2.1. Data sources and searches

A search strategy with 3 domains (study design, disease, and intervention) was developed, and the key search terms were modified in accordance with the glossary of each database and combined using Boolean operators. A search strategy designed for MEDLINE is given in Supplement Table 1 (available at http://links.lww.com/PAIN/B513). We searched MEDLINE (Ovid), EMBASE (Ovid), AMED (Ovid), PsycINFO (Ovid), CINAHL (EBSCOhost), and Web of Science (Core collection) from their dates of inception until September 2017 and first 100 articles on Google Scholar. In addition, the bibliographies of previous SRs[32,76,82,121] were searched manually to augment the literature search. The search was updated in June 2020.

2.2. Study selection

Studies were eligible for inclusion if they were RCTs comparing a nonpharmacological intervention with either usual care, waiting list, placebo, or sham treatment, in people aged 16 years or more with either physician-diagnosed fibromyalgia or meeting any of the fibromyalgia classification or diagnostic criteria.[175,200–202] A modified nonpharmacological intervention classification system was prepared based on previous reviews or guidelines[81,114] (Supplement Table 2, available at http://links.lww.com/PAIN/B513). Nonpharmacological interventions such as education, different forms of exercise, electrotherapy, balneotherapy, complementary and alternative medicine, and psychological treatments were included. If the exercise intervention included 2 or more exercise types from aerobic, strengthening, flexibility, or mind–body exercise, it was considered as mixed exercise for the purpose of this SR. Psychological treatments included cognitive behavioural treatment (CBT), mindfulness, hypnosis, acceptance and commitment therapy, and attachment-based compassion therapy. Patient education was classified as present if it was delivered either face to face or by a leaflet. In this SR, multidisciplinary treatment (MDT) referred to an intervention that included exercise intervention, patient education, and psychological treatment.

The following studies were excluded: quasirandomised studies and nonrandomised trials; studies including participants with other musculoskeletal disease (eg, rheumatoid arthritis), chronic fatigue syndrome, chronic widespread pain not meeting classification criteria for fibromyalgia or where those criteria were not applied, age $<$ 16 years; studies evaluating combinations of pharmacological and nonpharmacological interventions or comparing pharmacological treatment with a nonpharmacological treatment; studies not assessing any prespecified outcomes; and studies only reported as conference abstract. There was no language restriction.

Disease-specific QoL assessed using Fibromyalgia Impact Questionnaire (FIQ) was the primary outcome measure. Pain, fatigue, sleep, and depression were secondary outcomes. As different outcome measures were used in different trials, we took a broad approach and data for all outcome measures for each secondary outcome were extracted. Where multiple outcome measures were used to report on an outcome, we used a prespecified hierarchy based on the OMERACT recommendations[124] (Supplement Table 3, available at http://links.lww.com/PAIN/B513).

Citations were imported to Endnote X8. After removal of duplicates, titles and abstracts were examined against inclusion and exclusion criteria. The study selection process, including title–abstract screening and full-text screening, was conducted by one reviewer (B.K.) and subsequently another reviewer (J.K.) undertook validation on 10% of randomly selected studies. The validation exercise was completed for each step of the study selection process, and the discrepancies were discussed with the 4 senior authors as a group (A.A., M.D., W.Z., and M.H.) before proceeding with completing that particular step in the review. There was 95% agreement between 2 reviewers (more than 80% agreement as recommended by AMSTAR 2), and this was considered sufficient to continue to the next stage.[171]

2.3. Data extraction and quality assessment

A Microsoft Access database was developed, and the data were extracted and entered. The risk of bias (RoB) was evaluated using a modified version of the Cochrane RoB assessment tool consisting of a checklist of 7 items that assess RoB by evaluating the procedures of selection, detection, attrition, and reporting.[86]

Data extraction and RoB assessment were conducted by B.K., and another author (J.K.) independently performed validation in a 10% of random sample. There was 92% agreement (more than 80% agreement as recommended by AMSTAR 2).[171] Any disagreement between reviewers was resolved by a senior researcher (A.A.) who served as a adjudicator.

Missing data: Where required data were not published, the authors were contacted for additional information. If this was unsuccessful, the missing data were estimated using other values reported in the articles (eg, If SD was not reported, it was calculated from SE or 95% confidence interval (CI) and sample size as recommended in the Cochrane handbook). The formulae used for these calculations are included in Supplement Table 4 (available at http://links.lww.com/PAIN/B513). Where this calculation was not possible because of insufficient information, the largest SD among eligible studies for that outcome was substituted, provided the outcome scale was named in the publication. If the name of the outcome scale was not reported, the arithmetic mean of all SDs for that outcome was used as recommended by Agency for Healthcare Research and Quality (United States).[66]

2.4. Data synthesis and analysis

Standardised mean difference or Cohen *d* was used to measure the effect size (ES) as the data were continuous. The mean change score from baseline was used to calculate the ES. All analyses were based on the random-effects model using the DerSimonian and Laird method. Heterogeneity between studies was assessed using the I^2 statistic. Interpretation of an I^2 value was as follows: 0% to 40%—heterogeneity might not be important, 30% to 60%—moderate heterogeneity, 50% to 90%—substantial heterogeneity, and 75% to 100%—considerable heterogeneity.[86]

Studies were analysed separately based on their comparison types, namely, usual care, placebo or sham controlled, and A + B vs B designed studies. For the purpose of this review A + B vs B

Table 1

Interventions examined in eligible studies and participant characteristics—nonpharmacological intervention vs control arm (usual care, waiting list, no treatment, placebo, or sham treatment).

Interventions	No. of trials	No. of patients	No. of women (%)	Age (y)	BMI	FIQ baseline
Exercise	35	2013	1916 (95.2)	49 (37-59.3)	27.3 (23.8-31.4)	58.2 (54.9-73.1)
Aerobic	9	568	576 (98.6)	46.5 (41.6-50)	28.4 (27-31.4)	64.9 (54.9-69.7)
Flexibility	2	98	98 (100)	—	—	—
Mind–body	10	632	613 (96.9)	48.1 (44.4-57.7)	27.2 (25.1-27.9)	53.9 (60-73.1)
Mixed	11	487	421 (86.5)	50.8 (43.5-59.3)	27.3 (23.8-29)	60.3 (48.6-72.1)
Strengthening	4	221	221 (100)	46.7 (37-51)	29 (26.7-29)	56.1 (44.3-67.3)
Education	9	1004	818 (90.8)	47.2 (43-55.1)	—	56 (26.3-67.8)
Psychological Tx	29	2447	1989 (81.3)	50.8 (44.5-55.4)	27.1 (25.4-29.3)	58.6 (56.5-77.1)
CBT	8	566	559 (98.8)	49.8 (44.5-53.5)	27.1 (25.4-29.3)	64.3 (55.6-69.6)
Mindfulness	8	630	539 (85.5)	52.3 (47.6-53.4)	—	63.6 (56.5-77.1)
Multidisciplinary Tx	10	1023	817 (79.9)	45.8 (37.4-55.4)	26.8 (24.4-28.4)	59.9 (55-72.5)
Balneotherapy	13	685	667 (97.9)	44.1 (33.4-57)	27.4 (24.8-29.2)	54.3 (17-77.1)
Acupuncture	8	518	483 (93.2)	49.1 (43.6-56.26)	27.6 (27.1-28.2)	62.3 (42.4-73.3)
Massage	2	115	—	41.2 (39.9-42.5)	26.4 (26-26.7)	61.1 (35.7-64.9)
Manual therapy	6	355	214 (60.3)	53 (47-55.5)	29 (27.5-33.1)	66.7 (57.9-71.3)
Electrotherapy	10	609	554 (90.9)	44.5 (36.4-54)	29.6 (28.8-33.6)	59.9 (41.3-67.5)
Laser	4	131	100 (76.4)	41.4 (36.4-54)	28.6 (28.8-31)	59.3 (48.9-67.5)
tDCS	13	568	500 (88)	31.3-55.3	28.9-31.2	61.4 (49.2-67.2)
Biofeedback	2	115	107 (93)	43 (35.3-44.4)	—	—
Cupping therapy	1	95	93 (97.9)	55.3 (54.4-56.3)	28.3 (27.2-29.4)	58.8 (55.7-61.8)
Homeopathy	2	109	102 (93.6)	47.6 (43.9-49.1)	—	65.1 (64.7-65.4)
HOT	1	50	35 (70)	40.2 (39.9-40.5)	—	—
Magnetotherapy	4	255	188 (73.7)	45.6 (40.9-51.2)	25.5 (25.5-25.6)	52.4 (66-76)
Material of cloth	2	89	89 (100)	44.5 (37.4-51.5)	26.9 (26.1-27.6)	76.1 (66.6-78.8)
Music	6	297	231 (77.8)	49.6 (42.9-52.3)	—	72.5 (67.9-76.9)
Nutrition	9	398	394 (98.9)	48 (41-55)	27.4 (26.1-30.2)	61.6 (47.8-68.6)
Topical oil	1	51	51 (100)	53.4 (51.5-55.2)	—	—
WBV	2	71	71 (100)	55.4 (52.4-60.1)	27.9-28	56 (48.9-56.9)
Weight loss	1	86	75 (87.2)	45.6 (44.8-46.3)	32.6 (32.3-32.8)	53.9 (53.2-54.6)
Cryotherapy	1	60	60 (100)	—	—	68.9 (64.1-73.8)
Total	167	11,012	9719 (88.3)	48.4 (31.3-60.1)	27.6 (23.8-33.6)	59.2 (17-78.8)

All values are median and range unless stated.

BMI, body mass index; CBT, cognitive behavioural therapy; FIQ, Fibromyalgia Impact Questionnaire; HOT, hyperbaric oxygen therapy; tDCS, transcranial direct current stimulation; Tx, treatment; WBV, whole-body vibration.

study designs were defined as studies that compared 2 interventions that were offered actively against a single intervention, for example, Relton et al. (2009), Kibar et al. (2015), Kutlu et al. (2020), etc. Studies that evaluated an intervention against continued usual care, waiting list, or no treatment were not considered as A + B designs for the purpose of this review as continued usual care would be available to participants on wait list or those not being offered any additional treatment in the trial and also to participants in the intervention arm.

Egger test and the visual inspection of funnel plot asymmetry were used to assess publication bias. The ES of each intervention category (eg, exercise, psychological therapies etc.) was examined. Additionally, the ES of different exercise types, for example, aerobic, flexibility, mind body, strengthening, and mixed (ie, exercise packages that include 2 or more types of exercise), and different psychological treatments, for example, cognitive behavioural therapy (CBT) and mindfulness, were pooled separately.

All time points at which outcomes were assessed were extracted. The most commonly reported end point (12 weeks or closest to 12 weeks) was used as the primary time point for the MA. Effect sizes for A + B vs B designs were presented separately.

Subgroup analyses were undertaken according to participant characteristics (age and body mass index [BMI]), recruitment source (hospital, community based, or mixed), source of funding (noncommercial, commercial, both, or no specific funding), and sample size to explore their impact on heterogeneity and ES. Metaregression was used to investigate the impact of various study characteristics on ES for interventions with >10 trials.[85] A time-dependent subgroup analysis was conducted, stratifying studies according to the time point from which outcomes were meta-analysed (1–8 weeks, 9–15 weeks, and more than 16 weeks). A further subgroup analysis was performed to see the influence of time gap between end-of-treatment and outcome assessment (0-0.5 weeks, 2-6 weeks, 10-14 weeks, and 18-44 weeks).

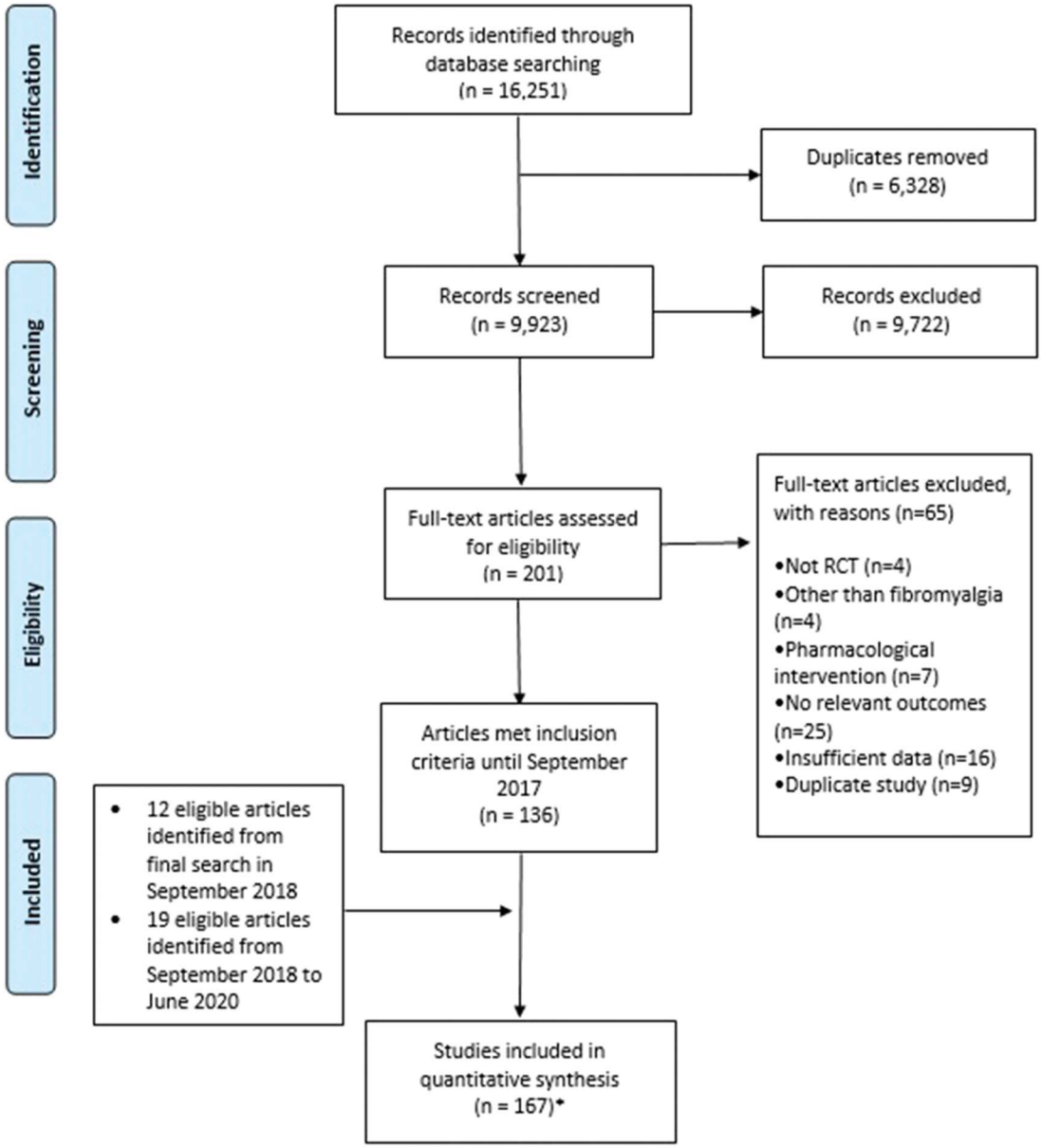

Figure 1. Screening flow. *All studies included in the systematic review were included in the meta-analysis. RCT, randomised controlled trial.

The robustness of the results of the MA was examined by undertaking sensitivity analyses on primary outcome by excluding studies that (1) had a high RoB on allocation concealment and attrition, (2) required imputation of SD, and (3) used end point scores rather than change scores for calculating the ES. Data were analysed using StataSE 16.

3. Results

Sixteen thousand two hundred fifty-one records were identified from the systematic literature search from the inception date of the databases until September 2017. Duplicates were removed, and the title and abstracts of the remaining 9923 articles were scrutinised. A further 9722 articles were excluded. The full text of 201 remaining articles was retrieved for detailed screening and data extraction. After full-text screening, 65 articles did not meet the inclusion criteria and were excluded, leaving a total of 136 articles that met the inclusion criteria. In the update searches undertaken in June 2020, a further 31 articles met the eligibility criteria. Data from 167 RCTs (n = 11,012 participants) investigating 22 nonpharmacological interventions (**Table 1**) were included in this MA (**Fig. 1**).[109] Of these, there were 15 A + B vs B study designs.[16,41,55,71,96,98,101,104,138,147,154,157,164,192,205]

Of the 11,012 participants included in these trials, 88% were women, and the median age, BMI, and FIQ score were 49 years, 27.6 kg/m^2, and 59.2, respectively. Ten percent of the articles reported data on race group or ethnicity. The risk-of-bias assessment is shown in **Figure 2**. Owing to the exclusion of nonrandomised studies, there were no studies with high RoB on random sequence generation, with 64% at low risk, whereas 36% had unclear RoB. It was unclear if the allocation was adequately concealed in 74% of the studies. There was high RoB on blinding of participant and personnel and also for the outcome assessment in 80% and 70% of studies, respectively.

Funnel plots for publication bias on FIQ, pain, fatigue, sleep, and depression outcomes are presented in Supplement Table 5 (available at http://links.lww.com/PAIN/B513). Overall, asymmetry was apparent on visual inspection suggesting publication bias

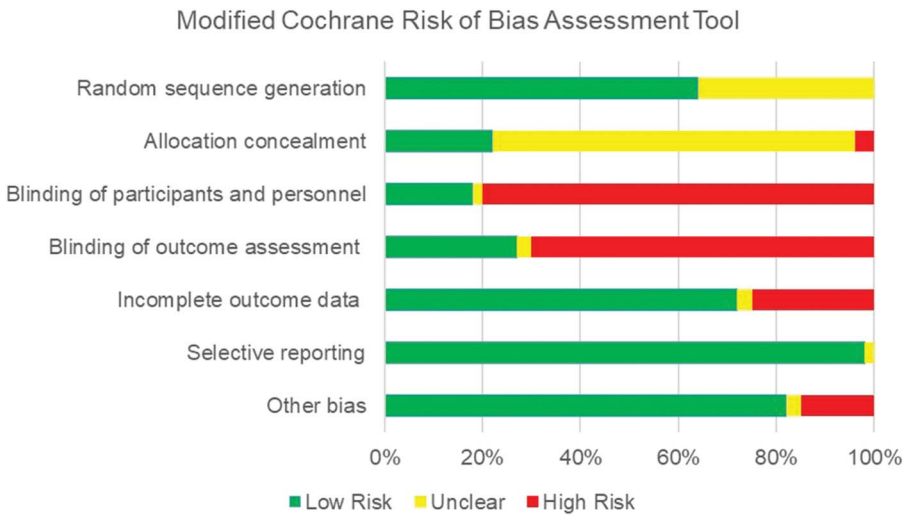

Figure 2. Risk-of-bias assessment.

for each of the outcomes. This was confirmed by the Egger test ($P < 0.05$ for each outcome).

3.1. Exercise

Of the 35 trials [6,12,14,15,18,26,35,47,63,67,71–73,77,89,91,94,98,110,116,117,126,136,137,139,148,157,161–163,166,167,183–185] (n = 2013 participants) evaluating any type of exercise, 28 (n = 1487) reported data on FIQ. The ES of any exercise intervention on FIQ was moderate (**Fig. 3**) in comparison with usual care; however, there was considerable heterogeneity. As a group, exercise interventions resulted in large improvement in pain, fatigue, and sleep and moderate improvement in depression (**Table 2**). Substantial heterogeneity (50%-90%) was present for all outcomes. There was evidence of publication bias for FIQ, pain, and fatigue outcomes (Supplement Table 6a, available at http://links.lww.com/PAIN/B513).

Exercise interventions could be classified into 5 types. Of these, mixed exercise[12,47,67,72,117,137,148,162,163,184,185] was the most often studied (11 trials, n = 487 participants). Mind–body,[6,15,26,35,91,98,110,116,166,183] aerobic,[18,63,73,89,126,136,139,161,167] strengthening,[14,77,94,157] and flexibility exercises[14,71] were examined in 10 (n = 632 participants), 9 (n = 568 participants), 4 (n = 221 participants), and 2 studies (n = 98), respectively (**Table 1**).

Aerobic, mixed, and strengthening exercises showed improvement in FIQ with considerable heterogeneity (**Fig. 3**). However, flexibility (−0.24; 95% CI −0.98 to 0.51) and mind–body exercises (−0.23; 95% CI −0.87 to 0.41) did not improve FIQ (**Fig. 3**). All exercise types except for flexibility exercise were effective at relieving pain and depression. Only, mind–body and strengthening exercises were effective at improving fatigue, whereas aerobic, flexibility, and strengthening exercises were effective at improving sleep (**Table 2**).

There was considerable heterogeneity in studies assessing aerobic exercise and substantial or unimportant heterogeneity in other exercise types (Supplement Table 7a, available at http://links.lww.com/PAIN/B513). Because there were fewer than 10 studies, statistical testing for publication bias was not assessed for other exercise types.

3.2. Education

Nine studies[5,31,64,65,78,99,142,176,190] (n = 1004) assessed education vs usual care (**Table 1**). Three trials (n = 251) that reported data on fatigue showed an improvement (−0.31; 95% CI −0.55 to −0.06). However, education alone was no better than usual care for other outcomes with moderate heterogeneity (30%-60%) (Supplement Table 8, available at http://links.lww.com/PAIN/B513).

3.3. Psychological treatments

Twenty-nine trials with 2447 participants evaluated psychological treatments[8,10,28,29,34,37,52,58,68,84,90,105,112,122,123,133,134,144,149,151,152,168,170,174,178,189,193,198,199] including CBT[52,58,90,105,122,123,189,199] and mindfulness[8,10,37,134,149,151,168,170] (**Table 1**). Psychological treatments were more efficacious than usual care for FIQ, pain, sleep, and depression (**Fig. 3**, **Table 2**). However, they showed no improvement in fatigue.

There was substantial heterogeneity for FIQ, fatigue, and sleep outcomes and moderate heterogeneity for pain and sleep outcomes. The Egger test did not detect publication bias for any outcome (Supplement Table 9, available at http://links.lww.com/PAIN/B513).

Eight studies (n = 566) assessed CBT, and 8 studies (n = 630) assessed mindfulness (**Table 1**). Both improved FIQ. Although CBT significantly improved pain, mindfulness was superior relative to usual care for fatigue and depression but not for pain. There was no improvement in depression and sleep outcomes for these interventions (**Table 2**).

3.4. Multidisciplinary treatment

Ten trials with 1023 participants[7,9,40,43,95,106,108,120,153,165] showed significant improvements in FIQ, pain, sleep, and depression with MDT compared with usual care (**Table 2**; Supplementary Table 10, available at http://links.lww.com/PAIN/B513). There was no improvement in fatigue with MDT. There was evidence of publication bias for pain outcome ($P = 0.043$). Owing to <10 studies, publication bias could not be assessed for other outcomes.

3.5. Balneotherapy

This intervention type covered all aquatic interventions that involve adopting a static position in water with different minerals or in sea water. It was examined in 13 trials (n = 685).[13,17,33,51,55,56,59,60,96,101,145,195,205] These showed efficacy

for FIQ, pain, and depression relative to usual care with considerable heterogeneity (Supplement Table 11a, available at http://links.lww.com/PAIN/B513). Evidence from 3 studies (n = 147) that reported fatigue outcomes demonstrated no effect (−0.23; 95% CI −0.56 to 0.09). However, it showed significant improvements on fatigue when it was applied as an adjunctive treatment to exercise in A + B vs B design (−0.94; 95% CI −1.47 to −0.41)[55,96,101,205] (Supplement Table 11b, available at http://links.lww.com/PAIN/B513).

Publication bias could not be assessed because there were less than 10 trials for each outcome. I^2 test identified considerable heterogeneity for FIQ, pain, and depression (Supplement Table 11a, available at http://links.lww.com/PAIN/B513).

3.6. Acupuncture

Eight acupuncture trials[36,50,80,92,118,177,180,188] (n = 518) were analysed. Six of these (n = 340) had sham acupuncture as a comparator, whereas the remaining 2 (n = 178) had usual care comparison arms.

Acupuncture was more effective than sham acupuncture (−0.88; 95% CI −1.75 to −0.02) and usual care (−0.59; 95% CI −0.99 to −0.19) for FIQ. It showed greater pain reduction compared with sham acupuncture (−0.98; 95% CI −1.56 to −0.40) and usual care (−0.64; 95% CI −0.96 to −0.31) as well as greater improvement in fatigue compared with sham acupuncture (−0.50; 95% CI −0.90 to −0.10) and usual care (−0.41; 95% CI −0.80 to −0.01). There was no improvement in sleep. Although acupuncture was more effective than sham for depression (−0.57; 95% CI −1.03 to −0.10), there was no effect relative to usual care (−0.23; 95% CI −0.63 to 0.16). Considerable heterogeneity of placebo-controlled trials was observed in FIQ, pain, and sleep (Supplement Table 12, available at http://links.lww.com/PAIN/B513).

3.7. Other interventions

The efficacy of other nonpharmacological interventions including massage,[39,41] manual therapy,[1,25,38,135,147,187] electrotherapy,[48,49,75,88,103,138,146,158,181,192] laser,[75,146,158,192] transcranial direct current stimulation,[57,62,74,79,97,102,104,127,130,150,172,182,203] biofeedback,[16,191] nutritional supplement,[4,19,53,119,129,131,156,159,197] homeopathy,[21,154] magnetotherapy,[2,46,115,179] music,[3,42,128,143,186,196] weight loss,[169] cupping therapy,[107] material of cloth,[11,100] hyperbaric oxygen therapy,[204] topical oil,[160] cryotherapy,[155] and whole-body vibration[141,164] are presented in Supplement Tables 13 a to q (available at http://links.lww.com/PAIN/B513). Although electrotherapy showed significant improvements on FIQ, fatigue, and sleep, manual therapy was better than usual care for pain. Some of the interventions showed larger effect sizes such as hyperbaric oxygen therapy (one trial with 50 participants) and material of cloth (2 trials with 89 participants) that refers to wearing a wool shirt or t-shirt with bioceramic solution. There were 1 or 2 A + B vs B study designs for some of the other interventions included in the review, and firm inferences on their effect size could not be drawn[16,41,71,157]

3.8. Subgroup analysis

Subgroup analyses were undertaken for (1) all nonpharmacological interventions and (2) exercise interventions alone. There was no effect of age, BMI, setting, and funding source on improvement in FIQ when all nonpharmacologic interventions were considered (Supplement Table 14, available at http://links.lww.com/PAIN/B513). Studies with <50 participants (−0.79; 95% CI −0.99 to −0.60) showed greater improvement in FIQ compared with studies with > 50 participants (−0.51; 95% CI −0.66 to −0.35) with similar levels of heterogeneity (87.4% vs 71.1%) when all nonpharmacological interventions were analysed. Similar results were observed within exercise interventions alone, where studies with <50 participants had higher ES than those with >50 participants (−0.99 [−1.41 to −0.57] vs −0.45 [−0.85 to −0.05]) with similar levels of heterogeneity (89.7% vs 72.9%) (Supplement Table 14b, available at http://links.lww.com/PAIN/B513).

3.9. Time-dependent analysis

A secondary analysis for time-dependent effects was undertaken on FIQ for commonly studied interventions. Outcome assessment time points were grouped into 3 intervals of similar duration (1-8 weeks, 9-15 weeks and ≥16 weeks).

All interventions except for electrotherapy showed a peak effect size in the first 8 weeks. After this, the treatment responses diminished for all interventions except electrotherapy that showed a greater magnitude of effect size (Supplement Table 15, available at http://links.lww.com/PAIN/B513).

We conducted a further subgroup analysis to examine the influence of the time gap between the end of treatment and outcome assessment. All included studies were subgrouped based on the number of weeks between these 2 time points: 0 to 0.5 weeks, 2 to 6 weeks, 10 to 14 weeks, and 18 to 44 weeks. The ESs remained stable to up to 14 weeks after theend of intervention and diminished if the gap was greater than 18 weeks (Supplement Table 16, available at http://links.lww.com/PAIN/B513). Substantial heterogeneity was still present in each of these subgroups.

3.10. Sensitivity analysis

Sensitivity analysis was conducted for all nonpharmacological interventions, as well as within-exercise interventions for FIQ. Although the pooled ES for all nonpharmacological interventions was −0.63 (−0.75 to −0.50), it was −0.75 (−0.95 to −0.55) for studies that performed an intention-to-treat analysis and −0.62 (−0.86 to −0.39) for studies that properly concealed the allocation (Supplement Table 17, available at http://links.lww.com/PAIN/B513). Sensitivity analysis on exercise trials showed similar findings (Supplement Table 17b, available at http://links.lww.com/PAIN/B513).

3.11. Clinical significance

Using mean baseline FIQ score of 62 and the estimated minimally clinically important difference (14%; 95% CI 13-15), from Bennett et al.,[22] the minimally clinically important difference on a 0 to 100 scale is estimated as 8.4. The ES of each intervention on FIQ was multiplied by the SD from the Bennett et al. study to back translate to 0 to 100 score. All nonpharmacological interventions showed a clinically meaningful improvement except for psychological treatment, CBT, MDT, and weight loss that provided less than clinically relevant change (Supplement Table 18, available at http://links.lww.com/PAIN/B513).

4. Discussion

This is by far the largest SR including 167 RCTs examining the efficacy of 22 nonpharmacological interventions in fibromyalgia.

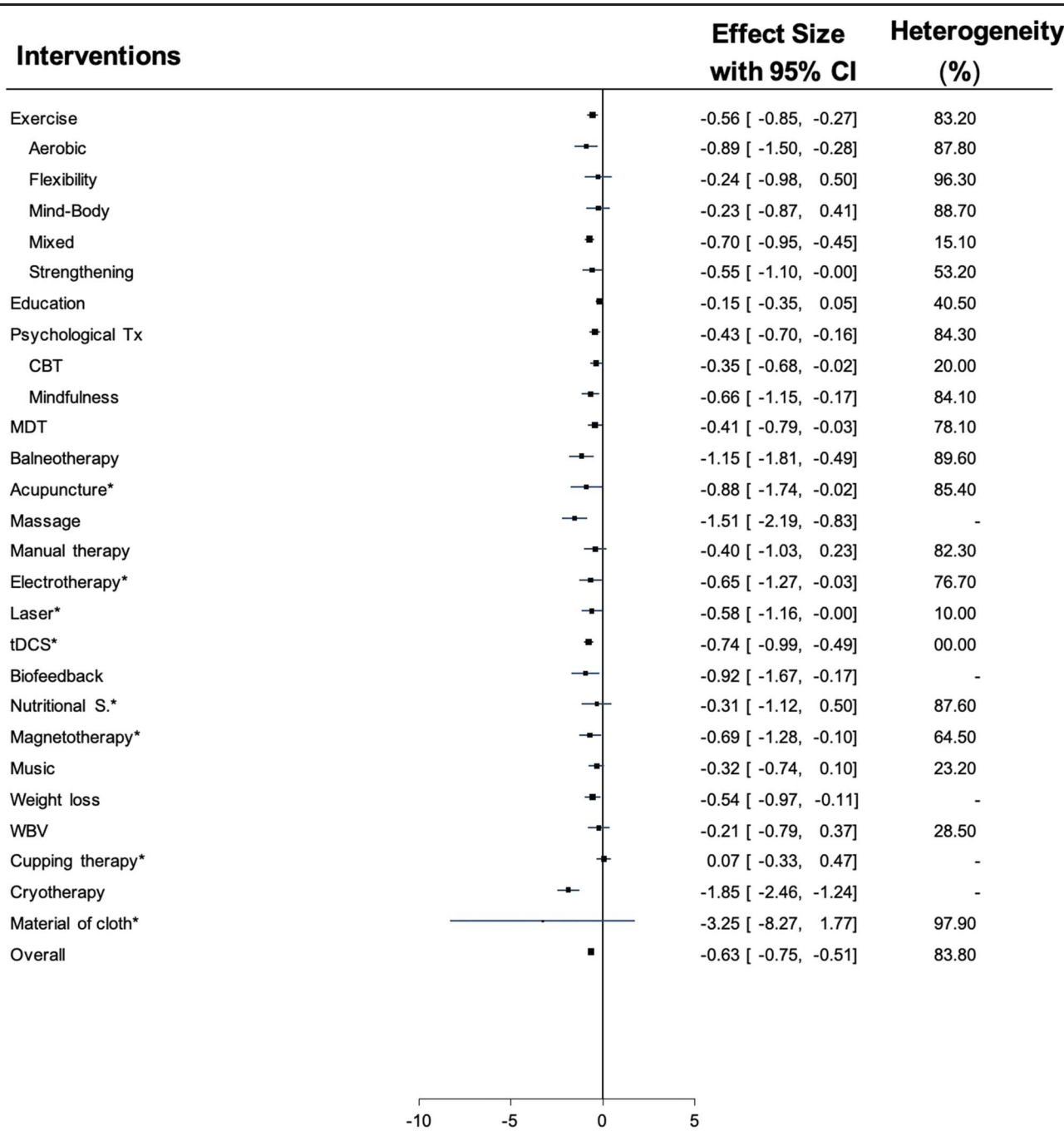

Figure 3. Effect size (95% CI)—intervention vs control arm (usual care or placebo or sham): FIQ. CBT, cognitive behavioural therapy; CI, confidence interval; FIQ, Fibromyalgia Impact Questionnaire; MDT, multidisciplinary treatment; tDCS, transcranial direct current stimulation; WBV, whole-body vibration. *Data come from placebo or sham-controlled trials. Negative value favours treatment.

It evaluated 5 patient-centred outcomes in fibromyalgia: disease-specific QoL (FIQ), pain, fatigue, sleep, and depression. The main findings are as follows: (a) several nonpharmacological interventions are effective for FIQ, pain, fatigue, sleep, and depression; (b) different interventions benefit different outcomes; and (c) exercise overall seems to improve all outcomes but the benefits vary between types of exercise for each specific outcome, for example, although all types of exercise were effective for pain apart from flexibility exercise, only aerobic and strengthening exercises were effective for sleep. These findings were also confirmed in analyses restricted to high-quality studies and in a sensitivity analysis based on the data used to compute ES, that is, change score or end point score.

Exercise is superior to usual care and has moderate-to-large ES for improving FIQ, pain, sleep, fatigue, and depression. However, studies included were prone to high RoB especially on blinding of the participant and the outcome assessor. No previous MA has assessed all exercise types for fibromyalgia. Our results are consistent with MAs in similar conditions such as osteoarthritis and chronic low back pain (CLBP).[70,83] With respect to different exercise types, all forms of exercise improved pain and depression except for flexibility exercise. Mind–body

Table 2

Effect size (95% confidence interval)—intervention vs control arm (usual care or placebo or sham*): pain, fatigue, sleep, and depression.

Interventions	Pain	Fatigue	Sleep	Depression
Exercise	**−0.84 (−1.13 to −0.55)**	**−0.89 (−1.33 to −0.45)**	**−0.81 (−1.24 to −0.38)**	**−0.76 (−1.09 to −0.42)**
Aerobic	**−0.72 (−1.37 to −0.07)**	−1.46 (−3.05 to 0.14)	**−1.33 (−2.55 to −0.11)**	**−1.22 (−2.22 to −0.21)**
Flexibility	−0.56 (−1.32 to 0.19)	−0.49 (−1.24 to 0.27)	−0.88 (−1.66 to −0.10)	−0.28 (−1.03 to 0.46)
Mind–body	**−0.92 (−1.41 to −0.43)**	**−1.00 (−1.47 to −0.53)**	−0.61 (−1.41 to 0.19)	**−0.67 (−1.07 to −0.26)**
Mixed	**−0.96 (−1.49 to −0.44)**	−0.12 (−0.73 to 0.50)	−0.65 (−1.33 to 0.04)	**−0.35 (−0.65 to −0.05)**
Strengthening	**−0.84 (−1.75 to −0.08)**	**−0.77 (−1.34 to −0.20)**	**−0.74 (−1.56 to −0.07)**	**−1.06 (−1.65 to −0.47)**
Education	−0.17 (−0.37 to 0.04)	**−0.31 (−0.55 to −0.06)**	−0.25 (−0.61 to 0.11)	−0.08 (−0.35 to 0.20)
Psychological treatment	**−0.45 (−0.59 to −0.30)**	−0.20 (−0.53 to 0.12)	**−0.55 (−0.94 to −0.15)**	**−0.37 (−0.52 to −0.22)**
CBT	**−0.45 (−0.80 to −0.10)**	0.43 (−0.55 to 1.41)	−1.35 (−4.20 to 1.51)	−0.12 (−0.33 to 0.10)
Mindfulness	−0.29 (−0.71 to 0.13)	**−0.49 (−0.91 to −0.07)**	0.37 (−1.11 to 0.37)	**−0.46 (−0.75 to −0.17)**
MDT	**−1.33 (−2.16 to −0.49)**	−0.58 (−1.22 to 0.06)	**−1.15 (−2.11 to −0.18)**	**−1.26 (−2.06 to −0.45)**
Balneotherapy	**−1.11 (−1.66 to −0.56)**	−0.23 (−0.56 to 0.09)	0.30 (−0.19 to 0.78)	**−0.69 (−1.29 to −0.09)**
Acupuncture	**−0.98 (−1.56 to −0.40)***	**−0.50 (−0.90 to −0.10)***	1.12 (−1.11 to 3.35)*	**−0.57 (−1.03 to −0.10)***
Massage	**−1.05 (−1.69 to −0.41)**	**−0.95 (−1.58 to −0.31)**	**−0.73 (−1.35 to −0.11)**	−0.73 (−1.83 to 0.37)
Manual therapy	**−0.86 (−1.32 to −0.41)**	−0.44 (−1.02 to 0.13)	0.10 (−1.22 to 1.41)	−0.32 (−0.96 to 0.32)
Electrotherapy	−0.28 (−0.69 to 0.14)	**−0.79 (−1.45 to −0.13)***	**−0.97 (−1.51 to −0.43)***	−0.32 (−0.83 to 0.20)
Laser	**−0.69 (−1.09 to −0.29)***	**−1.25 (−2.15 to −0.35)***	**−0.97 (−1.51 to −0.43)***	**−0.88 (−1.46 to −0.29)***
tDCS	**−0.84 (−1.21 to −0.47)***	**−0.73 (−1.28 to −0.19)***	**−0.58 (−0.92 to −0.24)***	**−0.31 (−0.49 to −0.12)***
Biofeedback	−0.42 (−1.18 to 0.33)	−0.09 (−0.54 to 0.36)	—	—
Nutritional supplement	−0.29 (−0.69 to 0.11)*	**−0.41 (−0.77 to −0.05)***	**−0.43 (−0.79 to −0.06)***	−0.04 (−0.99 to 0.90)*
Homeopathy	**−0.73 (−1.41 to −0.05)**	−0.19 (−0.69 to 0.31)*	**−0.91 (−1.60 to −0.22)**	**−0.56 (−1.07 to −0.06)***
Magnetotherapy	**−0.89 (−1.74 to −0.04)***	**−2.61 (−3.70 to −1.52)***	**−1.00 (−1.83 to −0.16)***	−0.11 (−0.64 to 0.41)*
Music	−0.58 (−1.24 to 0.07)	−0.11 (−0.72 to 0.50)	—	**−0.54 (-0.92 to -0.15)**
Weight loss	—	—	**−0.66 (−1.11 to −0.22)**	**−0.68 (−1.13 to −0.24)**
Cupping therapy	−0.09 (−0.49 to 0.32)*	0.06 (−0.34 to 0.46)*	−0.20 (−0.60 to 0.21)*	—
Material of cloth	−2.89 (−6.82 to 1.04)*	**−5.97 (−7.29 to −4.65)***	**−8.94 (−10.8 to −7.07)***	**−3.36 (−4.23 to −2.49)***
Cryotherapy	**−1.41 (−1.99 to −0.84)**	**−1.42 (−1.99 to −0.84)**	—	—
HOT	**−2.22 (−2.93 to −1.51)**	—	—	—
Topical oil	0.21 (−0.39 to 0.81)*	—	—	—

CBT, cognitive behavioural therapy; HOT, hyperbaric oxygen therapy; MDT, multidisciplinary treatment; tDCS, transcranial direct current stimulation.
* Data come from placebo or sham-controlled trials. Text in bold shows significant values. Negative value favours treatment.

and strengthening exercises improved fatigue, whereas aerobic and strengthening exercises improved sleep. Some of our findings differ from those reported in previous SRs. For example, while we found a significant moderate ES of aerobic exercise on pain (−0.72; 95% CI −1.37 to −0.07), a Cochrane review by Busch et al. (2007) reported nonsignificant differences (0.65; 95% CI −0.09 to 1,39) for this outcome. This may be due to a larger number of studies (8 vs 5) and total sample size (512 vs 183) in the current SR.

Our study reports that education alone may not be superior to usual care for FIQ, pain, sleep, and depression but may improve fatigue. A SR by Sim and Adams[173] reported modest improvement on pain from an education program in people with fibromyalgia. However, their findings were based on a study that used a cognitive approach rather than education alone, and improvements were not maintained during follow-up. Similarly, previous reviews on CLBP and chronic musculoskeletal pain[44,111] found significant improvements. Clarke et al.[44] evaluated 2 studies (n = 122) and reported small improvements on CLBP (5/100 mm on a Visual Analogue Scale). Louw et al.[111] systematically reviewed 13 articles and reported significant findings for pain but their population group comprised different musculoskeletal conditions. Nevertheless, it is difficult to study education as a discrete component of care as it is a core requirement and an integral component of shared decision-making in any nonpharmacological intervention.

We examined 29 psychological intervention studies including CBT, mindfulness, hypnosis, acceptance, and commitment therapy that were more effective than usual care on FIQ, pain, sleep, and depression but not fatigue. Our results are broadly in line with those of previous studies.[24,69] We found that CBT was more efficacious for pain, whereas mindfulness was better than usual care for fatigue and depression. We did not find a significant effect of CBT on depression in contrast to an earlier review by Bernardy et al.[24] However, we were strict in our definition of "CBT" as an intervention; this was specified as "CBT" that was delivered by a trained professional, whereas Bernardy et al. considered as CBT, any psychological treatment based on a CBT model or framework.

Glombiewski et al.[69] reviewed 23 psychological treatment studies and reported significant improvements on fatigue. This conflicting result may reflect the type of interventions studied.

Although we excluded studies including another nonpharmacological intervention (ie, exercise) in combination with psychological treatments, Glombiewski et al.'s review included multimodal programs if the psychological treatment accounted for at least 60% of treatment time. Because of the difficulty in knowing the proportion of time spent on the intervention from articles, we classified these interventions as MDT.

We defined MDT as combined nonpharmacological intervention that includes components of exercise, education, and psychological treatment. We found that MDT was superior to usual care on FIQ, pain, sleep, and depression. Further to this, it indicated larger ESs compared with exercise only, education only, and psychological treatment only. No previous MA has assessed the effect of MDT exclusively in fibromyalgia. Previous qualitative analyses,[30,93] however, suggest that MDT is effective for decreasing pain and fibromyalgia impact.

We observed differential effect of interventions on different manifestations of fibromyalgia. Aerobic, strengthening, and mind–body exercise but not flexibility exercise reduces neuroinflammation, increase endogenous opioid and serotonin release, and influence dopamine and norepinephrine levels explaining improvement in most symptoms of fibromyalgia by the first 3 exercise types.[27] Similarly, other interventions such as acupuncture and massage therapy that affect both central and peripheral pain mechanisms and have sympatholytic and inhibitory effects on the hypothalamic pituitary adrenal axis improved most symptoms.[54] Transcranial direct current stimulation improved all manifestations given the role of central wind-up in all fibromyalgia manifestations.[20] Our SR also raises the possibility that exercise and balneotherapy may be more clinically effective with combined with other interventions. There were few studies, and more such studies are needed.

This SR shows that the efficacy of nonpharmacological intervention for fibromyalgia seems to drop after 14 weeks. This suggests that patients completing a nonpharmacological treatment programme for fibromyalgia should be reviewed approximately 3 monthly and the treatments reinforced as required. We tested a wide range of nonpharmacological interventions in this study. Several interventions such as transcranial direct current stimulation, balneotherapy, mind–body exercises, and acupuncture may not be widely available across different healthcare systems. Indeed, there may be low acceptability of some of these interventions, such as psychological treatments or acupuncture, in certain cultures.

This study provides data that will help healthcare professionals and patients to select the nonpharmacological interventions, that is, most are likely to give the best results according to the patients' individual clinical features. It is a comprehensive review with no language or geographic restriction and includes all nonpharmacological interventions and their impact on disease-specific QoL (FIQ) and common symptoms in fibromyalgia—pain, fatigue, sleep, and depression.

However, the present MA is subject to several caveats. First, more than half of the studies (53%) had small sample size (<50). Second, there was a high RoB for blinding, and allocation concealment was unclear for most trials. However, because of the nature of nonpharmacological interventions, it is usually not possible to blind participants and those delivering the intervention. These studies with a small sample size and high RoB skewed the funnel plot to the left. For example, Evcik et al.[56] included 42 participants and had unclear RoB in allocation concealment and high RoB in blinding. This may have affected overall effect size and often overestimated the overall ESs.[140] Nevertheless, the sensitivity analysis for allocation concealment indicated that the findings were unlikely to be biased by study quality. In addition, it was not possible to synthesise all published evidence because of incomplete and inconsistent outcome reporting. Visual asymmetry of the funnel plots suggested that this loss of data may have biased the results. However, we attempted to impute missing data and sensitivity analyses on imputed data indicated that results are less likely to be biased because of data imputation. Moreover, most participants in the studies were predominantly middle-aged women living in a developed country. Further studies are required to confirm the generalisability of the results to all populations with fibromyalgia and in all settings. Secondary outcomes such as pain, fatigue, sleep, and depression were measured using different patient-reported outcome measures. This may have biased the ESs on these outcomes. However, the main analysis using primary outcome measure (FIQ) does not suffer from this caveat. Finally, some groups of interventions were quite heterogeneous. For example, different types of acupuncture were used in acupuncture trials including traditional acupuncture, electroacupuncture, or dry needling. Furthermore, intervention programmes and control groups are not standardised and vary considerably between studies. Substantial heterogeneity was present on subgroup analysis raising the possibility that variability in intervention such as number and duration of sessions, overall duration of treatment programme, way of delivery, expertise of the therapist, setting, and follow-up duration may have caused the heterogeneity. Researchers should describe these in detail so that their effect may be explored in future SRs.

In summary, these results suggest that several nonpharmacological interventions are effective for fibromyalgia and that different interventions improve different patient-centred outcomes. Exercise is the most beneficial for improving multiple patient-centred outcomes, but different types of exercise preferentially benefit different outcomes, supporting the possibility of individualised nonpharmacological management according to predominant symptom(s), a strategy that warrants testing in clinical trials. Future trials that address the methodological limitations highlighted above are also required, especially high-quality trials with larger sample size, longer duration of follow-up, the use of consistent terminology, and well-described intervention programmes.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content

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