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Effect of Exercise on Fatigue in Multiple Sclerosis Patients: A Network Meta-analysis

Authors
Yuting Chen[#][1, 3], Shanshan Xu[#][1, 3], Jiran Shen[2, 3], Hui Yang[1, 3], Wei Xu[1, 3], Ming Shao[1, 3], Faming Pan[1, 3]

Affiliations
1   Department of Epidemiology and Biostatistics, Anhui Medical University, Hefei, Anhui, China
2   Department of Internal Medicine, First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China
3   The Key Laboratory of Major Autoimmune Diseases, Anhui Medical University, Hefei, Anhui, China

Correspondence
Faming Pan
Department of Epidemiology and Biostatistics
Anhui Medical University
81 Meishan Road
Hefei
Anhui
230032
China
Tel.: 15856954540, Fax: 15856954540
famingpan@ahmu.edu.cn

Supplementary material is available under
https://doi.org/10.1055/a-1524-1935

ABSTRACT

Few studies have directly compared the effects of different exercise therapies on reducing fatigue in patients with multiple sclerosis. Thus, we conducted a Frequentist network meta-analysis to analyze and compare the effectiveness of different types of exercise on reducing multiple sclerosis-related fatigue. Relevant randomized controlled trials were searched in Pub-Med, Web of Science and Cochrane Library databases from the date of their inception up to April 1, 2021. In total, 27 articles involving 1470 participants and 10 types of interventions met the inclusion criteria. The results indicated that aquatic exercise ranked as the most effective among these interventions, and aerobic exercise had small-to-moderate effect sizes. Most of the interventions were shown to be better than the control group, except for climbing. Climbing was the only intervention that ranked worse than the controls. All of these findings merit further investigation in future clinical trials.

Introduction

Multiple sclerosis (MS) is often described as a chronic, inflammatory disorder of the central nervous system that is characterized by demyelination and axonal loss [1]. MS is one of the leading causes of non-traumatic disability in young adults, and there are more than 2.3 million people with MS worldwide [2]. The global median prevalence of MS is 33 per 100 000 population, with significant dif-

ferences between countries [3]. Common manifestations in MS include, but are not limited to, symptomatic fatigue, depression, spasticity, mobility and balance problems, cognitive decline, and muscle weakness [4–9]. Among them, fatigue is intrinsic to MS and is the most frequently reported symptom [10]. Up to 75–90 % of people with MS complain of fatigue, and 60 % regard it as the most disabling complication that seriously reduces quality of life [11]. People with MS tend to engage in less physical activity than the general population, which in turn increases fatigue and the risk of developing secondary diseases such as obesity and diabetes

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\#   Yuting Chen and Shanshan Xu contributed equally to this work and should be considered as main contributors.

[12, 13]. The bi-directional connections between fatigue and physical inactivity accelerate the functional decline in patients with MS.

For years, people with MS were advised not to take part in exercise because it was thought to cause worsening symptoms or fatigue. However, in recent decades, a number of types of exercise have been shown to reduce MS-related fatigue in extensive trials, systematic reviews, and meta-analyses, such as aerobic exercise, yoga, resistance training, and endurance training [14–16]. The American Physical Therapy Association has built preferred practice patterns for patients, including those with MS [17]. However, information about specific patterns of physical activity in MS patients is still limited. Previous meta-analyses reported that exercise could reduce fatigue in MS patients, but all of these studies were traditional pairwise meta-analyses that only considered direct comparisons and did not rank the interventions [18–20]. It remains unclear which anti-fatigue intervention has the greatest effects on relieving fatigue. Therefore, it is a problem for MS patients to find the most effective anti-fatigue interventions based on their interests and needs.

To provide a comprehensive overview, we applied the network meta-analysis (NMA) approach to analyze and compare the effectiveness of different types of exercise on relieving MS-related fatigue.

Materials and Methods

The study was performed in line with the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and the Cochrane Intervention Review that Compares Multiple Interventions, as well as the Ethical Standards in Sport and Exercise Science Research and this journal [21, 22]. The protocol was previously written but was not registered.

In this NMA, aerobic exercise is defined as a unique form of activity, which involves the integration of large muscle groups, such as the rhythmic propulsion of body mass during the movements of varying intensities (for example, walking, jogging, or running) or activities with lower mechanical impact (for example, cycling) [23]. Resistance training is a type of progressive overload strength training in which the muscles exert force against an external load [24]. Endurance training is characterized by the repeated isotonic contraction of large skeletal muscle groups (for example, cross-country skiing or speed skating in winter sports) [25]. Aquatic exercise, also known as pool therapy, hydrotherapy, or balneotherapy, mainly describes exercise that is done in the water.

Search strategy and selection criteria

PubMed, Web of Science, Cochrane Library of Systematic Reviews and Cochrane Controlled Clinical Trials databases were searched from the date of their inception up to April 1, 2021 to collect relevant randomized controlled trials (RCTs). Keywords and search strategy were as follows: ("multiple sclerosis" OR "MS") AND ("fatigue" OR "lassitude") AND (random *). Titles, abstracts, and key words were scanned, and full-text articles were evaluated if they met the inclusion criteria. The references of the included studies, systematic reviews, and meta-analyses were also manually searched to find additional topic-related literature. In the case of insufficient data, we tried to email the corresponding author to obtain the necessary information.

A number of studies were retrieved, but only studies meeting the following criteria were considered eligible: (1) an RCT protocol was applied to evaluate the effect of at least one exercise arm; (2) participants were adults who were clinically diagnosed with MS; (3) a questionnaire was used at baseline and follow-up to evaluate fatigue symptoms; (4) sufficient data should have been provided to calculate the effect sizes of outcome variables; and (5) studies were published in English.

Exclusion criteria

Our study focused on different types of exercise on alleviating fatigue in MS patients. Therefore, trials comparing drugs, neurofeedback, acupuncture, electroacupuncture, acupressure, energy conservation management, light therapy, and other contactless rehabilitation (e. g., telephone-administered healing) were excluded. In addition, studies with intervention periods <2 weeks were excluded. Quasi-RCTs, conference abstracts, editorials, letters, and case reports were also excluded.

Data extraction

Two reviewers independently extracted data using a standardized scheme. Extracted data were double-checked by the corresponding author. Any discrepancies were resolved by discussion and careful reexamination until an agreement was reached. The following information was collected: first author's name, publication year, country, sample size, sex ratio, age, characteristics of participants, type of intervention, duration of intervention, outcome measurements, and other additional information.

Risk of bias and quality assessment

Risk of bias in the included studies was assessed by using Cochrane Collaboration's Tool for Assessing Risk of Bias [26]. We evaluated the studies based on seven criteria (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias). Each study was scored as high, low, and unclear risk of bias. The process was completed by two reviewers independently, and consensus was reached by consulting another author.

Summary of outcomes

Our primary outcome variables included mean, standard deviations (SD), and sample sizes (n) to calculate the mean change from baseline to endpoint in fatigue symptoms. If more than one post-treatment fatigue score was reported in a study, we used only the point-in-time score that was assessed immediately after the end of the intervention period. When data were presented as median, range and/or interquartile range, we transformed them to mean and SD [27]. Fatigue was measured by different assessment scales, and the standard mean difference (SMD) was used as the effect size index to eliminate the influence of metrics. SMD values of 0.2, 0.5, and 0.8 indicate small, medium, and large effect sizes, respectively [28].

Data synthesis

An NMA combining direct and indirect evidence in a network of trials was conducted, and a random effects model was adopted to compare the relative effects of each intervention [29]. All data anal-

ysis and graph generation were completed by using Stata 11.0 statistical software (StataCorp, College Station, TX, USA).

First, a network plot visually expressed the comparison between different interventions. Moreover, a forest plot showed the SMD based on sample sizes and their 95% confidence interval (CI), and heterogeneity evaluated by Higgins I^2 was also given. Additionally, surface under the cumulative ranking curve (SUCRA) probabilities were calculated using the Markov chain Monte Carlo (MCMC) model to rank the interventions [30]. The SUCRA indicated the relative probability of each studied intervention among the optimal options, and a larger SUCRA value represents a higher ranking of an intervention [31]. A two-sided $p < 0.05$ was considered as statistically significant. The application of the network meta-analysis method overcame the lack of direct comparisons and allowed for a comprehensive conclusion.

Assessment of inconsistency

The loop-specific model and Wald test were used to examine the global consistency between direct and indirect comparisons [32, 33]. The 95% CI of inconsistency factor (IF) excludes 0 or the alpha value ≤ 0.05 indicating statistically significant inconsistency. The node-splitting model was adopted to further explore the local inconsistency across each network.

Subgroup analysis and sensitive analysis

To examine the sources of heterogeneity, subgroup analysis was performed according to median intervention duration and median age. Because of the characteristics of exercise therapy, it is impossible to blind both participants and personnel. The included studies tend to have a high blinding risk. Therefore, sensitive analysis

was performed by excluding studies that failed to achieve outcome assessment blinding.

Meta-regression analysis and publication bias

Meta-regression analysis was performed by publication year, sex ratio, sample size and intention to treat. Additionally, a funnel plot was used to detect potential publication bias and small-study effects.
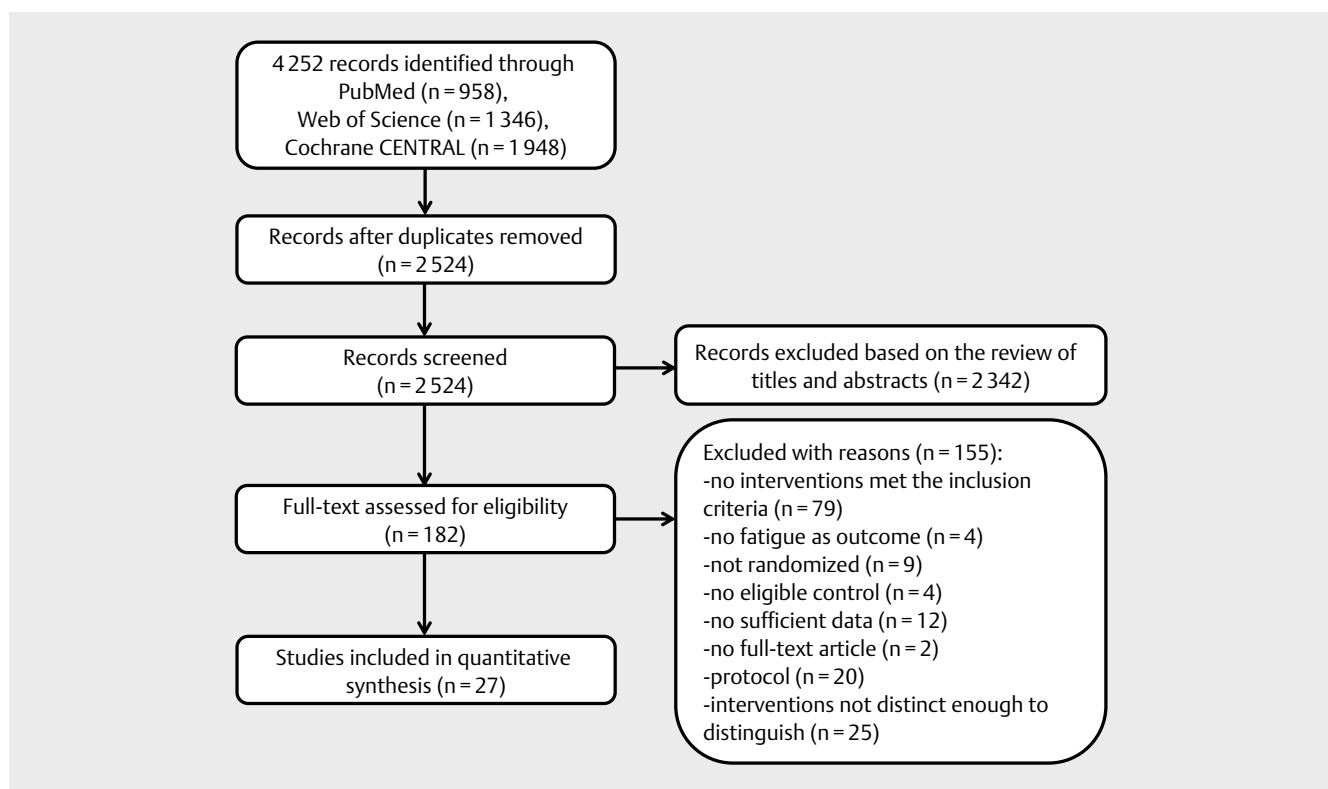
Results

Study identification and selection

A total of 4252 records were identified in the online databases listed above, 958 from PubMed, 1,346 from Web of Science, and 1,948 from Cochrane Library, respectively. After removal of the duplicates, titles and abstracts of 2524 records were browsed to find potential relevance. A total of 182 articles was included in the full-text assessment. Finally, 27 articles satisfied the inclusion criteria and were considered as eligible for further analyses. The flowchart of the whole literature retrieval process is shown in ▶ **Fig. 1**.

Characteristics of the studies

The baseline characteristics of the studies included in this NMA are detailed in ▶ **Table 1**. All 27 articles were published in English between 1996 and 2019. Sample sizes ranged from 11 to 314 patients; 6 came from Iran [34–39], 4 from America [40–43]; 3 each from Britain [44–46] and Germany [47–49]; two each from Italy [50, 51], Denmark [52, 53], and Australia [54, 55]; and 1 each from

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┌─────────────────────────────┐
│  4 252 records identified    │
│  through PubMed (n = 958),   │
│  Web of Science (n = 1 346), │
│  Cochrane CENTRAL (n = 1 948)│
└─────────────────────────────┘
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              ▼
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│  Records after duplicates    │
│  removed (n = 2 524)         │
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┌─────────────────────────────┐       ┌──────────────────────────────┐
│  Records screened            │──────▶│  Records excluded based on    │
│  (n = 2 524)                 │       │  the review of titles and     │
└─────────────────────────────┘       │  abstracts (n = 2 342)        │
              │                        └──────────────────────────────┘
              ▼
┌─────────────────────────────┐       ┌──────────────────────────────┐
│  Full-text assessed for      │──────▶│  Excluded with reasons        │
│  eligibility (n = 182)       │       │  (n = 155):                   │
└─────────────────────────────┘       │  -no interventions met the    │
              │                        │   inclusion criteria (n = 79) │
              ▼                        │  -no fatigue as outcome (n = 4)│
┌─────────────────────────────┐       │  -not randomized (n = 9)      │
│  Studies included in         │       │  -no eligible control (n = 4) │
│  quantitative synthesis      │       │  -no sufficient data (n = 12) │
│  (n = 27)                    │       │  -no full-text article (n = 2)│
└─────────────────────────────┘       │  -protocol (n = 20)           │
                                       │  -interventions not distinct  │
                                       │   enough to distinguish (n = 25)│
                                       └──────────────────────────────┘
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▶ **Fig. 1** Flow chart of the study selection process.

▶ **Table 1** Main characteristics of all eligible studies.

Author (year)	Country	Reported Inclusion/ Exclusion Criteria	Sample Size (n) Total Patients (N) Intervention (I) Control (C)	Sex (F/M)	Age of Intervention and Control, Mean±SD, yr	Completion n/N	Intention-to-treat	Groups	Intervention Duration	Adherence (%)	Fatigue Outcome Measures
Grazioli et al. (2019)	Italy	Yes/No	N=20 I=10 C=10	15, 5	45.91±12.09, 39.40±10.26	20/20	N/R	G1: Combined aerobic and resistance training, G2: UC	12 weeks	100	FSS
Bahmani et al. (2019)	Iran	Yes/Yes	N=62 I=31 C=31	62, 0	37.96±8.69, 37.90±9.91	47/62	N/R	G1: Endurance exercise, G2: NE	8 weeks	N/R	FSS
Young et al. (2018)	America	Yes/Yes	N=81 I1=27 I2=26 C=28	66, 15	49.67±9.40, 48.35±9.95, 47.29±10.33	81/81	N/R	G1: Dance, G2: Yoga, G3: WC	12 weeks	53.7, 67.7	Fatigue-Short Form 8a
Negaresh et al. (2018)	Iran	Yes/Yes	N=66 I=36 C=30	40, 21	31.7±7.0, 30.6±12.0	61/66	N/R	G1: Aerobic exercise, G2: NE	8 weeks	92.4	FSS
Feys et al. (2017)	Belgium	Yes/Yes	N=42 I=21 C=21	38, 4	36.6±8.5, 44.4±8.5	35/42	Yes	G1: Aerobic exercise, G2: WC	12 weeks	94	FSMC
Heine et al. (2017)	Netherlands	Yes/Yes	N=89 I=43 C=46	65, 24	43.1±9.8, 48.2±9.2	73/89	Yes	G1: Aerobic exercise, G2: UC	16 weeks	74	MFIS
Kargarfard et al. (2017)	Iran	Yes/No	N=40 I=20 C=20	32, 0	36.5±9.0, 36.2±7.4	32/40	Yes	G1: Aquatic exercise, G2: NE	8 weeks	N/R	MFIS
Kooshiar et al. (2015)	Iran	Yes/Yes	N=40 I=20 C=20	40, 0	N/R	37/40	N/R	G1: Aquatic exercise, G2: UC	8 weeks	N/R	MFIS
Kerling et al. (2015)	Germany	Yes/Yes	N=60 I=30 C=30	44, 16	42.3±9.0, 45.6±11.4	37/60	Yes	G1: Combined endurance and resistance training, G2: Endurance training	12 weeks	>90	MFIS
Skjerbaek et al. (2014)	Denmark	Yes/No	N=11 I=6 C=5	8, 3	62.0±5.9, 55.2±8.2	10/11	N/R	G1: Endurance training, G2: UC	4 weeks	96	FSMC
Ahmadi et al. (2013)	Iran	Yes/Yes	N=31 I1=10 I2=11 C=10	31, 0	36.80±9.17, 32.27±8.68, 36.70±9.32	31/31	N/R	G1: Aerobic exercise, G2: Yoga, G3: WC	8 weeks	N/R	FSS
Carter et al. (2013)	Britain	Yes/Yes	N=120 I=60 C=60	86, 34	45.7±9.1, 46.0±8.4	107/120	Yes	G1: Aerobic exercise, G2: UC	12 weeks	81	MFIS
Gervasoni et al. (2013)	Italy	Yes/No	N=30 I=15 C=15	12, 18	49.6±9.4, 45.7±8.9	30/30	N/R	G1: Aerobic exercise, G2: UC	2 weeks	N/R	FSS
Garrett et al. (2012)	Britain	Yes/Yes	N=314 I1=80 I2=77 I3=86 C=71	182, 60	51.7±10, 49.6±10, 50.3±10, 48.8±11	242/314	N/R	G1: Aerobic exercise, G2: Yoga, G3: Combined aerobic and resistance exercise, G4: UC	10 weeks	73	MFIS
Dodd et al. (2011)	Australia	Yes/Yes	N=76 I=39 C=37	52, 19	47.7±10.8, 50.4±9.6	71/76	Yes	G1: Resistance training, G2: UC	10 weeks	92	MFIS

▲ **Table 1** Continued

Author (year)	Country	Reported Inclusion/ Exclusion Criteria	Sample Size (n) Total Patients (N) Intervention (I) Control (C)	Sex (F/M)	Age of Intervention and Control, Mean±SD, yr	Completion n/N	Intention-to-treat	Groups	Intervention Duration	Adherence (%)	Fatigue Outcome Measures
Hebert et al. (2011)	America	Yes/Yes	N=26 I=13 C=13	22, 4	42.6±10.4, 50.2±9.2	25/26	Yes	G1: Endurance exercises, G2: UC	6 weeks	N/R	MFIS
Learmonth et al. (2011)	Britain	Yes/Yes	N=32 I=20 C=12	23, 9	51.4±8.06, 51.8±8.0	25/32	Yes	G1: Resistance exercise G2: UC	12 weeks	N/R	FSS
Cakt et al. (2010)	Turkey	Yes/Yes	N=30 I=15 C=15	15, 8	36.4±10.5, 35.5±10.9	23/30	N/R	G1: Resistance training, G2: NE	8 weeks	93	FSS
Dalgas et al. (2010)	Denmark	Yes/Yes	N=38 I=19 C=19	20, 11	47.7±10.4, 49.1±8.4	31/38	N/R	G1: Resistance training, G2: UC	12 weeks	N/R	FSS
Velikonja et al. (2010)	Slovenia	Yes/Yes	N=20 I=10 C=10	N/R	40±6, 39.5±6	20/20	N/R	G1: Climbing, G2: Yoga	10 weeks	N/R	MFIS
Ahmadi et al. (2010)	Iran	Yes/Yes	N=20 I=10 C=10	20, 0	36.80±9.17, 36.70±9.32	20/20	N/R	G1: Aerobic exercise, G2: WC	8 weeks	N/R	FSS
Dettmers et al. (2009)	Germany	Yes/Yes	N=31 I=16 C=15	21, 9	45.8±7.9, 39.7±9.1	30/31	N/R	G1: Endurance exercise, G2: NE	3 weeks	N/R	MFIS
Oken et al. (2004)	America	Yes/Yes	N=69 I1=26 I2=21 C=22	53, 4	49.8±7.4, 48.8±10.4, 48.4±9.8	57/69	N/R	G1: Yoga, G2: Aerobic exercise, G3: WC	24 weeks	N/R	MFI
Schulz et al. (2004)	Germany	Yes/Yes	N=28 I=15 C=13	19, 9	39±9, 40±11	28/28	N/R	G1: Aerobic exercise, G2: WC	8 weeks	N/R	MFIS
Mostert et al. (2001)	Switzerland	Yes/No	N=26 I=13 C=13	21, 5	45.23±8.66, 43.92±13.90	26/26	N/R	G1: Aerobic exercise, G2: NE	3–4 weeks	N/R	FSS
Sutherland et al. (2001)	Australia	Yes/No	N=22 I=11 C=11	12, 10	47.18±4.75, 45.45±5.05	22/22	N/R	G1: Aerobic exercise, G2: NE	10 weeks	N/R	The Profile of Mood States–Short Form
Petajan et al. (1996)	America	Yes/No	N=46 I=21 C=25	31, 15	41.1±9.17, 39.0±8.50	46/46	N/R	G1: Aerobic exercise, G2: NE	12 weeks	97	FSS

F, female; FSS, fatigue severity scale; FSMC, fatigue scale for motor and cognitive function; G, group; M, male; MFI, multidimensional fatigue inventory; MFIS, Modified Fatigue Impact Scale; N, number; NE, non-exercising; N/R, not reported; SD, standard deviation; UC, usual care; WC, wait-list control; yr, year.
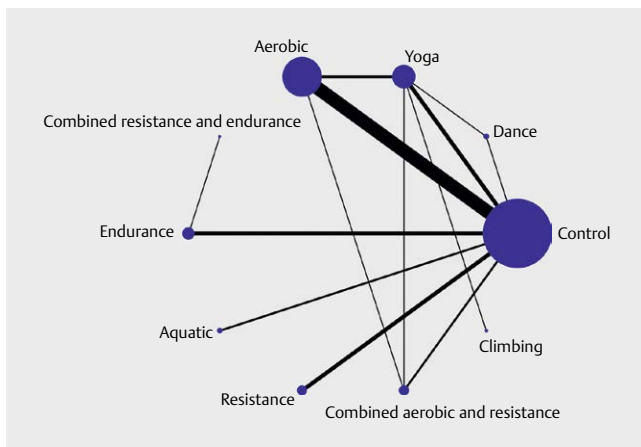
▶ Fig. 2 Network of intervention comparisons from trials included in the network meta-analysis. The size of the nodes corresponds to the total number of patients randomized to each intervention group. The width of the lines represents the number of direct comparisons that were performed in head-to-head trials.

Switzerland [56], Turkey [57], the Netherlands [58], Belgium [59] or Slovenia [60]. Four of them were multi-arm RCTs and the rest were two-arm parallel group trials. The average age of the participants ranged from 31 to 62, and the duration of the interventions ranged from 2 to 24 weeks. The studies included different types of exercise, such as aquatic exercise, aerobic exercise, resistance training, endurance training, dance, yoga, climbing, etc.

Risk of bias and quality assessment

The risk of bias within the studies was generally low (or probably low). Among all comparisons, random sequence generation was adequate in 21 trials (77.8%), and allocation concealment was adequate in 17 trials (63.0%). Blinding of outcome assessment (detection bias) was not conducted in five trials (18.5%) [38, 48–50, 55], and incomplete outcome data (attrition bias) was identified in four RCTs (17.4%) [34, 36, 52, 57]. Eight trials reported an intention-to-treat analysis (36.4%). High 'other sources of bias' was mainly due to low adherence (<80%) [40, 46, 58]. Notably, the limitations of the study design made it difficult for both participants and personnel to be blinded to exercise interventions, leading to a high risk of performance bias in all studies. The details of assessing the risk of bias can be found in **Supplementary Figure S1**.

Network meta-analysis for exercise and nonpharmaceutical interventions

Twenty-seven trials (59 arms, 1,470 participants) were included in the analysis of fatigue. The network consisted of 23 studies with two arms, 3 studies with three arms, and 1 study with four arms reporting on 10 different kinds of interventions (13 arms on aerobic, 5 yoga, 4 resistance training, 5 endurance training, 2 aquatic exercise, 2 combined aerobic and resistance training, 1 combined resistance and endurance training, 1 dance, 1 climbing; 25 arms on control groups). The network plot of pairwise comparisons across these trials is shown in **▶ Fig. 2**.

The results of the loop-specific model (95% CIs of all loops were truncated at zero) and Wald test (x^2 (5df) = 6.09, p = 0.298) showed no evidence of significant inconsistency (**Supplementary Figure S2 and S3**). In the node-splitting model, all p-values of direct and indirect comparisons were more than 0.05. Therefore, a consistency model was used for the subsequent analysis.

The results of the network meta-analysis were detailed in **▶ Table 2**. **▶ Fig. 3a** shows the outcomes presented as SMD and 95%CI for different types of exercise compared to control group.

Among these interventions, aquatic exercise ranked as the best intervention on reducing fatigue with an SMD of −1.73 (95%CI = −2.64 to −0.82). Small-to-moderate effect sizes were observed for aerobic exercise (SMD = −0.49, 95%CI = −0.79 to −0.20), compared with the control group. Despite large or moderate effect sizes, comparisons between some interventions were not statistically significant owing to sample size constraints.

Rank probability analysis indicated that aquatic exercise had the highest probability of being ranked as the most effective intervention (SUCRA = 99.1%), followed by aerobic exercise (SUCRA = 68.9%), dance (SUCRA = 65.0%) and resistance training (SUCRA = 54.5%). Climbing ranked as the least effective intervention (SUCRA = 11.4%), followed by the control group (SUCRA = 22.3%) and combined aerobic and resistance training (SUCRA = 36.3%). The ranking probability of all included interventions is shown in **▶ Figs. 3a** and **4**.

Subgroup analysis and sensitivity analysis

The subgroup analysis indicated that dance ranked as the most effective fatigue reduction intervention in the subgroups of intervention duration ≥ 10 weeks and age ≥ 45, followed by aerobic exercise and resistance training (**Supplementary Figure S4**). In the sensitivity analysis to test the impact of blinding risk, the effect sizes for the 10 kinds of interventions remained almost unchanged, suggesting that the overall results were robust. Moreover, small rises were observed in the ranking probabilities of aerobic exercise, resistance training, endurance training, combined resistance and endurance training as well as combined aerobic and resistance training (**▶ Fig. 3b**).

Meta-regression analysis and publication bias

To further search for the sources of heterogeneity, meta-regression analysis was conducted by publication year, sex ratio, sample size and intention to treat. The results suggested that none of these factors had significant modification effects. The shape of the funnel plot was judged and no obvious asymmetry was found, implying that there was no publication bias from small-study effects (**Supplementary Figure S5**).

Discussion

The current NMA is the first analysis to provide comparable evaluation of the effects of different types of exercise on reducing MS-related fatigue. We considered 27 RCTs and compared 10 kinds of interventions, involving 1,470 patients and combining direct and indirect evidence. Several valuable findings were generated in our study.

▶ **Table 2** Matrix of the treatment effect estimates of all comparisons according to indirect comparison meta-analysis.

	Aquatic	Aerobic	Dance	Resistance	Yoga	Endurance	RE	AR	Control	Climbing
Aquatic	Aquatic	1.23 (0.31, 2.16)	1.19 (−0.08, 2.45)	1.38 (0.33, 2.42)	1.40 (0.40, 2.39)	1.50 (0.42, 2.58)	1.52 (0.09, 2.95)	1.60 (0.48, 2.72)	**1.73 (0.82, 2.64)**	2.27 (0.69, 3.84)
Aerobic	−1.23 (−2.16, −0.31)	Aerobic	−0.05 (−0.97, 0.88)	0.14 (−0.46, 0.74)	0.16 (−0.31, 0.64)	0.27 (−0.37, 0.91)	0.28 (−0.85, 1.42)	0.37 (−0.28, 1.02)	**0.49 (0.20, 0.79)**	1.04 (−0.27, 2.34)
Dance	−1.19 (−2.45, 0.08)	0.05 (−0.88, 0.97)	Dance	0.19 (−0.85, 1.23)	0.21 (−0.68, 1.10)	0.31 (−0.74, 1.37)	0.33 (−1.08, 1.74)	0.41 (−0.65, 1.48)	**0.54 (−0.35, 1.43)**	1.08 (−0.43, 2.59)
Resistance	−1.38 (−2.42, −0.33)	−0.14 (−0.74, 0.46)	−0.19 (−1.23, 0.85)	Resistance	0.02 (−0.68, 0.72)	0.12 (−0.64, 0.89)	0.14 (−1.07, 1.35)	0.23 (−0.59, 1.04)	**0.35 (−0.17, 0.87)**	0.89 (−0.51, 2.29)
Yoga	−1.40 (−2.39, −0.40)	−0.16 (−0.64, 0.31)	−0.21 (−1.10, 0.68)	−0.02 (−0.72, 0.68)	Yoga	0.10 (−0.63, 0.83)	0.12 (−1.07, 1.31)	0.21 (−0.49, 0.90)	**0.33 (−0.13, 0.79)**	0.87 (−0.35, 2.09)
Endurance	−1.50 (−2.58, −0.42)	−0.27 (−0.91, 0.37)	−0.31 (−1.37, 0.74)	−0.12 (−0.89, 0.64)	−0.10 (−0.83, 0.63)	Endurance	0.02 (−0.92, 0.95)	0.10 (−0.73, 0.94)	**0.23 (−0.33, 0.79)**	0.77 (−0.65, 2.19)
RE	−1.52 (−2.95, −0.09)	−0.28 (−1.42, 0.85)	−0.33 (−1.74, 1.08)	−0.14 (−1.35, 1.07)	−0.12 (−1.31, 1.07)	−0.02 (−0.95, 0.92)	RE	0.08 (−1.17, 1.34)	**0.21 (−0.88, 1.30)**	0.75 (−0.95, 2.45)
AR	−1.60 (−2.72, −0.48)	−0.37 (−1.02, 0.28)	−0.41 (−1.48, 0.65)	−0.23 (−1.04, 0.59)	−0.21 (−0.90, 0.49)	−0.10 (−0.94, 0.73)	−0.08 (−1.34, 1.17)	AR	**0.13 (−0.50, 0.75)**	0.67 (−0.74, 2.07)
Control	**−1.73 (−2.64, −0.82)**	**−0.49 (−0.79, −0.20)**	**−0.54 (−1.43, 0.35)**	**−0.35 (−0.87, 0.17)**	**−0.33 (−0.79, 0.13)**	**−0.23 (−0.79, 0.33)**	**−0.21 (−1.30, 0.88)**	**−0.13 (−0.75, 0.50)**	Control	**0.54 (−0.76, 1.84)**
Climbing	−2.27 (−3.84, −0.69)	−1.04 (−2.34, 0.27)	−1.08 (−2.59, 0.43)	−0.89 (−2.29, 0.51)	−0.87 (−2.09, 0.35)	−0.77 (−2.19, 0.65)	−0.75 (−2.45, 0.95)	−0.67 (−2.07, 0.74)	**−0.54 (−1.84, 0.76)**	Climbing

AR, aerobic and resistance; CBT, cognitive behavior therapy; ER, endurance and resistance; **Reference:** the intervention listed in the row; Data are presented as SMD and their 95 % CI, and a negative value indicates a better effect for the treatment written above.
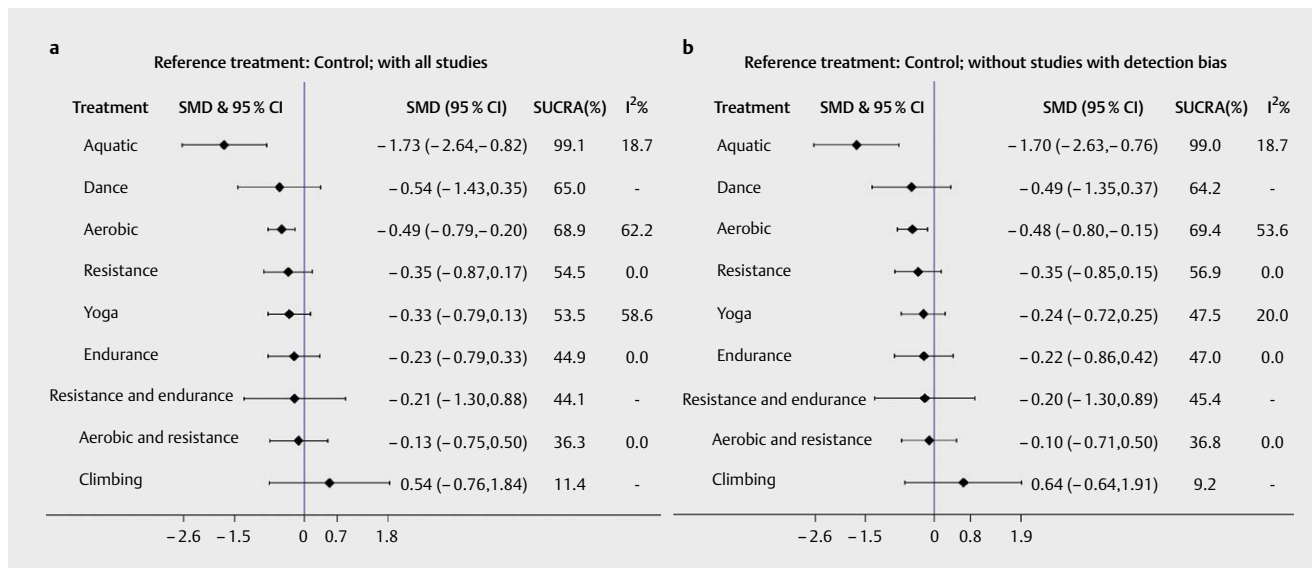
▶ **Fig. 3** Forest plots for the comparisons between the active interventions and the control intervention (**a**: with all studies; **b**: without studies with detection bias).
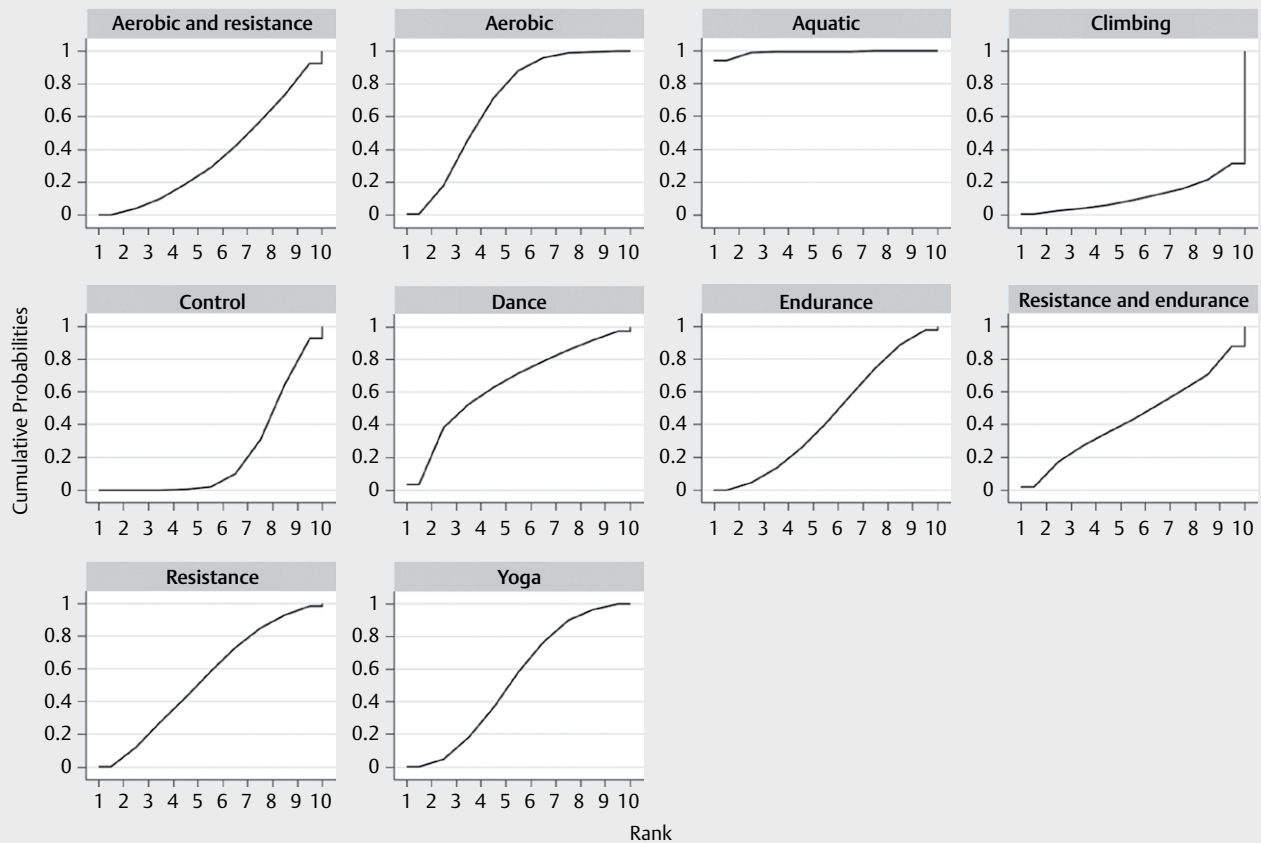
▶ Fig. 4 Cumulative ranking probability plot for the assessment of fatigue relief in patients with MS.

According to the cumulative ranking, aquatic exercise is the most effective intervention (ranking 99.1 %) which is followed by aerobic exercise, dance, resistance training, yoga, endurance training, combined resistance and endurance training, combined aerobic and resistance training, control and climbing. These results were generally consistent with previously published traditional meta-analyses [61].

The findings emphasized the usefulness of several kinds of exercise as a valid adjunct therapy against fatigue symptoms in MS patients. Helpful and hitherto unavailable information about the comparisons between these interventions were provided. The lack of global and local inconsistency as well as the lack of small-study effects strengthened the outcomes, and the results of meta-regression and sensitivity analysis further indicated the robustness. Our ranked interventions can provide reference for future clinical trials.

The fact that aquatic exercise was more effective than other interventions may be due to the following possibilities: (a) The buoyancy, viscosity, turbulence and hydrostatical pressure of water are favorable for people with physical weakness to carry out physical activities [62]; (b) people with MS are highly sensitive to heat events, and exercise in water can reduce the temperature of body via the water temperature and prolonged training sessions [63]; and (c) water immersion can influence the activity of endogenous systems related to sodium homeostasis, including the sympathet-ic nervous system, atrial natriuretic peptide system, and renal do-pa-dopamine system [64]. Aerobic exercise was observed to have small-to-moderate effect sizes in relieving fatigue in our study. Research has demonstrated the benefits of improving aerobic fitness, including reducing the risk of heart attack, lowering blood pressure, improving mental health, and improving bone mineralization [65–67]. Despite a lack of statistical differences between some comparisons, most of the interventions were shown to be better than the control group, except for climbing. Climbing was the only intervention that ranked worse than the control group, which may be correlated with the increased altitude and body temperature during climbing [68]. Our data did not support further analyses to explore these or other assumptions, and more RCTs on these topics are required in the future.

The study has several advantages. First, to our knowledge, this is the first systematic review that uses the NMA method to determine the effects and grades of a comprehensive range of exercise. Moreover, we evaluated and ranked the interventions, which can help practitioners and MS patients prioritize evidence-based interventions and then make more informed decisions.

Study limitations

Potential limitations in our NMA also merit further consideration. First, the small number of the studies for some interventions (for example, dance, climbing and aquatic exercise), limits the power

of the results because the findings could be coincidental. Second, the interventions of the included studies were difficult to classify due to the different kinds of intervention combinations. Third, follow-up data were collected over a wide range of time intervals, from 2 to 24 weeks. The long-term effects of these interventions have not been fully elucidated and might become a focus for future research. Collectively, given the reasons above, the results must be interpreted with caution, and any association observed in the current NMA should be tested in original RCTs.

Conclusion

Although exercise has shown promising effects in relieving fatigue in MS patients, comparisons between different types of exercise are still lacking. The current indirect-comparison NMA shows the beneficial effects of aquatic exercise and aerobic training on reducing MS-related fatigue. These findings enable people with MS to choose their preferred exercise as adjunct therapy to achieve optimal management of fatigue symptoms.

Conflict of Interest

The authors declare that they have no conflict of interest.

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