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Meta-analysis

The type of exercise most beneficial for quality of life in people with multiple sclerosis: A network meta-analysis

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ABSTRACT

Background: There is overwhelming evidence regarding the beneficial effects of exercise on the management of symptoms, functionality and health-related quality of life (HRQoL) of people with multiple sclerosis (MS). However, few analyze have compared different types of exercise.
Objective: The aim of this network meta-analysis (NMA) was to assess which type of physical exercise has the greatest positive effect on HRQoL in people with MS.
Methods: MEDLINE, Cochrane Library, Embase, Web of Science, Physiotherapy Evidence Database and SPORTDiscus databases were searched from inception to June 2021 to identify randomized controlled trials (RCTs) examining the effect of physical exercise on HRQoL in people with MS. The NMA included pairwise and indirect comparisons. We ranked the effect of interventions calculating the surface under the cumulative ranking (SUCRA).
Results: We included 45 RCTs in this NMA (2428 participants; 76% women; mean age 45 years). Five types of physical exercises were ranked. Sensorimotor training had the highest effect size (0.87, 95% confidence interval [CI] 0.60; 1.15) and the highest SUCRA (87%) for total HRQoL. The highest effect size and SUCRA for physical and mental HRQoL were for aerobic exercise (0.85, 95% CI 0.28; 1.42) (89%) and mind-body exercises (0.54, 95% CI 0.03; 1.06) (89%). Sensorimotor training was the best exercise for mild disease and aerobic exercise for severe disease for total HRQoL.
Conclusions: Sensorimotor training seems the most effective exercise to improve HRQoL and aerobic and mind-body exercises to improve physical and mental HRQoL, respectively.

Introduction

Multiple sclerosis (MS) is a long-term immune-mediated neurological disorder that affects approximately 2 in 1000 people worldwide [1]. MS can present in different clinical forms: relapsing-remitting, primary progressive, secondary progressive and progressive relapsing, with relapsing-remitting the most prevalent [2]. Relapsing-remitting MS is characterized by relapses that leave residual symptoms in many cases [3], whereas in primary progressive MS, symptoms are presented progressively. Secondary progressive and progressive relapsing MS are characterized by a combination of both relapse and progression [2]. The symptoms include fatigue, pain, spasticity, incontinence, sexual dysfunction, and disturbed mobility, vision, sensitivity and cognition [4,5], all having a major impact on health-related quality of life (HRQoL) [3].

HRQoL is defined as the subjective perception of the degree to which the disease affects physical and mental domains of health [6], which include other components such as physical function, emotional well-being, role limitations, health distress, sexual function, satisfaction with sexual function, cognitive function, energy, pain and social function [7].

People with MS are less physically active than the general adult population [8,9], although previous reviews [10,11] have synthesized the evidence regarding the beneficial effects of physical exercise on

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the HRQoL of people with MS. The mechanism of these effects includes improvements in managing the symptoms of the disease and preventing secondary cardiovascular conditions [12]. These studies are a valuable contribution to the non-pharmacological approach of the disorder, but they have not revealed what type of exercise is the most suitable for improving the HRQoL of people with MS.

Network meta-analysis (NMA) allows for conducting a single analysis to compare multiple interventions and rank them according their effectiveness [13], which could lead to more individualized recommendations for improving a specific outcome. Thus, the aims of this NMA were to 1) assess which type of physical exercise has the greatest positive effect on HRQoL in people with MS and 2) determine the best type of physical exercise for each stage of disease severity.

Methods

This NMA was reported in accordance with the Preferred Reporting Items for Systematic Reviews incorporating Network Meta-analysis (PRISMA-NMA) guidelines [14] (Table A.1) and the Cochrane Collaboration Handbook [13]. The protocol of this study was registered at PROSPERO (No.: CRD42020157164).

Search strategy and selection criteria

Two reviewers (SR-G and AT-C) independently searched for articles in the MEDLINE (via PubMed), Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Embase, Web of Science, Physiotherapy Evidence Database and SPORTDiscus databases from inception to June 2021. Any disagreements were resolved by consensus or with a third researcher (IC-R). The search strategy combined relevant terms related to (1) multiple sclerosis, (2) exercise, (3) HRQoL, and (4) clinical trials. Moreover, the reference lists of articles included in this NMA and in previous reviews were reviewed for any additional relevant study.

Eligibility

Studies concerning the effect of physical exercise on HRQoL in patients with MS were included. The inclusion criteria were (1) patients with MS; (2) investigating any physical exercise intervention of any intensity, duration or frequency; (3) comparing physical exercise interventions of another category or control individuals undergoing usual care; (4) randomized controlled trial (RCT); and (5) the primary outcome being HRQoL (total score, physical or mental components).

The exclusion criteria were (1) combining physical exercise with other multidisciplinary interventions; (2) interventions consisting of only an educational component; (3) the type of physical exercise category being unclear; (4) not reporting sufficient data to calculate the effect size; (5) conference abstract without a fully published article; or (6) publication not written in English or Spanish. When more than one study provided data for the same sample, the study with the most detailed data or the largest sample size was selected.

Data extraction

Two reviewers (SR-G and AT-C) independently extracted the following information from each included study: (1) year of publication; (2) country; (3) sample size; (4) population characteristics (age, severity, type and duration of the disease); (5) physical exercise characteristics (type, training regime, duration, frequency and time); and (6) outcome measurement (HRQoL scale). Disagreements in the data extraction process were resolved by consensus or with a third researcher (IC-R). According to the Cochrane Collaboration Handbook recommendations, our estimates were based on standard errors, 95% confidence intervals (CIs), *p* values or t statistics to calculate the standard deviation when the standard deviation of change from baseline was missing.

Classification of the disease, interventions and outcome

For the disease characteristics, we extracted the severity, type (relapsing-remitting, primary progressive, secondary progressive or progressive relapsing) and duration of MS. The disease severity was reported in different ways in studies. In articles that reported disease severity by a scale, the total value at baseline was selected. For disease duration, some articles reported the time since diagnosis and symptoms, and time since diagnosis was selected because it was the most common in the remaining articles.

Physical exercise interventions were classified as aerobic exercise, resistance training, combined training (aerobic exercise with resistance training), sensorimotor training, mind-body exercises and control.

Aerobic exercise included interventions aimed at increasing energy expenditure and heart rate, such as treadmill, cycling or walking; interval training was considered aerobic exercise. Resistance exercises aimed to increase muscular strength and power. Sensorimotor training included exercises aimed at improving the neuromuscular system by coordination and balance and could add strength or aerobic exercise and included interventions with reduced pressure forces, such as robotic assistance or aquatic exercises. Mind-body exercises included those based on balance and strength, focusing on breathing and postural control, such as pilates or yoga.

HRQoL outcomes were measured by one or more self-reporting questionnaires in all studies, most indicating that higher scores meant better HRQoL. However, when a study was reverse scored (higher scores indicated worse HRQoL), the mean of each group was multiplied by -1. The different questionnaires were combined into one main outcome calculating the standardized mean difference. When the scale was subdivided into domains, the total, physical and mental HRQoL components were used for the analyze. Finally, when the study reported the same value with more than one scale, we calculated a pooled estimate.

Risk of bias assessment

Two researchers (PL-M and SNA-A) independently assessed the risk of bias of the included RCTs by using the Cochrane Collaboration's Risk of Bias 2 tool (RoB-2) for assessing risk of bias [15]. Disagreements were resolved by consensus with a third reviewer (IC-R). This tool evaluates the risk of bias according to 5 domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Overall bias was scored as "low risk of bias" if all the domains of the study were classified as "low risk"; "some concerns" if at least one domain was scored as "some concerns"; and "high risk of bias" if at least one domain was rated as "high risk" or several domains were scored as "some concerns" and could affect the validity of the results.

Assessing the quality of evidence

The certainty of the evidence in the network estimates of the main outcomes (i.e., efficacy, acceptability, and safety) was assessed by using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) ratings [16]. In the GRADE framework, the quality of evidence is rated high, moderate, low, or very low on the basis of the study limitations, risk of bias, inconsistency, indirectness, imprecision, and publication bias.

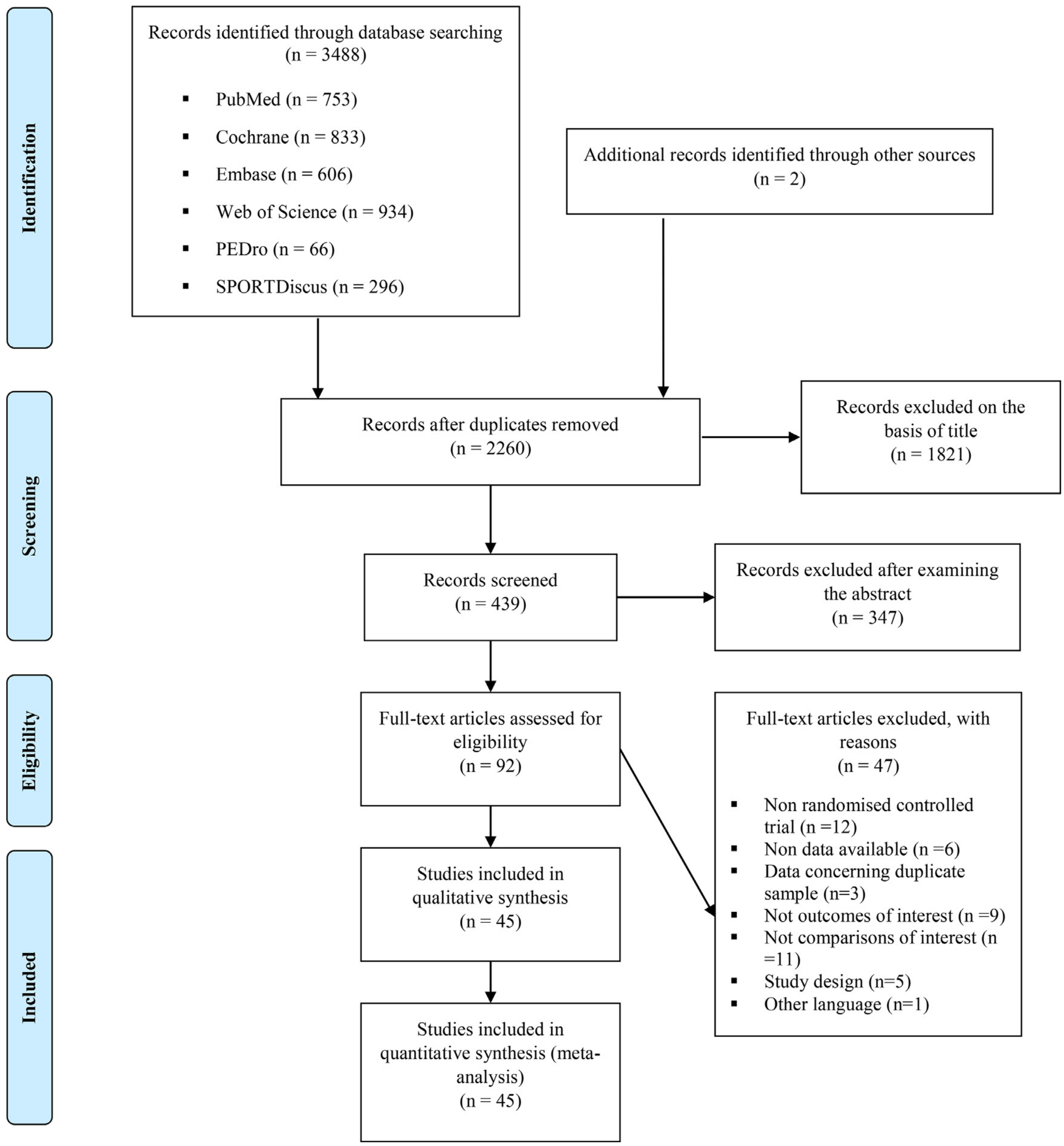

Fig. 1. Flow of the selection of articles.

Data synthesis and statistical analysis

The NMA involved the following 5 steps. First, to assess the strength of the available evidence, we used a network geometry graph in which the size of the nodes was proportional to the number of studies included for each intervention and the width of the lines connecting nodes was proportional to the trials directly comparing the 2 interventions [17].

Second, we assessed consistency by checking that intervention effects estimated from direct comparisons were consistent with those estimated from indirect comparisons. Confidence was assessed with the Confidence In Network Meta-Analysis (CINeMA) web application [18].

Third, a standard pairwise meta-analysis was conducted for each direct comparison by using the DerSimonian-Laird random effects method [19]. We calculated the standardized mean difference score by using Cohen's d as the effect size statistic: values ⟨ 0.2 were considered low effect size, 0.2 to 0.5 moderate effect size, 0.5 to 0.8 strong effect size, and ⟩ 0.8 very strong effect size. Moreover, statistical heterogeneity was examined with the I^2 statistic, with I^2 = 0% to 40% considered not important, I^2 = 30% to 60% moderate, I^2 = 50% to 90% substantial and I^2 = 75% to 100% considerable heterogeneity; the corresponding p-values were also considered [13]. Finally, to determine the size and clinical relevance of heterogeneity, we calculated the τ^2 statistic. An τ^2 ⟨ 0.14 was considered low degree of clinical relevance of heterogeneity, 0.14 to 0.40 moderate heterogeneity, and ⟩ 0.40 substantial heterogeneity. These results were displayed by generating a league table.

Fourth, we assessed transitivity by checking whether the synthesis of the direct comparisons of interventions used samples with similar clinical characteristics. Thus, one should assume that the populations included in these studies were similar in the baseline distribution of the effect modifiers (sex, age, disease severity and disease duration).

Fifth, once we estimated the effectiveness of the interventions, we used rankograms to graphically present the probability of each type of exercise being the most effective. Moreover, the surface under the cumulative ranking (SUCRA) was estimated for each intervention. SUCRA involves assigning a numerical value from 0 to 1 to simplify the classification in the rankogram, with values close to 1 being the

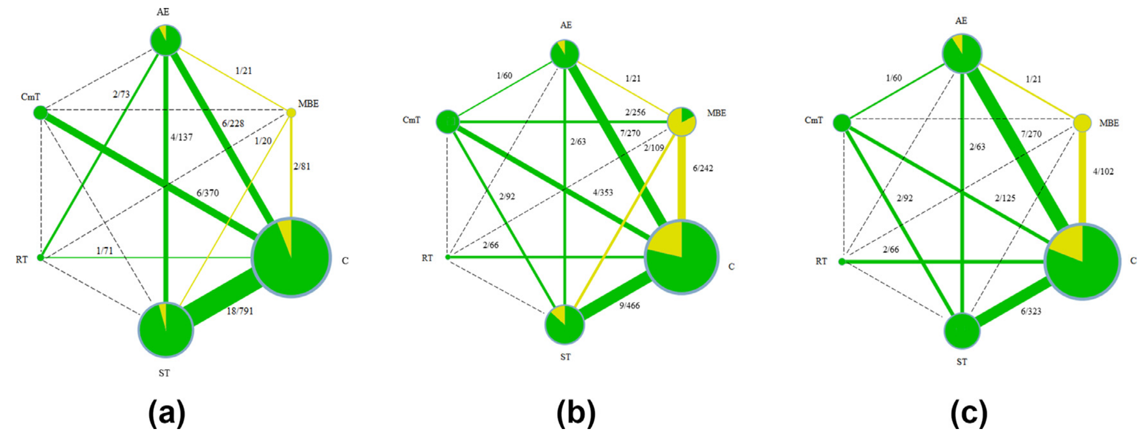

Fig. 2. Network of available comparisons between different exercise interventions on HRQoL in multiple sclerosis: (i) total HRQoL; (ii) physical HRQoL; (iii) mental HRQoL. The size of the nodes is proportional to the number of trials included for each intervention and the line width corresponds to studies directly comparing the 2 interventions (no. of studies/ no. of participants). Dashed lines represent indirect comparisons. Coloured areas correspond to the proportion of studies for each node that meet transitivity assumptions, as follows: green for the 4 covariates (sex, age, disease severity and disease duration), yellow for 2 or 3 covariates, and red for 1 or 0 covariates. HRQoL, health-related quality of life; AE, aerobic exercise; C, control; CI, confidence interval; CmT, combined training; MBE, mind-body exercises; RT, resistance training; ST, sensorimotor training.

best intervention and 0 the worst [17,20]. These data were also displayed by using a rank-heat plot according to the SUCRA [21].

Additionally, subgroup analyze were used to assess the effectiveness of the physical exercise categories by disease severity. For these analyze, we used only studies that reported a quantitative value on a scale of disease severity. The disease was classified according to Haber (1985) and Alonso et al. (2021) as mild (Expanded Disability Status Scale [EDSS] score 0 to 5) and severe (EDSS score $\geq$ 5) [22, 23]. Random-effects meta-regression analyze were used to evaluate whether the group with relapsing-remitting MS affected the association of physical exercise and HRQoL outcomes.

To assess the robustness of estimates and to detect whether a particular study represented a large proportion of the heterogeneity, we conducted sensitivity analysis removing data for individual studies one at a time. Moreover, a sensitivity analysis excluded studies with high risk of bias.

Finally, to assess publication bias, we used a network funnel plot to visually examine the criterion of symmetry and Egger's regression asymmetry test, considering $p < 0.10$ as statistically significant [24]. All analyze involved using Stata 16.0 (Stata, College Station, TX, USA).

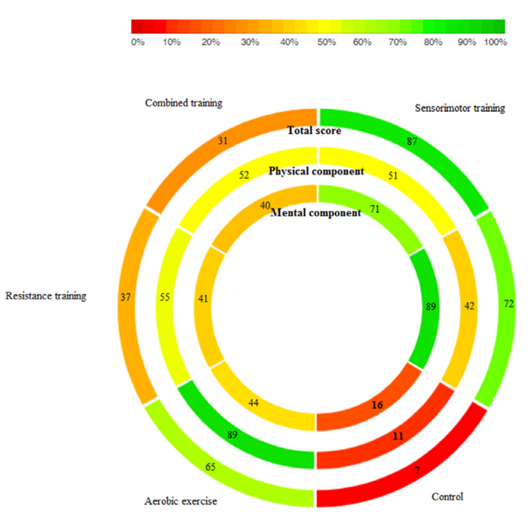

Fig. 3. Rank-heat plot with SUCRA values for scoring in total, physical and mental HRQoL. SUCRA, surface under the cumulative ranking curve.

Results

From the 3490 articles identified in the literature search, 45 RCTs [S1-S45] (2428 participants) were included in this NMA (Fig. 1). Six studies had 3 arms (2 interventions and 1 control), 2 studies had 4 arms (3 interventions and 1 control), and 1 study had 5 arms (4 interventions and 1 control) (Table A.2). Overall, 76% of participants were women, the age of participants ranged from 29 to 58 years, and the mean disease duration ranged from 2.69 to 18.7 years. Disease severity examined was mild in 28 studies and severe in 7. The most common exercise was sensorimotor training (n = 27 interventions), followed by aerobic (n = 15), combined (n = 11), mind-body (n = 8) and resistance exercise (n = 4) (more information on meta-demographic data is in Table 1). Finally, 29 studies evaluated total HRQoL and 27 and 24 physical and mental HRQoL, respectively.

Risk of bias

As evaluated by the RoB-2, 4 studies were assessed as low risk of bias, 33 as having some concerns, and 8 as high risk of bias (Fig. A.1). For individual domains, 36% and 78% of studies had some concerns for the randomization process and the selection of the reported results, respectively; for deviations from intended interventions outcome, 31% had some concerns and 9% were at high risk of bias; for missing outcome data, 7% had some concerns and 4% were at high risk of bias; and for measurement of the outcome, 22% had some concerns and 4% were at high risk of bias. The GRADE evaluations are in Table A.3.

Network analyze

The network geometry graphs show the relative amount of evidence available for the effect of physical exercise interventions on total, physical and mental HRQoL, involving 9, 11 and 9 pairwise comparisons, respectively (Fig. 2). All interventions had at least one direct comparison with the control group. The colours on the graph correspond to the transitivity assumption, which was achieved for all comparisons for at least one outcome (sex, age, disease severity or disease duration). We found differences only for mind-body exercises by disease severity (2.08, 95% CI 1.73; 2.43). Risk of bias and indirectness contributions in network analyze were assessed with the CINeMA web application.

Table 1
Meta-demographic data for included studies.

	n	Country (studies)	Sex (% female)	Age (years)	Disease severity (EDSS)	% Relapsing-remitting	Disease duration (years)
Aerobic exercise	301	Belgium (1), Denmark (1), Germany (3), Hungary (1), Iran (2), Switzerland (1), UK (3), USA (3)	73.49 (64.04; 82.93)	46.32 (41.57; 51.07)	3.85 (2.52; 5.18)	55.53 (29.88; 81.19)	10.51 (7.36; 13.66)
Resistance training	87	Australia (1), Denmark (2), UK (1)	72.22 (58.42; 86.02)	46.90 (43.87; 49.93)	3.30 (2.57; 4.03)	84.72 (36.10; 133.34)	8.16 (5.43; 10.89)
Combined training	394	Finland (1), Germany (2), Iran (1), Ireland (3), Italy (2), UK (1), USA (1)	73.97 (67.68; 80.26)	46.59 (43.42; 49.77)	3.74 (1.99; 5.49)	62.22 (30.58; 93.86)	10.39 (7.29; 13.49)
Sensorimotor training	585	Hungary (3), Iran (2), Ireland (2), Italy (4), Spain (2), Switzerland (1), Turkey (7), UK (3), USA (3)	76.00 (69.93; 82.06)	45.17 (42.83; 47.51)	4.15 (3.58; 4.72)	59.18 (43.39; 74.98)	10.56 (8.13; 12.99)
Mind-body exercises	168	Canada (1), Iran (2), Ireland (2), Turkey (3)	79.17 (60.95; 97.39)	44.52 (38.61; 50.43)	2.08 (1.73; 2.43)	61.47 (−16.27; 139.22)	10.18 (6.73; 13.63)
Control	893	Australia (1), Belgium (1), Canada (1), Denmark (3), Finland (1), Germany (3), Hungary (1), Iran (6), Ireland (3), Italy (2), Spain (1), Turkey (5), UK (5), USA (5)	78.58 (73.81; 83.34)	43.56 (41.43; 45.69)	3.52 (2.79; 4.25)	71.67 (59.62; 83.73)	8.94 (7.83; 10.04)
Total	2428		76.42 (73.54; 79.30)	45.24 (43.83; 46.66)	3.39 (2.50; 4.28)	65.26 (57.58; 72.94)	9.93 (9.07; 10.79)

Data are mean (95% confidence interval).
EDSS: Expanded Disability Status Scale.

Effect on HRQOL by exercise modality

Table 2 shows the effect size estimates for total, physical and mental HRQoL. Although some effect sizes were not significant, all estimates favoured physical exercise for all 3 outcomes, except for resistance training in the pairwise comparisons for mental HRQoL. The highest effects for pairwise comparisons were for sensorimotor training versus the control (ranging from 0.65 to 1.00) and aerobic exercise versus the control (ranging from 0.28 to 0.81). The highest effects for total, physical and mental HRQoL were for sensorimotor training (0.87, 95% CI 0.60; 1.15), aerobic exercise (0.85, 95% CI 0.28; 1.42) and mind-body exercises (0.54, 95% CI 0.03; 1.06), respectively, compared to the control.

Probabilities

The highest SUCRA for total, physical and mental HRQoL was for sensorimotor training (87%), aerobic exercise (89%) and mind-body exercises (89%), respectively (Fig. A.2). The rank-heat plot for the 3 outcomes is in Fig. 3.

Subgroup, meta-regression and sensitivity analyze, heterogeneity and publication bias

Subgroup analysis was not possible for the association of severe disease and physical and mental HRQoL because of the low number of studies for each comparison (0, 1 or 2) (Table A.4). The highest statistically significant effect size for mild disease was sensorimotor training versus the control for total (0.61, 95% CI: 0.34; 0.88), physical (0.76, 95% CI 0.17; 1.35), and mental HRQoL (0.81, 95% CI 0.22; 1.41). For severe disease associated with total HRQoL, the highest statistically significant effect size was for aerobic exercise versus sensorimotor training (0.91, 95% CI 0.61; 1.20).

The random-effects meta-regression models indicated that the group with relapsing-remitting MS did not affect the estimates of the association between physical exercise and HRQoL ($p > 0.05$) (data not shown).

In the sensitivity analysis, the pooled effect size estimates for the association between physical exercise and all dimensions of HRQoL were not significantly modified in magnitude or direction when the data for individual studies were removed one at a time. When studies with high risk of bias were excluded from the pairwise comparison analysis, some effect sizes were slightly modified, but the statistical significance did not change.

Sensorimotor training versus control showed considerable heterogeneity for total, physical and mental HRQoL (I^2= 72%, τ^2= 0.2078; I^2= 81%, τ^2= 0.4494; and I^2= 82%, τ^2= 0.4904, respectively). Additionally, for total, physical and mental HRQoL, considerable heterogeneity was shown for aerobic exercise versus sensorimotor training (I^2= 75%, τ^2= 0.1436), aerobic exercise versus control (I^2= 77%, τ^2= 0.4431) and resistance training versus control (I^2=79%, τ^2=0.5331), respectively.

Finally, on Egger's test, publication bias was found for combined training versus control for total HRQoL (p = 0.081) and physical HRQoL (p = 0.099).

Discussion

This NMA based on 45 RCTs (2428 patients) aimed at comparing the effectiveness of different types of exercise for improving HRQoL in people with MS. Sensorimotor training and aerobic and mind-body exercises were the most effective exercise modalities improving total, physical and mental HRQoL, respectively. Sensorimotor training had the highest effect for mild disease, whereas aerobic exercise versus sensorimotor training was the best exercise intervention for severe disease in total HRQoL, perhaps because aerobic capacity and

Table 2
Absolute and relative effect size estimates for (1) total HRQoL and (2) physical and (3) mental HRQoL. Upper right triangle gives the effect size from pairwise comparisons (column intervention relative to row); lower left triangle gives the effect size from the network meta-analysis (row intervention relative to column).

(1) Total HRQoL					
Control	**0.39 (0.16; 0.62)**	0.24 (−0.23; 0.70)	0.08 (−0.22; 0.38)	**0.65 (0.40; 0.91)**	0.13 (−0.28; 0.54)
0.66 (0.28; 1.04)	Aerobic exercise	−0.29 (−0.75; 0.16)	NA	**−0.71 (−1.14; −0.28)**	0.06 (−0.80; 0.92)
0.34 (−0.40; 1.07)	−0.32 (−1.04; 0.40)	Resistance exercise	NA	NA	NA
0.27 (−0.22; 0.77)	−0.38 (−1.01; 0.24)	−0.06 (−0.95; 0.83)	Combined exercice	NA	NA
0.87 (0.60; 1.15)	0.22 (−0.19; 0.62)	0.54 (−0.23; 1.30)	**0.60 (0.03; 1.16)**	Sensorimotor training	0.00 (−0.88; 0.88)
0.76 (0.04; 1.47)	0.10 (−0.66; 0.87)	0.42 (−0.58; 1.43)	0.49 (−0.39; 1.36)	−0.11 (−0.85; 0.62)	Mind-body exercises
(2) Physical HRQoL					
Control	**0.81 (0.23; 1.39)**	0.29 (−0.22; 0.80)	0.13 (−0.08; 0.34)	**0.67 (0.17; 1.16)**	0.11 (−0.15; 0.36)
0.85 (0.28; 1.42)	Aerobic exercise	NA	0.07 (−0.57; 0.72)	0.05 (−0.45; 0.55)	−0.49 (−1.36; 0.38)
0.46 (−0.82; 1.74)	−0.39 (−1.80; 1.01)	Resistance training	NA	NA	NA
0.40 (−0.19; 0.99)	−0.45 (−1.20; 0.30)	−0.06 (−1.47; 1.35)	Combined training	0.02 (−0.30; 0.35)	−0.09 (−0.33; 0.16)
0.38 (−0.11; 0.87)	−0.47 (−1.15; 0.21)	−0.08 (−1.45; 1.29)	−0.02 (−0.69; 0.65)	Sensorimotor training	−0.42 (−0.86; 0.02)
0.29 (−0.27; 0.86)	−0.56 (−1.30; 0.19)	−0.17 (−1.57; 1.23)	−0.11 (−0.80; 0.58)	−0.09 (−0.74; 0.57)	Mind-body exercises
(3) Mental HRQoL					
Control	**0.28 (0.03; 0.53)**	−0.19 (−1.33; 0.95)	0.04 (−0.31; 0.40)	**1.00 (0.37; 1.63)**	**0.45 (0.04; 0.85)**
0.14 (−0.15; 0.43)	Aerobic exercise	NA	−0.28 (−0.93; 0.37)	0.07 (−0.43; 0.57)	0.63 (−0.25; 1.51)
0.11 (−0.58; 0.80)	−0.04 (−0.78; 0.71)	Resistance training	NA	NA	NA
0.13 (−0.20; 0.46)	−0.02 (−0.41; 0.38)	0.02 (−0.74; 0.79)	Combined training	0.08 (−0.24; 0.41)	NA
0.30 (0.04; 0.57)	0.16 (−0.19; 0.51)	0.20 (−0.54; 0.94)	0.18 (−0.16; 0.51)	Sensorimotor training	NA
0.54 (0.03; 1.06)	0.40 (−0.17; 0.97)	0.43 (−0.43; 1.30)	0.41 (−0.20; 1.02)	0.24 (−0.34; 0.82)	Mind-body exercises

Data are effect sizes (95% confidence intervals).
NA, not available; HRQoL: health-related quality of life.
Effect size **in bold**: statistically significant.
Combined training is aerobic exercise and resistance training.
Positive effect sizes mean that the first intervention of the comparison improves quality of life compared to the second intervention.

fatigue endurance are important for total HRQoL in this degree of disease severity.

Regarding total HRQoL, our results indicate that the best type of exercise is sensorimotor training, that is, based on strength or aerobic exercise, balance and coordination training. Impairments in strength, particularly balance, have been identified as risk factors for falls in people with MS [25, 26]. Falling is associated with both physical (by increased risk of fracture worsening mobility) and mental (by the consequent fear of falling and loss of autonomy) dimensions of HRQoL [27, 28]. Thus, by improving strength and balance and consequently reducing the risk of falling, sensorimotor training may improve HRQoL. Moreover, those interventions based on body weight support (with reduced pressure forces) were included in the sensorimotor training category and have been found to improve spasticity [29]. Additionally, our analyze showed that mind-body exercises were effective in improving total HRQoL, probably because they alleviated pain [30].

For physical HRQoL, according to a previous review [31], our NMA showed that the best intervention was aerobic exercise. Aerobic exercise is well known to improve aerobic capacity [S34, 32], which enhances functional independence and fatigue resistance in people with MS [10]. Moreover, other studies have found a relation between aerobic capacity and HRQoL [33], specifically with physical function and physical role domains [34].

For improving mental HRQoL, the most effective intervention was mind-body exercise, which includes pilates and yoga. Apart from improving muscular strength, flexibility and balance, mind-body exercises focus on breathing and posture [35, 36]. A previous meta-analysis showed that pilates improves mental health with all these enhancements [37], which may be due to developing body and mental awareness. Yoga may create a sense of well-being [38], which is an important outcome when evaluating mental HRQoL. However, when we assessed transitivity, the mean disease severity score was significantly lower for patients doing mind-body exercises versus most of the other physical exercise interventions. These results agree with previous evidence showing EDSS scores of 1.00 to 4.50 in populations doing mind-body exercises, so generalization to patients with a more severe disease stage is questionable [39]. However, our data show that sensorimotor training could also be effective in improving mental health and when analysing mild disease severity, probably because this type of exercise, similar to mind-body exercises, is based on strength and balance training.

Finally, sex, age and disease duration were similar in intervention groups. Thus, they did not affect the effect estimates.

We should consider some limitations of our NMA. First, we did not consider the characteristics of the intervention, such as intensity, duration, frequency, and time, because they varied widely between the studies and limited the generalizability of our results. Furthermore, the combined training interventions could not be classified as aerobic exercise or resistance training because approximately the same time was spent on each type of exercise and this would reduce the power of the analysis. Second, we analysed the total, physical and mental HRQoL, but other dimensions of HRQoL, such as pain or sexual function, could be confounders or mediators of the effect of exercise on HRQoL. Third, the instruments used to evaluate the outcomes varied across studies (general, disease-specific HRQoL questionnaires), which might affect the results. In addition, some studies of total HRQoL did not disaggregate the results by components, so we could not separately analyze the effect of exercise interventions on each of the HRQoL dimensions. Fourth, estimates by disease severity are weak because of the scarcity of information in studies. Fifth, combined training versus control comparisons showed publication bias, as evidenced by Egger's test results; thus, the findings of this NMA could be modified by unpublished results of that comparison. Finally, a large proportion of studies were assessed as having some concerns (73%) and high risk of bias (18%), which could be attributed, in most studies, to unpublished previous protocols, lack of blinding, and a moderate number of withdrawals in the follow-up. Nevertheless, to overcome these limitations, we conducted sensitivity analyze by excluding studies one at a time and those with high risk of bias.

In conclusion, exercise represents a beneficial approach to improve the HRQoL of people with MS. Sensorimotor training seems the most effective type of exercise to improve HRQoL as a whole and aerobic and mind-body exercises to improve physical and mental HRQoL, respectively. Therefore, from our results, on the basis of the best available evidence published so far, programmes combining exercise aimed at improving strength, aerobic capacity and balance may be the best strategy to improve the HRQoL of people with MS.

Declaration of Competing Interest

None declared.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rehab.2021.101578.

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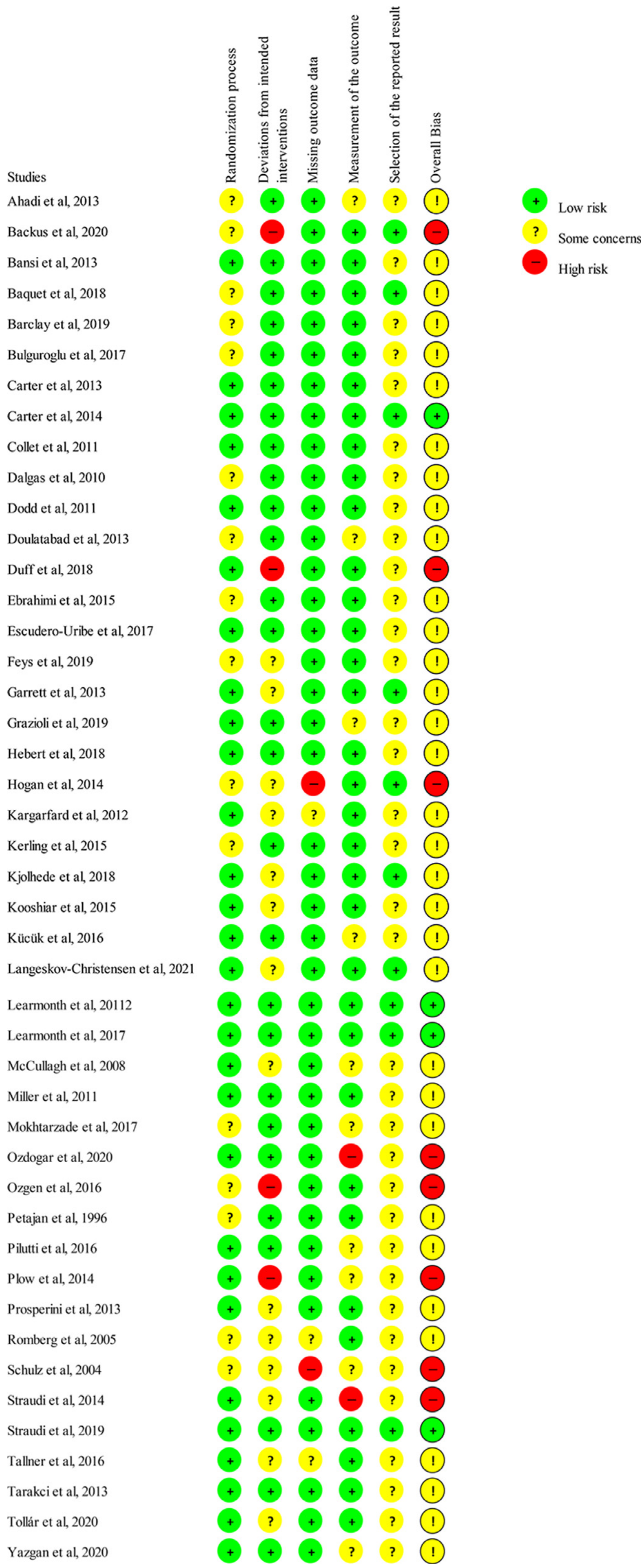

Fig. A.1. Risk of bias for studies of physical exercise interventions.

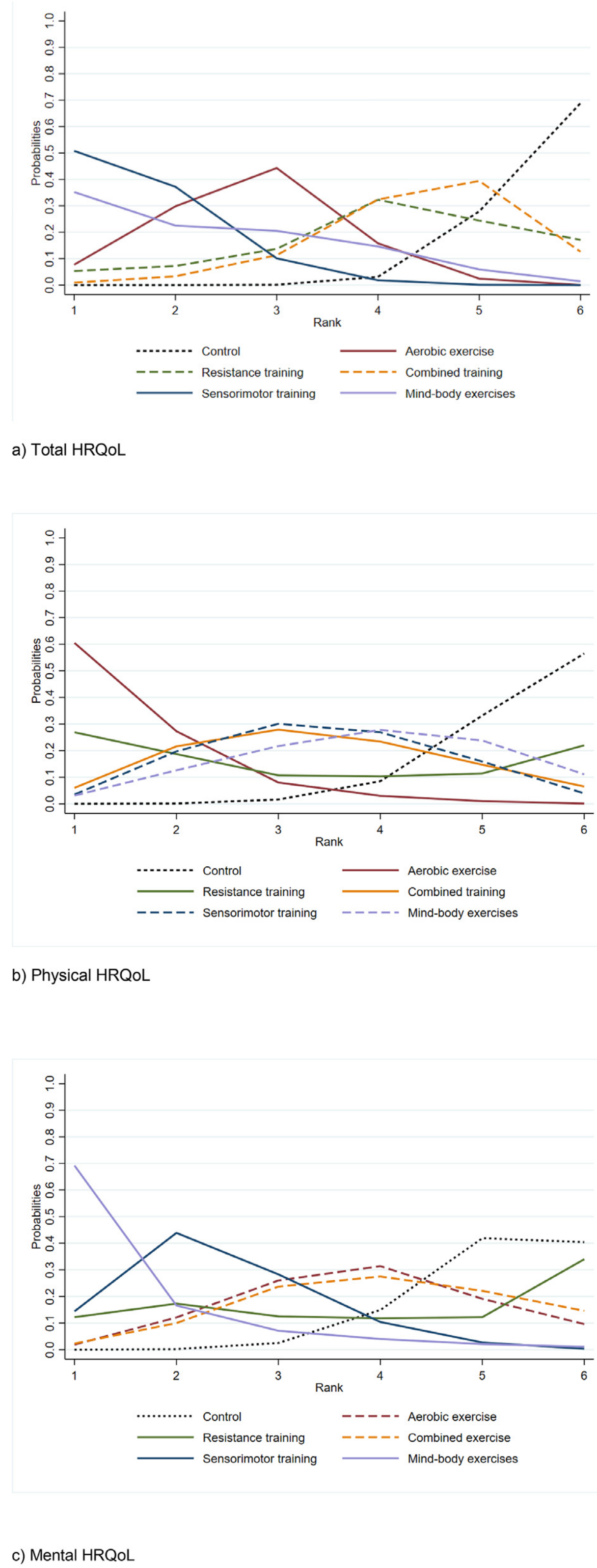

Fig. A.2. Rankogram for each intervention on HRQoL score in multiple sclerosis. HRQoL, health-related quality of life.

Table A.1
PRISMA NMA checklist.

Section/Topic	Item	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyze for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted.*	4
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4,5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	5 (pending updated)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	5,6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6, 7
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	8, 9
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyze.*	8, 9
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyze; and* • *Assessment of model fit.*	8, 9
Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyze	16	Describe methods of additional analyze if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyze; • Meta-regression analyze; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyze (if applicable).*	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10, Fig. 1
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Fig 2

(*continued*)

Table A.1 (*Continued*)

Section/Topic	Item	Checklist Item	Reported on Page #
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	10, 11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10, Tables 1, A.2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	10, Fig. A.1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	Table A.2
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.	11, Table 2, Figs. 3, A.2
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, P values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	11, Table 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	10, Table A.3
Results of additional analyze	23	Give results of additional analyze, if done (e.g., sensitivity or subgroup analyze, meta-regression analyze, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyze, and so forth).	11, 12, Table A.4
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	14, 15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	16

PICOS = population, intervention, comparators, outcomes, study design.
*Text in italics indicates wording specific to reporting of network meta-analyze that has been added to guidance from the PRISMA statement.

Table A.2
Characteristics of the randomized controlled trials included in the network meta-analyze.

STUDY Study (year)	Country	N (female)	POPULATION Age (years), mean (SD)	Disease severity, mean (SD)	Type of MS	Disease duration (years), mean (SD)	Groups by intervention	INTERVENTION Training regime	Duration (weeks)	Frequency (x/week)	Time min/ repetitions	OUTCOME Health-related quality of life scale
Ahadi et al. [S1]	Iran	10 (10)	Overall: 34.15 (mean)	Overall: EDSS: 1; 4	NR	NR	IG1: aerobic exercise	Treadmill training (40–75% MHR), stretching and flexion and rotation movements	8	3	30	MSQOL-54
		11 (11)	Overall: 34.15 (mean)	Overall: EDSS: 1; 4	NR	NR	IG2: mind-body exercises	Hatha yoga	8	3	60–70	
		10 (10)	Overall: 34.15 (mean)	Overall: EDSS: 1; 4	NR	NR	CG	Own routine treatment program				
Backus et al. [S2]	USA	6 (3)	56.17 (10.01)	EDSS: 7 (median)	RR/SP/ Undefined: 2/3/1	NR	IG: aerobic exercise	FES cycling at 35 to 50 rpm	12	3	35	MSQOL-54
		6 (4)	54.67 (11.55)	EDSS: 7.5 (median)	RR/SP/ Undefined: 1/1/4	NR	CG	Wait period				
Bansi et al. [S3]	Switzerland	28 (18)	52 (46.7; 56.3)*	EDSS: 4.7 (4.1; 5.3)*	NR	NR	IG1: aerobic exercise	Cycling on an ergometer (70% of HR-peak or 60% VO2peak)	3	5	30	SF-36
		25 (17)	50 (44.6; 55.1)*	EDSS: 4.6 (4.0; 5.2)*	NR	NR	IG2: sensorimotor training	Aquatic cycling (70% of HR-peak or 60% VO2peak)	3	5	30	
Baquet et al. [S4]	Germany	34 (21)	38.2 (9.6)	EDSS: 1.7 (0.9)	RR: 34	6.8 (5.5)	IG: aerobic exercise	Bycicle ergometry training	12	2–3	3–5 x 3–20 min	HAQUAMS
		34 (25)	39.6 (9.7)	EDSS: 1.8 (1.0)	RR: 34	5.7 (6.3)	CG	Wait list				
Barclay et al. [S5]	UK	15 (9)	54.9 (2.6)	EDSS: 7.2 (0.2)	RR/PP/SP: 2/3/10	14.6 (2.3)	IG: aerobic exercise	Active-passive trainer cycling (26 min active at RPE 12–14)+ usual care	4	5	30	MSQOL-54
		9 (6)	53.6 (2.7)	EDSS: 7.3 (0.2)	RR/PP/SP: 1/2/6	16.9 (4.5)	CG	Usual care				
Bulguroglu et al. [S6]	Turkey	12 (NR)	45 (39.3; 49.5)*	EDSS: 1.8 (1.1; 3.3)*	NR	4.5 (3; 13.3) *	IG1: mind-body exercises	Mat Pilates with elastic bands	8	2	60 or 90	MSQOL-54
		13 (NR)	37 (29.5; 40)*	EDSS: 2 (1; 3) *	NR	5 (2; 10) *	IG2: mind-body exercises	Reformer Pilates	8	2	60 or 90	
		13 (NR)	40 (26; 43)*	EDSS: 1 (0.5; 2) *	NR	3 (1; 8.5) *	CG	Relaxation and respiration exercises				
Carter et al. [S7]	UK	16 (14)	39.5 (6.5)	EDSS: 3.0 (1.1)	NR	NR	IG: sensorimotor training	Aerobic component (50 to 69% MHR), balance, strength, flexibility and stretching	10	3	60	MSQOL-54
		14 (12)	40.9 (8.7)	EDSS: 3.1 (1.7)	NR	NR	CG	Usual care				
Carter et al. [S8]	UK	60 (43)	45.7 (9.1)	EDSS: 3.8 (1.5)	RR/PP/SP: 51/2/7	8.4 (7.4)	IG: sensorimotor training	Aerobic exercise (50 to 69% MHR) + strength (1–3 sets of 5 –20 rep) and balance	12	3	60	MSQOL-54
		60 (43)	46.0 (8.4)	EDSS: 3.8 (1.5)	RR/PP/SP: 47/2/11	9.2 (7.9)	CG	Usual care				
Collett et al. [S9]	UK	20 (16)	52 (8)	NR	RR/SP/PP/undefined: 8/ 10/2/0	15 (8)	IG1: aerobic exercise	Continuous (static bike at 45% peak power)	12	2	20	SF-36
		17 (9)	55 (10)	NR	RR/SP/PP/undefined: 7/ 7/3/0	12 (11)	IG2: aerobic exercise	Combined (intermittent + continuous)	12	2	10 + 10	
		18 (14)	50 (10)	NR	RR/SP/PP/undefined: 7/ 8/2/1	11 (7)	IG3: resistance training	Intermittent (static bike 30 s on, 30 s off at 90% peak power)	12	2	20	
Dalgas et al. [S10]	Denmark	15 (10)	47.7 (10.4)	EDSS: 3.7 (0.9)	RR: 15	6.6 (5.9)	IG: resistance training	Progressive resistance: leg press, knee extension, hip flexion, hamstring curl and hip extension; with 5 min warm up on a stationary bicycle	12	2	1–2 week: 15 RM 3 set/10 rep 3–4 week: 12 RM 3set/12 rep 5–6 week: 12 RM 4 set/12 rep 7–8 week: 10 RM 4 set/10 rep 9–10 week: 8 RM 4 set/8 rep 11–12 week:8RM 3 set/8 rep	SF-36
		16 (10)	49.1 (8.4)	EDSS: 3.9 (0.9)	RR: 16	8.1 (6.0)	CG	Previous daily activity level				
Dodd et al. [S11]	Australia	36 (26)	47.7 (10.8)	NR	RR: 36	NR	IG: resistance training	Progressive resistance training: core exercises 10–12 rep max	10	2	45	WHOQOL-BREF
		35 (26)	50.4 (9.6)	NR	RR: 35	NR	CG	Usual care (habitual exercise) + social program	10	1	60	
Doulatabad et al. [S12]	Iran	30 (30)	Overall: 31.6 (8)	NR	NR	Overall: at least 2	IG: mind-body exercises	Ashtanga Yoga	12	8/month	90	MSQOL-54

(continued on next page)

Table A.2 (*Continued*)

STUDY Study (year)	Country	N (female)	POPULATION Age (years), mean (SD)	Disease severity, mean (SD)	Type of MS	Disease duration (years), mean (SD)	Groups by intervention	INTERVENTION Training regime	Duration (weeks)	Frequency (x/week)	Time min/ repetitions	OUTCOME Health-related quality of life scale
		30 (30)	Overall: 31.6 (8)	NR	NR	Overall: at least 2	CG	No intervention				
Duff et al. [S13]	Canada	15 (12)	45.7 (9.4)	NR	RR/SP/PP: 14/0/1	NR	IG: mind-body exercises	Pilates + massage therapy	12	2 + 1	50+60	MSQOL-54
		15 (11)	45.1 (7.4)	NR	RR/SP/PP: 11/2/2	NR	CG	Massage therapy	12	1	60	
Ebrahimi et al. [S14]	Iran	16 (11)	37.06 (8.42)	EDSS: 3.12 (1.19)	RR: 16	6.5 (4.17)	IG: combined training	Cycle ergometer + Low intensity exercise and WBV training and stretching and massage	10	3	5–10 + 15 sets of 30 s - 2 min	MSQOL-54
		14 (12)	40.75 (10.56)	EDSS: 3.10 (0.76)	RR: 14	10.5 (6.4)	CG	Routine life				
Escudero-Uribe et al. [S15]	Spain	16 (10)	43.1 (10.2)	EDSS: 3.0 (1.0)	RR: 16	10.5 (8.8)	IG1: sensorimotor training	Mobilizations, aerobic, circuit exercises (body weight, coordination and balance with WBV), stretching	12	2	60 (first week) - 100 (ninth week)	MusiQoL
		14 (9)	40.3 (8.9)	EDSS: 3.2 (1.1)	RR: 14	7.4 (5.0)	IG2: sensorimotor training	Mobilizations, aerobic, circuit exercises (body weight, coordination and balance with Balance Trainer), stretching	12	2	60 (first week) - 100 (ninth week)	
		18 (14)	43.0 (9.3)	EDSS: 3.2 (1.1)	RR: 18	8.0 (5.4)	CG	Wait list				
Feys et al. [S16]	Belgium	21 (20)	36.6 (8.5)	NR	NR	8.1 (6.1)	IG: aerobic exercise	Walking to run 5 km	12	3	NR	MSIS-29
		21 (18)	44.4 (8.5)	NR	NR	9.2 (5.3)	CG	Wait list				
Garrett et al. [S17]	Ireland	63 (50)	51.7 (10)	NR	RR/SP/PP/benign/ unknown: 35/9/5/0/ 14	9.8 (7)	IG1: combined training	Resistance + aerobic exercise (65% MHR)	10	1 + 2	60+30	MSIS-29
		67 (45)	50.3 (10)	NR	RR/SP/PP/benign/ unknown: 33/13/9/ 3/9	10.5 (6.9)	IG2: combined training	Progressive resistance and aerobic exercise	10	1	60	
		63 (44)	49.6 (10)	NR	RR/SP/PP/benign/ unknown: 38/7/8/1/ 9	11.6 (8)	IG3: mind-body exercises	Yoga	10	1	60	
		49 (43)	48.8 (11)	NR	RR/SP/PP/benign/ unknown: 27/10/3/ 1/8	10.6 (8.2)	CG	Exercise habits				
Grazioli et al. [S18]	Italy	10 (8)	39.4 (10.26)	EDSS: 4.40 (2.26)	NR	NR	IG1: sensorimotor training	Conventional physiotherapy (passive and active exercises for upper and lower limbs-Bobath and Vojta methods)	12	2	60	MSQOL-54
		10 (7)	45.91 (12.09)	EDSS: 4.73 (0.90)	NR	NR	IG2: combined training	Strength training: squat, lateral lunges, calf + leg flexion, biceps curl + arm extension and triceps push (2 sets of 10–15 rep/exercise at 50% 1RM); Aerobic training: 10 min of cycle ergometer at 65% Hrmax); Stretching and breathing exercises.	12	2	60	
Hebert et al. [S19]	USA	44 (37)	46.5 (8.8)	NR	NR	8.34 (5.7)	IG: sensorimotor training	Vestibular rehabilitation program (postural control, balance and eye movement) supervised + home exercise	6 (phase 1) 8 (phase 2)	2 + 7 1 + 7	NR NR	PDQ and SF-36
		44 (38)	43.0 (10.8)	NR	NR	8.54 (7.6)	CG	Non-exercising				
Hogan et al. [S20]	Ireland	48 (30)	57 (10)	NR	RR/SP/PP /unknown: 13/20/8/7	18 (9)	IG1: sensorimotor training	Group physiotherapy (balance and strength)	10	1	60	MSIS-29
		35 (20)	52 (11)	NR	RR/SP/PP /unknown: 7/16/11/1	13 (8)	IG2: sensorimotor training	Individual physiotherapy (balance and strength)	10	1	60	
		13 (8)	58 (8)	NR	RR/SP/PP /unknown: 4/5/2/2	15 (8)	IG3: mind-body exercises	Yoga	10	1	60	
		15 (13)	49 (6)	NR	RR/SP/PP /unknown: 5/5/5/0	10 (3)	CG	Were asked not to change exercise habits				
Kargarfard et al. [S21]	Iran	10 (10)	33.7 (8.6)	EDSS: 2.9 (0.9)	RR: 10	4.9 (2.3)	IG: sensorimotor training	Aquatic exercise (50–75% estimated MHR: joint mobility, strength, balance, posture, functional activities and intermittent walking) + current treatment	8	3	60	MSQOL-54
		11 (11)	31.6 (7.7)	EDSS: 3.0 (0.7)	RR: 11	4.6 (1.9)	CG	Current treatment				
Kerling et al. [S22]	Germany	30 (24)	42.3 (9.0)	EDSS: 2.6 (1.1)	NR	NR	IG1: aerobic exercise	Aerobic training program	12	2	40	SF-36
		30 (20)	45.6 (11.4)		NR	NR	IG2: combined training		12	2	20+20	

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Table A.2 (*Continued*)

STUDY Study (year)	Country	N (female)	POPULATION Age (years), mean (SD)	Disease severity, mean (SD)	Type of MS	Disease duration (years), mean (SD)	Groups by intervention	INTERVENTION Training regime	Duration (weeks)	Frequency (x/week)	Time min/ repetitions	OUTCOME Health-related quality of life scale
				EDSS: 3.1 (1.3)				Bicycle ergometer + resistance training				
Kjølhede et al. [S23]	Denmark	18 (NR)	43 (8)	EDSS: 2.9 (2; 4)	RR: 18	7 (7)	IG: resistance training	Progressive resistance training	24	2	3 × 10 rep to 5 × 6 rep	MSIS-29
		17 (NR)	43 (8)	EDSS: 2.9 (2; 4)	RR: 17	7 (7)	CG	Wait list	24			
Kooshiar et al. [S24]	Iran	18 (18)	Overall: 29.24 (7.98)	Overall: EDSS: 2.5 (1.1)	Overall: RR/PP/SP: 28/6/3	Overall: 18.62 (9.58) (months)	IG: sensorimotor training	Aquatic exercise (strengthening, aerobic, balance)	8	3	45	MQLIM
		19 (19)	Overall: 29.24 (7.98)	Overall: EDSS: 2.5 (1.1)	Overall: RR/PP/SP: 28/6/3	Overall: 18.62 (9.58) (months)	CG	Normal treatments				
Kücük et al. [S25]	Turkey	9 (6)	49.7 (8.9)	EDSS: 2.8 (1.4)	NR	14.2 (9.5)	IG1: sensorimotor training	Traditional exercise program (strength, balance and coordination exercise)	8	2	45	MusiQoL
		11 (7)	47.2 (9.5)	EDSS: 3.2 (2.2)	NR	14.8 (7.4)	IG2: mind-body exercises	Mat Pilates	8	2	45	
Langeskov-Christensen et al. [S26]	Denmark	43 (26)	44.0 (9.5)	EDSS: 2.7 (1.4)	RR/PP/SP: 41/2/0	10.9 (7.9)	IG: aerobic exercise	One continuous and one interval exercise session, increasing intensity from 65 to 95% of individual MHR	24	2	30–60	MSIS-29
		43 (26)	45.6 (9.3)	EDSS: 2.8 (1.6)	RR/PP/SP: 34/4/5	8.6 (6.0)	CG	Habitual lifestyle				
Learmonth et al. [S27]	UK	20 (15)	51.4 (8.06)	EDSS: 6.14 (0.36)	NR	13.4 (6.4)	IG: combined training	Circuit exercise: aerobic and resistance	12	2	60	LMSQOL
		12 (8)	51.8 (8.0)	EDSS: 5.82 (0.51)	NR	12.6 (8.1)	CG	Usual routine				
Learmonth et al. [S28]	USA	29 (28)	48.7 (10.4)	SR-EDSS: 1.25 (0.6; 2.5)*	RR/SP: 26/0	14.8 (8.5)	IG: combined training	Progressive aerobic (moderate-intensity walking) and resistance (10 exercises with elastic bands for lower-upper body and core muscle groups) exercises	16	2	10–30 min and 1,2 sets, 10 –15 rep	MSIS and LMSQOL
		28 (27)	48.2 (9.1)	SR-EDSS: 2 (0.5; 5.3)*	RR/SP: 25/1	13.0 (7.7)	CG	Waitlist control				
McCulllagh et al. [S29]	Ireland	17 (14)	40.5 (12.68)	NR	RR/SP: 9/3	5.4 (4.35)	IG: combined training	Treadmill, cycling, stair-master training, arm-strengthening, volleyball and walking + home exercise	12	2 + 1	50 + 40–60 min	FAMS and MSIS-29
		13 (10)	33.58 (6.1)	NR	RR/SP: 8/4	5 (3.52)	CG	Visit the physiotherapist to discuss any issues	12	1 monthly		
Miller et al. [S30]	UK	15 (11)	56.3 (9.0)	EDSS: 7 (0.5)	PP/SP: 6/9	13 (9.1)	IG: sensorimotor training	Strengthening, gait, balance and stretching	8	2	60	MSIS-29 and LMSQOL
		15 (8)	52.9 (6.3)	EDSS: 7.1 (0.8)	PP/SP: 5/10	18.7 (8.1)	CG	Usual care				
Mokhtarzade et al. [S31]	Iran	22 (22)	32.04 (2.81)	EDSS: 1.84 (0.35)	RR: 22	2.69 (1.84)	IG: aerobic exercise	Upper and lower-limb aerobic interval training at 60% until 75% W max in the last week	8	3	42 (first session) - 66 (last session)	MSQOL-54
		18 (18)	31.27 (3.28)	EDSS: 1.57 (0.64)	RR: 18	3.47 (1.26)	CG	Non-exercising				
Ozdogar et al. [S32]	Turkey	21 (16)	39.2 (8.6)	EDSS: 2.7 (1.8)	RR/SP: 18/3	7.5 (4.5)	IG1: sensorimotor training	Game console Xbox One and Kinect motion sensor (core stabilization, balance, arm and leg function)	8	1	45	MusiQoL
		19 (12)	43.6 (10.5)	EDSS: 2.11 (0.9)	RR/SP: 18/0	6.43 (5.9)	IG2: sensorimotor training	Conventional rehabilitation (balance, arm and core stability exercises)	8	1	45	
		20 (15)	37.9 (12.4)	EDSS: 2.25 (1.2)	RR/SP: 18/2	5.93 (4.2)	CG	Non-exercising				
Ozgen et al. [S33]	Turkey	20 (16)	42.5 [22; 60]	EDSS: 3.5 [2.0; 6.5]**	RR/PP/SP: 8/3/9	10 [1; 24]**	IG: sensorimotor training	Vestibular rehabilitation aerobic and balance) supervised + home program	8	1 + 7	30–45 + 2 × 15 –20	MSQOL-54
		20 (12)	39.5 [24; 56]	EDSS: 3.5 [2.0; 6.0]**	RR/PP/SP: 9/4/7	5.5 [1; 20]**	CG	Wait list (usual medical care)	8			
Petajan et al. [S34]	USA	21 (15)	41.1 (2.0)	EDSS: 3.8 (0.3)	NR	9.3 (1.6)	IG: aerobic exercise	Arm and leg ergometry (30% of VO2 max warm-up and then 60%) and stretching	15	3	45–50	SIP
		25 (16)	39.0 (1.7)	EDSS: 2.9 (0.3)	NR	6.2 (1.1)	CG	Non-exercising				
Pilutti et al. [S35]	USA	5 (3)	58.8 (3.0)			15.2 (8.9)	IG1: aerobic exercise		12	3	30	MSQOL-54

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Table A.2 (*Continued*)

STUDY Study (year)	Country	N (female)	POPULATION Age (years), mean (SD)	Disease severity, mean (SD)	Type of MS	Disease duration (years), mean (SD)	Groups by intervention	INTERVENTION Training regime	Duration (weeks)	Frequency (x/week)	Time min/ repetitions	OUTCOME Health-related quality of life scale
				EDSS: 7.0 (1.75)	PP/SP: 2/3			Total-body recumbent stepper training				
		5 (2)	48.2 (4.3)	EDSS: 7.0 (1.5)	PP/SP: 2/3	12.7 (11.2)	IG2: sensorimotor training	Body weight-supported treadmill	12	3	30	
Plow et al. [S36]	USA	14 (14)	47 (9)	NR	RR: 14	8 (7)	IG: sensorimotor training	Cycling, stretching, balance, and strength training	24	3–5	30–45	SF-12 and MSIS-29
		16 (16)	48 (10)	NR	RR: 16	10 (7)	CG	The same intervention after waiting 12 weeks				
Prosperini et al. [S37]	Italy	18 (13)	35.3 (8.6)	EDSS: 3.0 (1.5; 5.0)**	NR	12.2 (6.0)	IG: sensorimotor training	Home-based training with Nintendo Wii Balance Board System	12	5	30	MSIS-29
		18 (12)	37.1 (8.8)	EDSS: 3.5 (1.5; 5.0)**	NR	9.3 (5.3)	CG	The same intervention after waiting 12 weeks				
Romberg et al. [S38]	Finland	47 (30)	43.8 (6.3)	EDSS: 2.0 (1.5; 3.5)*	NR	6.0 (6.5)	IG: combined training	Resistance + aerobic (supervised) Resistance + aerobic (home exercise)	Weeks 1–3 Weeks 4–26	5 3–4 + 1	NR NR	MSQOL-54
		48 (31)	43.9 (7.1)	EDSS: 2.5 (2; 3.5)*	NR	5.5 (6.4)	CG	Wait list				
Schulz et al. [S39]	Germany	15 (11)	39 (9)	EDSS: 2.0 (1.4)	Overall: RR/PP/SP: 19/2/5	Overall: 11.4 (1.6)	IG: aerobic exercise	Interval-training of 75% of W max in cycle ergometer	8	2	30	HAQUAMS
		13 (8)	40 (11)	EDSS: 2.5 (0.8)	Overall: RR/PP/SP: 19/2/5	Overall: 11.4 (1.6)	CG	Wait list				
Straudi et al. [S40]	Italy	12 (7)	49.92 (7.51)	EDSS: 4.95 (0.61)	RR/PP/SP: 4/5/3	12.16 (6.91)	IG: sensorimotor training	Task-oriented circuit training (aerobic and balance) + Home-based training (gait training, stretching and strengthening)	2 + 12	5 + 3	120 + 60	MSIS-29
		12 (10)	55.25 (13.82)	EDSS: 4.83 (0.49)	RR/PP/SP: 2/5/5	18.25 (9.46)	CG	Usual care				
Straudi et al. [S41]	Italy	36 (25)	55 (11)	EDSS: 6.5 (6; 6.5) *	PP/SP: 18/18	18 (9; 25) *	IG1: combined training	Conventional therapy (assisted overground walking)+ stretching and strengthening	4	3	60 (40 min of walking) + 60	SF-36 and MSIS-29
		36 (24)	56 (11)	EDSS: 6.5 (6; 6.5) *	PP/SP: 16/20	12 (6; 19) *	IG2: sensorimotor training	Robot-assisted gait training + stretching and strengthening	4	3	60 (30 min of RAGT) + 60	
Tallner et al. [S42]	Germany	59 (44)	40.9 (10.4)	EDSS: 2.8 (0.8)	RR/SP: 52/7	9.8 (9.2)	IG: combined training	Home-based aerobic + strength training	24	1 + 2	10–60 + 6 rep 2,3 times	HAQUAMS
		67 (50)	40.7 (9.5)	EDSS: 2.7 (0.8)	RR/SP: 57/10	9.2 (7.2)	CG	The same intervention after waiting three months				
Tarakci et al. [S43]	Turkey	51 (34)	41.49 (9.37)	EDSS: 4.38 (1.37)	RR/PP/SP: 32/10/9	9 (4.71)	IG: sensorimotor training	Flexibility, ROM, strength, stabilization, balance, coordination and functional activities	12	3	60	MusiQoL
		48 (30)	39.65 (11.18)	EDSS: 4.21 (1.44)	RR/PP/SP: 33/8/7	8.42 (5.38)	CG	Wait list				
Tollár et al. [S44]	Hungary	14 (13)	48.1 (5.65)	EDSS: 5.0 (5; 6) **	RR/PP: 9/5	13.2 (4.42)	IG1: aerobic exercise	Cycling training	5	5	60	MSIS-29 and EQ-5D
		14 (12)	48.2 (5.48)	EDSS: 5.0 (5; 6) **	RR/PP: 7/7	12.1 (2.68)	IG2: sensorimotor training	Xbox 360 core system (sensorimotor and visuomotor agility training)	5	5	60	
		14 (12)	46.9 (6.46)	EDSS: 5.0 (5; 6) **	RR/PP: 9/5	13.6 (4.07)	IG3: sensorimotor training	Dynamic and static balance and stepping exercises in multiple directions	5	5	60	
		14 (13)	46.9 (5.57)	EDSS: 5.0 (5; 6) **	RR/PP: 9/5	12.7 (4.25)	IG4: sensorimotor training	Proprioceptive neuromuscular facilitation	5	5	60	
		12 (11)	44.4 (6.76)	EDSS: 5.0 (5; 6) **	RR/PP: 8/4	14.0 (4.11)	CG	Wait list: not to alter habitual activity				
Yazgan et al., [S45]	Turkey	15 (13)	47.46 (10.53)	EDSS: 4.16 (1.37)	RR/PP/SP/PR: 11/1/1/2	12.06 (6.56)	IG1: sensorimotor training	Nintendo Wii Fit: balance game section	8	2	60	MusiQol
		12 (12)	43.08 (8.74)	EDSS: 3.83 (1.49)	RR/PP/SP/PR: 8/0/1/3	14.91 (6.54)	IG2: sensorimotor training	Balance exercises in different directions with a device software	8	2	60	
		15 (13)	40.66 (8.82)	EDSS: 4.06 (1.26)	RR/PP/SP/PR: 14/0/0/1	11.06 (5.70)	CG	Waiting list				

CG, control group; EDSS, Expanded Disability Status Scale; EQ-5D, European Quality of Life-5 Dimensions; FAMS, Functional Assessment of Multiple Sclerosis; HAQUAMS, Hamburg Quality of Life Questionnaire in Multiple Sclerosis; HRmax, maximum heart rate; IG, intervention group; LMSQOL, Leeds Multiple Sclerosis Quality of Life; max, maximum; MHR, maximum heart rate; MQLIM, Multicultural Quality of Life Index; MSIS-29, Multiple Sclerosis Impact Scale; MSQOL-54, Multiple Sclerosis Quality of Life 54; MusiQoL, Multiple Sclerosis International Quality of Life Questionnaire; NR, not reported; PDQ, Perceived Deficits Questionnaire; PP, primary progressive; PR, progressive relapsing; RAGT, robot-assisted gait training; rep, repetition; RM, repetition maximum; ROM, range of motion; RPE, Rating of Perceived Exertion; RR, relapsing-remitting; SD, standard deviation; SF-36, Short Form 36; SIP, Sickness Impact Profile; SP, secondary progressive; SR, Self-reported Expanded Disability Status Scale; VO2, oxygen consumption; W, watt; WBV, whole body vibration; WHOQOL-BREF, World Health Organization Quality of Life – shorter version; x, times; *, median (IQR); **, median (range).

Table A.3
GRADE assessment.

Certainty assessment № of studies	Comparison	Risk of bias	Heterogeneity and inconsistency	Indirectness	Imprecision	Publications bias	№ of patients Intervention	Comparison	Effect Absolute (95% CI)	Certainty	Importance of the outcome
Effect of physical exercise interventions on total HRQoL											
6	Aerobic exercise vs control	Serious 83% of estimates from trials with moderate and 17% from high risk of bias	No heterogeneity. Both direct and indirect effect estimates very similar	Not serious[a]	Not serious	No	116	112	0.39 (0.16; 0.62)	Moderate (downgrade by 1 level for risk of bias)	Not important
1	Resistance training vs control	Serious 100% of estimate from studies of moderate risk of bias	No heterogeneity. Evidence for only one study	Not serious[a]	One direct comparison	No	36	35	0.24 (−0.23; 0.70)	Low (downgrade by 2 levels for risk of bias and imprecision)	Not important
6	Combined training vs control	Serious 33% of estimate from trials with low risk, 66% with moderate risk of bias	No heterogeneity. Similar estimates from direct and indirect evidence	Not serious[a]	Not serious	Publication bias detected by Egger's test $p = 0.081$	188	182	0.08 (−0.22; 0.38)	Low (downgrade by 2 levels for risks of bias and publication bias)	Not important
13	Sensorimotor training vs control	Serious 8% of estimate from trials with low risk, 69% with moderate risk, 23% from high risk of bias	Substantial heterogeneity I^2= 72%, τ2= 0.2078. Similar significant estimates from direct and indirect evidence	Serious[b]	Not serious	No	330	254	0.65 (0.40; 0.91)	Low (downgrade by 3 levels for risks of bias, heterogeneity and indirectness. Upgrade by 1 level for large treatment effect)	Critical
2	Mind-body exercises vs control	Serious 100% of estimate from studies of moderate risk of bias	No heterogeneity. Evidence for few studies with only indirect significant effect estimates	Serious[b]	Few comparisons	No	41	40	0.13 (−0.28; 0.54)	Very low (downgrade by 3 levels for risks of bias, indirectness and imprecision)	Not important
1	Aerobic exercise vs resistance training	Serious 100% of estimate from studies of moderate risk of bias	No heterogeneity. Evidence for only one study	Not serious[a]	Few comparisons	No	37	18	0.29 (−0.16; 0.75)	Low (downgrade by 2 levels for risks of bias and imprecision)	Not important
2	Aerobic exercise vs sensorimotor training	Serious 100% of estimate from studies of moderate risk of bias	Substantial heterogeneity I^2=75%, τ2=0.1436. Inconsistency between direct and indirect effect	Not serious[a]	Few comparisons	No	70	39	0.71 (0.28; 1.14)	Very low (downgrade by 4 levels for risk of bias, heterogeneity, inconsistency and imprecision)	Not important
1	Aerobic exercise vs mind-body exercises	Serious 100% of estimate from studies of moderate risk of bias	No heterogeneity. Evidence for only one study	Serious[b]	One direct comparison	No	10	11	−0.06 (−0.92; 0.80)	Very low (downgrade by 3 levels for risks of bias, indirectness and imprecision)	Not important
1	Sensorimotor training vs mind-body exercises	Serious 100% of estimate from studies of moderate risk of bias	No heterogeneity. Evidence for only one study. Inconsistency between direct and indirect effect	Serious[b]	One direct comparison	No	9	11	0.00 (−0.88; 0.88)	Very low (downgrade by 3 levels for risks of bias, inconsistency and imprecision)	Not important
Effect of physical exercise interventions on physical HRQoL											
7	Aerobic exercise vs control	Serious 86% of estimate from studies of moderate risk of bias, 14% of high risk of bias	Substantial heterogeneity I2= 77%, τ^2= 0.4431. Similar significant estimates from direct and indirect evidence	Not serious[a]	Not serious	No	138	132	0.81 (0.23; 1.39)	Moderate (downgrade by 2 levels for risks of bias, and heterogeneity. Upgrade by 1 level for large treatment effect)	Critical
2	Resistance training vs control	Serious 100% of estimate from studies of moderate risk of bias	No heterogeneity. Similar estimates from direct and indirect evidence	Not serious[a]	Few comparisons	No	33	33	0.29 (−0.22; 0.80)	Low (downgrade by 2 levels for risks of bias, and imprecision)	Not important
3	Combined training vs control	Serious 100% of estimate from studies of moderate risk of bias	No heterogeneity. Similar estimates from direct and indirect evidence	Not serious[a]	Not serious	Publication bias detected by Egger's test $p = 0.099$	193	111	0.13 (−0.08; 0.34)	Low (downgrade by 2 levels for risks of bias, and publication bias)	Not important
8	Sensorimotor training vs control	Serious 12% of estimate from trials of low risk, 50% from moderate risk of bias, 37% from high risk of bias	Substantial heterogeneity I^2= 81%, τ^2= 0.4494. Only significant estimates from direct evidence	Serious[b]	Not serious	No	259	192	0.67 (0.17; 1.16)	Low (downgrade by 3 levels for risks of bias, heterogeneity and indirectness. Upgrade by 1 level for large treatment effect)	Critical
5	Mind-body exercises vs control	Serious 50% of estimate from trials of moderate risk, 50% from high risk of bias	No heterogeneity. Similar estimates from direct and indirect evidence	Serious[b]	Not serious	No	111	98	0.11 (−0.15; 0.36)	Low (downgrade by 2 levels for risk of bias and indirectness)	Not important
1	Aerobic exercise vs combined training	Serious 100% of estimate from studies of moderate risk of bias	No heterogeneity. Evidence for only one study. Inconsistency between direct and indirect effect	Not serious[a]	One direct comparison	No	30	30	−0.07 (−0.72; 0.57)	Very low (downgrade by 3 levels for risk of bias, inconsistency and imprecision)	Not important
2	Aerobic exercise vs sensorimotor training	Serious 100% of estimate from trials of moderate risk of bias	No heterogeneity. Inconsistency between direct and indirect effect	Not serious[a]	Few comparisons	No	34	33	−0.05 (−0.55; 0.45)	Very low (downgrade by 3 levels for risk of bias, inconsistency and imprecision)	Not important
1	Aerobic exercise vs mind-body exercises	Serious 100% of estimate from studies of moderate risk of bias	No heterogeneity. Evidence for only one study	Serious[b]	One direct comparison	No	10	11	0.49 (−0.38; 1.36)	Very low (downgrade by 3 levels for risk of bias, indirectness, and imprecision)	Not important
2	Combined training vs sensorimotor training	Not serious 50% of estimate from trials of low	No heterogeneity. Evidence for only one study	Not serious[a]	Few comparisons	No	46	46	−0.02 (−0.35; 0.30)	Moderate (downgrade by 1 level for imprecision)	Not important

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Table A.3 (*Continued*)

Certainty assessment № of studies	Comparison	Risk of bias	Heterogeneity and inconsistency	Indirectness	Imprecision	Publications bias	№ of patients Intervention	Comparison	Effect Absolute (95% CI)	Certainty	Importance of the outcome
		risk, 50% from moderate risk of bias									
1	Combined training vs mind-body exercises	Serious 100% of estimate from studies of moderate risk of bias	No heterogeneity. Evidence for only one study	Not serious[a]	Few comparisons	No	130	63	0.09 (−0.16; 0.33)	Low (downgrade by 2 levels for risk of bias and imprecision)	Not important
1	Sensorimotor training vs mind-body exercises	Very serious 100% of estimate from studies of high risk of bias	No heterogeneity. Evidence for only one study.	Serious[b]	Few comparisons	No	83	13	0.42 (−0.02; 0.86)	Very low (downgrade by 2 levels for risk of bias, 1 level for indirectness, and 1 level for imprecision)	Not important
Effect of physical exercise interventions on mental HRQoL											
Certainty assessment **№ of studies**	**Comparison**	**Risk of bias**	**Heterogeneity and inconsistency**	**Indirectness**	**Imprecision**	**Publications bias**	**№ of patients** **Intervention**	**Comparison**	**Effect** **Absolute (95% CI)**	**Certainty**	**Importance of the outcome**
7	Aerobic exercise vs control	Serious 86% of estimate from studies of moderate risk of bias, 14% of high risk of bias	No heterogeneity. Only significant estimates from direct evidence	Not serious[a]	Not serious	No	138	132	0.28 (0.03; 0.53)	Moderate (downgrade by 1 level for risk of bias)	Not important
2	Resistance training vs control	Serious 100% of estimate from studies of moderate risk of bias	Substantial heterogeneity I^2= 79%, τ^2=0.5331. Evidence for few studies with inconsistency from direct and indirect evidence	Not serious[a]	Few comparisons	No	33	33	−0.19 (−1.33; 0.95)	Very low (downgrade by 4 levels for risk of bias, heterogeneity, inconsistency and imprecision)	Not important
2	Combined training vs control	Serious 100% of estimate from studies of moderate risk of bias	No heterogeneity. Similar estimates from direct and indirect evidence	Not serious[a]	Few comparisons	No	63	62	0.04 (−0.31; 0.40)	Low (downgrade by 2 levels for risk of bias, and imprecision)	Not important
6	Sensorimotor training vs control	Serious 17% of estimate from trials of low risk, 50% from moderate risk of bias, 33% from high risk of bias	Substantial heterogeneity: I^2= 82%, τ^2=0.4904. Similar significant estimates from direct and indirect evidence.	Serious[b]	Not serious	No	162	161	1.00 (0.37; 1.63)	Low (downgrade by 3 levels for risk of bias, heterogeneity and indirectness. Upgrade by 1 level for large treatment effect)	Critical
Certainty assessment **№ of studies**	**Comparison**	**Risk of bias**	**Heterogeneity and inconsistency**	**Indirectness**	**Imprecision**	**Publications bias**	**№ of patients** **Intervention**	**Comparison**	**Effect** **Absolute (95% CI)**	**Certainty**	**Importance of the outcome**
3	Mind-body exercises vs control	Serious 66% of estimate from trials of moderate risk, 33% from high risk of bias	No heterogeneity Similar significant estimates from direct and indirect evidence.	Serious[b]	Not serious	No	51	38	0.45 (0.04; 0.85)	Low (downgrade by 2 levels for risk of bias and indirectness)	Not important
1	Aerobic exercise vs combined training	Serious 100% of estimate from studies of moderate risk of bias	No heterogeneity. Evidence for only one study	Not serious[a]	One direct comparison	No	30	30	0.28 (−0.37; 0.93)	Low (downgrade by 2 levels for risk of bias, and imprecision.	Not important
2	Aerobic exercise vs sensorimotor training	Serious 100% of estimate from studies of moderate risk of bias	No heterogeneity. Similar estimates from direct and indirect evidence.	Not serious[a]	Few comparisons	No	34	33	−0.07 (−0.57; 0.43)	Very low (downgrade by 2 levels for risk of bias and imprecision).	Not important
2	Combined training vs sensorimotor training	Not serious 50% of estimate from trials of low risk, 50% from moderate risk of bias	No heterogeneity.	Not seriousa	One direct comparison	No	46	46	−0.08 (−0.41; 0.24)	Moderate (downgrade by 1 level for imprecision)	Not important

CI: confidence interval.

Explanation.

[a] There is transitivity between groups of interventions for the 3 outcomes (age, disease severity and disease duration).

[b] There is not transitivity between groups of interventions for 1 or 2 outcomes (age, disease severity or disease duration).

Table A.4
Subgroup analyses of physical exercise interventions for HRQoL by disease severity.

	Mild disease		Severe disease	
	No. of studies/ no. of participants	ES (95% CI)	No. of studies/ no. of participants	ES (95% CI)
Total HRQoL				
Aerobic exercise vs control	5/202	**0.43 (0.10; 0.75)**	1/26	0.35 (−0.04; 0.74)
Resistance training vs control		NA		NA
Combined training vs control	4/308	0.02 (−0.22; 0.25)	1/32	0.06 (−0.74; 0.86)
Sensorimotor training vs control	12/565	**0.61 (0.34; 0.88)**	4/108	**0.43 (0.22; 0.64)**
Mind-body exercises vs control	1/21	0.33 (−0.53; 1.19)		NA
Aerobic exercise vs resistance training		NA		NA
Aerobic exercise vs sensorimotor training	1/53	0.01 (−0.53; 0.56)	3/84	**0.91 (0.61; 1.20)**
Aerobic exercise vs mind-body exercises	1/21	−0.06 (−0.92; 0.80)		NA
Sensorimotor training vs mind-body exercises	1/20	0.00 (−0.88; 0.88)		NA
Physical HRQoL				
Aerobic exercise vs control	4/192	0.86 (−0.06; 1.79)	2/36	0.80 (−0.31; 1.91)
Resistance training vs control	2/66	0.29 (−0.22; 0.80)		NA
Combined training vs control	2/125	−0.09 (−0.44; 0.27)		NA
Sensorimotor training vs control	5/235	**0.76 (0.17; 1.35)**		NA
Mind-body exercises vs control	3/72	0.24 (−0.23; 0.72)		NA
Aerobic exercise vs combined training	1/60	−0.07 (−0.72; 0.57)		NA
Aerobic exercise vs sensorimotor training	1/53	0.03 (−0.52; 0.57)	1/10	−0.45 (−1.71; 0.80)
Aerobic exercise vs mind-body exercises	1/21	0.49 (−0.38; 1.36)		NA
Combined training vs sensorimotor training	1/20	0.09 (−0.78; 0.97)	1/72	−0.04 (−0.39; 0.31)
Combined training vs mind-body exercises		NA		NA
Sensorimotor training vs mind-body exercises		NA		NA
Mental HRQoL				
Aerobic exercise vs control	4/192	**0.32 (0.02; 0.62)**	2/36	0.02 (−0.65; 0.69)
Resistance training vs control	2/66	−0.19 (−1.33; 0.95)		NA
Combined training vs control	2/125	0.04 (−0.31; 0.40)		NA
Sensorimotor training vs control	5/235	**0.81 (0.22; 1.41)**		NA
Mind-body exercises vs control	3/72	**0.59 (0.12; 1.07)**		NA
Aerobic exercise vs combined training	1/60	0.28 (−0.37; 0.93)		NA
Aerobic exercise vs sensorimotor training	1/53	0.03 (−0.52; 0.58)	1/10	−0.61 (−1.88; 0.65)
Aerobic exercise vs mind-body exercises	1/21	−0.63 (−1.51; 0.25)		NA
Combined training vs sensorimotor training	1/20	0.11 (−0.77; 0.99)	1/72	−0.12 (−0.46; 0.23)

CI: confidence interval; ES: effect size; NA: not applicable; HRQoL: health-related quality of life.
Effect size **in bold**: statistically significant.