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REVIEW

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Effect of different types of exercise on fitness in people with multiple sclerosis: A network meta-analysis

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Background: It is assumed that people with multiple sclerosis (MS) who participate in programs of physical exercise improve their physical fitness.

Objective: The aim of this network meta-analysis (NMA) was to analyze the effect of different types of exercise on muscular fitness and cardiorespiratory fitness (CRF) among people with MS and to determine the best type of exercise according to disease severity.

Methods: MEDLINE, the Physiotherapy Evidence Database, the Cochrane Library, SPORTDiscus, Scopus, and Web of Science were searched from inception to April 2022 to identify randomized controlled trials (RCTs) concerning the effect of physical exercise on fitness in people with MS. We ranked the types of physical exercise by calculating the surface under the cumulative ranking (SUCRA).

Results: We included 72 RCTs involving 2543 MS patients in this NMA. A ranking of five types of physical exercise (aerobic, resistance, combined [aerobic and resistance], sensorimotor training, and mind–body exercises) was achieved. Combined and resistance training had the highest effect sizes (0.94, 95% CI 0.47, 1.41, and 0.93, 95% CI 0.57, 1.29, respectively) and the highest SUCRA (86.2% and 87.0%, respectively) for muscular fitness. The highest effect size (0.66, 95% CI 0.34, 0.99) and SUCRA (86.9%) for CRF was for aerobic exercise.

Conclusions: Combined and resistance training seem to be the most effective exercises to improve muscular fitness and aerobic exercise for CRF in people with MS.

KEYWORDS

CRF, physical activity, physiotherapy, rehabilitation, strength

PROSPERO registration number: CRD42020170903.

1 | INTRODUCTION

Multiple sclerosis (MS) is an early-onset immune-mediated neuroinflammatory disorder that leads to progressive deterioration with a wide variability of affected functional systems.[1] The worldwide prevalence of the disease has increased in recent decades, with approximately 2.8 million people affected by 2020.[2] Among the nonpharmacological interventions for the management of MS symptoms, physical exercise has accumulated evidence.

Physical exercise and physical fitness are often used as synonymous terms, but they are not interchangeable terms. Physical activity is a subset of physical exercise subject to numerous determinants; it is a planned, structured, and voluntary behavior.[3] Physical fitness is largely determined by genetics.[4] Increasing the level of physical activity in people with MS could have positive effects in managing symptoms, restoring function and improving their quality of life.[5–8] Despite these benefits, the MS population is not physically active enough compared to the healthy population, a behavior that would be related to the risk profile of MS.[9]

Furthermore, it is assumed that people with MS who participate in programs of physical exercise improve their physical fitness. However, previous evidence suggests unclear results, as a positive effect of exercise on both muscular and cardiorespiratory fitness (CRF),[10] but without differences between aerobic training and CRF.[11] When determining the effects of physical exercise, its type, characteristics, assessment, and influence on disease severity could be behind these differences.

Physical exercise and physical fitness are crucial outcomes related to disease severity, disability, walking speed, and cognitive processing speed, among others.[12–14] Improving muscular fitness and CRF is important for maintaining and regaining functional capacity, which is impaired among people with MS.[15] However, clinical trials comparing the effect of different types of exercise on muscular fitness and CRF are lacking, and standard meta-analyses cannot elucidate this important clinical question.

The network meta-analysis (NMA) approach allows us to perform a comprehensive and consistent analysis of randomized controlled trials (RCTs) comparing different interventions and ranking them according to their effectiveness.[16] Thus, this study aimed to analyze the effect of different types of exercise on muscular fitness and CRF among people with MS, integrating all available direct and indirect evidence though an NMA, and to determine the best type of exercise according to disease severity.

2 | METHODS

This systematic review with NMA was reported in accordance with the Preferred Reporting Items for Systematic Review incorporating Network Meta-Analysis (PRISMA NMA)[17] (Table S1) and the Cochrane Collaboration Handbook.[16] Moreover, the study protocol was previously registered in PROSPERO (No. CRD42020170903).

2.1 | Search strategy and selection criteria

Two researchers (SR-G and ABM-H) independently searched the following databases for articles: MEDLINE (via PubMed), Physiotherapy Evidence Database, Cochrane Central Register of Controlled Trials, SPORTDiscus, Scopus, and Web of Science, from inception to April 21, 2022. Any disagreements were settled by consensus or with a third researcher (CA-B). The search strategy combined the relevant terms related to (1) multiple sclerosis, (2) exercise, (3) fitness, and (4) clinical trials (the full search strategy for MEDLINE is in Table S2). Moreover, reference lists of previous reviews and articles included in this NMA were checked for additional studies.

2.2 | Eligibility

Studies on the effect of physical exercise on physical fitness, distinguishing between muscular fitness and CRF, in patients with MS were included in this NMA. Inclusion criteria were studies: (1) designed as RCT; (2) including people with MS; (3) investigating the effect of any physical exercise intervention at any frequency, duration, or intensity; (4) comparing the physical exercise intervention with usual care (control condition) or with a physical exercise intervention of another category; and (5) reporting fitness outcome (muscular fitness or CRF).

The exclusion criteria were as follows: (1) combining physical exercise with other multidisciplinary interventions, (2) including interventions based on an educational component, (3) where the type of exercise was unclear, (4) not reporting enough data to calculate effect size (ES), or (5) not written in English or Spanish.

2.3 | Data extraction

Two researchers (SR-G and ABM-H) independently extracted the following items from each included article: (1) study characteristics (year, country of publication, sample size, and percentage of women), (2) population characteristics (age, disease severity, and disease duration), (3) intervention characteristics (type, training regime, duration, frequency, time, and exercise intolerance), and (4) outcome measurement (tool used to measure muscle fitness or CRF). Disagreements in data extraction were settled by consensus or with a third researcher (CA-B).

2.4 | Classification of the disease, interventions and outcome

For disease characteristics, we extracted severity (baseline value of the scale), type (distinguishing among relapsing remitting, primary progressive, secondary progressive, or progressive relapsing), and duration of MS.

The exercise interventions included in the studies were classified as aerobic exercise, resistance training, combined training (aerobic with resistance), sensorimotor training, mind–body exercises (yoga or Pilates), and control.

Aerobic exercise included interventions aimed at increasing energy expenditure and heart rate to meet the oxygen requirements of activated muscle over a sustained period, such as exercise on treadmill, cycling, or walking. Interval training was considered aerobic exercise. Resistance training aimed to increase muscular strength and power. Sensorimotor training included exercises aimed at improving the neuromuscular system through coordination and balance that could be added to strength or aerobic exercise. Mind–body exercises included interventions based on balance and strength and focused on breathing and postural control, such as Pilates or yoga.

Physical fitness was measured by different parameters and tests, which were classified into muscular fitness or CRF. Muscular fitness considers the body's ability to generate and maintain muscular force through muscle contraction and is usually measured as muscular strength and endurance. CRF considers the body's ability to supply, extract, and use oxygen during prolonged endurance exercise and is usually measured as maximal aerobic capacity (VO_{2max}).[10]

2.5 | Risk of bias assessment

Two researchers (SNA-A and MJG-P) independently assessed the risk of bias of the included studies using the Cochrane Collaboration's tool for assessing risk of bias (RoB2).[18] Any disagreement was resolved by consensus or by discussion with a third reviewer (CA-B). The RoB2 tool evaluates the risk of bias according to five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Overall bias was scored as "low risk of bias" if the study was classified as "low risk" in all domains, "some concerns" if at least one domain was scored as "some concerns," and "high risk" if there was at least one domain rated as "high risk" or several domains as "some concerns" and could affect the validity of the results.

2.6 | Grading the quality of evidence

To evaluate the quality of evidence and make recommendations, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool was used.[19] The GRADE framework rated the quality of evidence as high, moderate, low, and very low based on study limitations, risk of bias, inconsistency, indirectness, imprecision, and publication bias.

2.7 | Data synthesis and statistical analysis

In accordance with the recommendations of the Cochrane Collaboration Handbook, our estimates were based on standard errors, 95% confidence intervals (CI), *p* values, or *t*-statistics to calculate the standard deviation when the standard deviation of the change from baseline was missing. When a study had an inverse score (higher scores indicated worse fitness), the mean of each group was multiplied by −1. When the study reported the same outcome through more than one parameter, we calculated a pooled estimate for those tests that had been previously validated, except for CRF, where if the maximum assessment was provided by VO_{2max}, only this value was taken.

This NMA was conducted according to the following steps. First, transitivity was assessed by checking whether the synthesis of the direct comparisons of interventions was conducted in samples with similar clinical characteristics at baseline. Thus, it should be assumed that the populations included in these studies were similar in the baseline distribution of effect modifiers (age, sex, disease severity, and disease duration).

Second, we used a network geometry graph to assess the distribution of available evidence. The size of the node was proportional to the number of studies included for each intervention, and the width of the continuous lines connecting the nodes was proportional to the trials directly comparing the two interventions.[20]

Third, consistency was assessed by checking whether the intervention effects estimated from the direct comparisons were consistent with those estimated from the indirect comparisons. Confidence was assessed with the Confidence In Network Meta-Analysis (CINeMA) web application.[21]

Fourth, a standard pairwise meta-analysis was conducted for each direct comparison using the DerSimonian–Laird random effects method.[22] The summary measure for the analysis was the standardized mean difference, which was calculated using Cohen's *d* as the ES statistic. Values below 0.2 were considered low ES, 0.2–0.5 moderate, 0.5–0.8 strong, and more than 0.8 very strong. Furthermore, statistical inconsistency was analyzed with the I^2 statistic, with $I^2=0\%–30\%$ considered not important, $I^2=30\%–50\%$ moderate, $I^2=50\%–75\%$ substantial, and $I^2=75\%–100\%$ considerable inconsistency; the corresponding *p* values were also considered.[16] Finally, t^2 was calculated to determine the size and clinical relevance of heterogeneity. A t^2 less than 0.14 was interpreted as a low degree of clinical relevance of heterogeneity, 0.14–0.40 moderate heterogeneity, and more than 0.40 substantial heterogeneity. These results were illustrated by generating a forest plot and a league table.

Fifth, the relative rankings of treatments were estimated, and rankograms were used to graphically present the probability that each intervention was the most effective. Furthermore, the surface under the cumulative ranking (SUCRA) was calculated for each intervention. SUCRA consists of assigning a numerical value from 0 to 1 to simplify the ranking in the rankogram, with values close to 1 being the best intervention and the worst intervention obtaining a value close to 0.[20,23] These data were also displayed by using a rank-heat plot according to SUCRA.[24]

Sixth, we conducted random-effects meta-regression analyses based on relapsing–remitting MS, percentage of women and adherence and the time, frequency, and duration of the exercise interventions to determine whether these variables could significantly influence the effect of physical exercise on muscular fitness and CFR of people with MS.

Moreover, subgroup analyses were used to assess the effectiveness of physical exercise categories according to disease severity and whether CRF was considered a maximal or submaximal test. For disease severity, we only used those studies that reported a quantitative value for severity level with the EDSS. Disease severity was classified according to Haber et LaRocca and Alonso et al. as mild (Expanded Disability Status Scale [EDSS] score 0–5) and severe (EDSS score ≥5).[25,26]

Seventh, we conducted a sensitivity analysis by removing data from individual studies one at a time to assess the robustness of the estimates and to detect whether a particular study represented a large proportion of the heterogeneity. In addition, a sensitivity analysis was conducted by excluding studies scored as high risk of bias.

Furthermore, we conducted a dose–response analysis on the exercise groups that were more effective for each outcome. An index was calculated by multiplying the number of weekly sessions by the number of weeks of the intervention. We tested whether there was a dose–response association using the Wald test, considering $p<0.05$ as statistically significant. If there was association, we estimated the dose–response curve to assess the minimal number of sessions required for a positive response.[27,28]

Finally, to assess publication bias, we used Egger's regression asymmetry test considering $p<0.10$ as statistically significant and a funnel plot to visually examine the criterion of symmetry.[29] All analyses were conducted using Stata 16.0 (Stata).

3 | RESULTS

From the 6283 full-text articles identified in the literature search, 72 RCTs[30–101] involving a total sample of 2543 participants with MS were included in this NMA (Figure 1). The excluded full-text studies with reasons are available in Table S3. Of the included articles, 11 had 3 arms (2 interventions and 1 control), 3 had 4 arms (3 interventions and 1 control), and 1 had 5 arms (4 interventions and 1 control) (Table S4).

The scales most frequently used to report disease severity were the Expanded Disability Status Scale[102] and the Patient-Determined Disease Steps.[103] For disease duration, some articles reported the time since diagnosis and symptoms. Time since diagnosis was selected because it was the most common in the remaining articles.

Overall, the age of the participants ranged from 31.3 to 65.1 years, and the mean disease duration ranged from 1.75 to 21.9 years. Disease severity was mild in 52 studies and severe in 12 studies. The most common exercise was sensorimotor training ($n=24$ interventions), followed by aerobic exercise ($n=23$ interventions) and resistance training ($n=20$ interventions). The physical exercise interventions varied across the included studies (Table S5). Finally, the tests used in the included studies are described in Table S6, and most of them indicate that higher scores mean better fitness. Muscular fitness was assessed in 46 studies and CRF in 49 studies.

3.1 | Risk of bias

As evaluated with RoB-2, 35 studies were assessed as having some concerns, and 37 were assessed as having a high risk of bias (Figure S1). Regarding each individual domain, 2.78% and 97.22% of studies had some concerns about the randomization process and the deviations from intended intervention outcomes, respectively. For missing

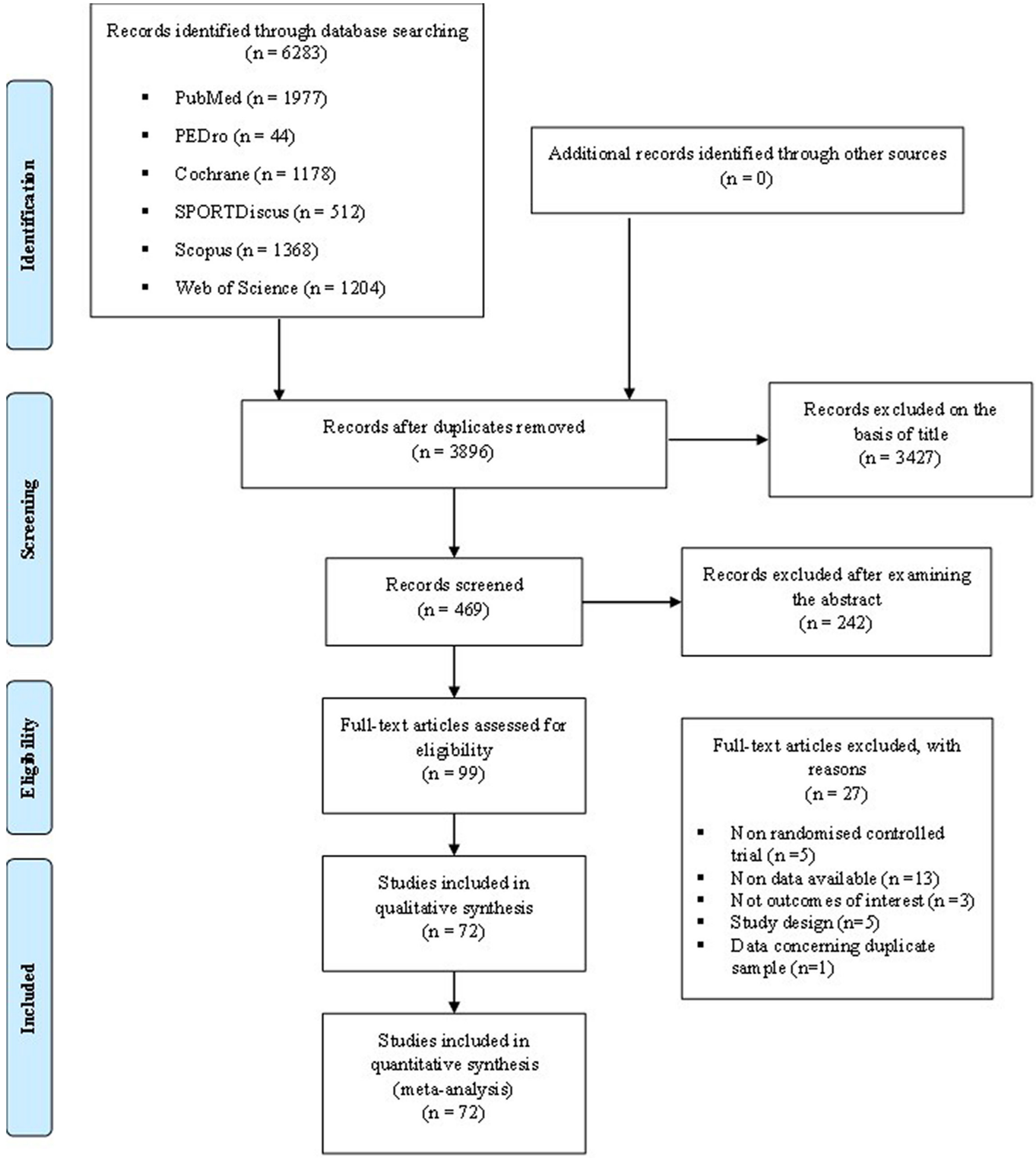

FIGURE 1 PRISMA flow diagram.

outcome data, 6.94% and 2.78% were assessed as high risk of bias and some concerns, respectively. For measurement of the outcome, 45.83% and 4.17% of studies were assessed as having a high risk of bias and some concerns, respectively. Finally, for selection of the reported results, all studies showed a low risk of bias. In addition, the GRADE assessment is shown in Table S7.

3.2 | Network analyses

The color of the graphs corresponds to the transitivity assumption, which was achieved for all comparisons in at least one variable (female [%], age, disease severity, or disease duration). There were differences only for sensorimotor training versus mind–body exercises to age and disease severity and for combined training versus sensorimotor training to disease severity (Table S8).

Network geometry graphs showed the relative amount of evidence for the effect of physical exercise interventions on muscular fitness and CRF, involving 10 and 12 pairwise comparisons, respectively (Figure 2). All physical exercise categories had at least one comparison versus the control. Risk of bias and indirectness contributions in the network analyses were assessed with the CINeMA web application (Confidence in Network Meta-Analysis) and are presented in Figures S2–S5.

3.3 | Effect on muscular fitness and CRF by exercise modality

The ESs for muscular fitness and CRF are shown in Table 1. Although some estimates were not statistically significant, all were in favor of exercise. The highest ESs for pairwise comparisons were for combined training versus the control for muscular fitness (0.77, 95% CI 0.44, 1.10) and aerobic exercise versus the control for CRF (0.60, 95% CI 0.28, 0.92). In the NMA, the highest effects were for combined training and resistance training versus the control in muscular fitness (0.94, 95% CI 0.47, 1.41, and 0.93, 95% CI 0.57, 1.29, respectively) and aerobic exercise and combined training versus the control in CRF (0.66, 95% CI 0.34, 0.99, and 0.53, 95% 0.15, 0.90, respectively).

3.4 | Probabilities

For muscular fitness, the highest SUCRA values were observed for resistance training (87.0%) and combined training (86.2%) (Table S9; Figure S6), and for CRF, the highest SUCRA values were observed for aerobic exercise (86.9%) and combined training (67.8%) (Table S10; Figure S7). The rank-heat plot for both outcomes is shown in Figure 3.

3.5 | Dose–response analyses, subgroup, meta-regression and sensitivity analyses, heterogeneity and publication bias

We conducted dose–response analyses for resistance training and combined training to improve muscular fitness, and for aerobic exercise to improve CRF. There was a dose–response association (Wald test <0.05) for all the groups. The dose–response curves (Figure S8) establish that, in general, there is a linear progression of the effect up to 30 sessions, thereafter the effect stabilizes, with no substantial improvement. In the case of combined training, after 40–50 sessions the effect decreases.

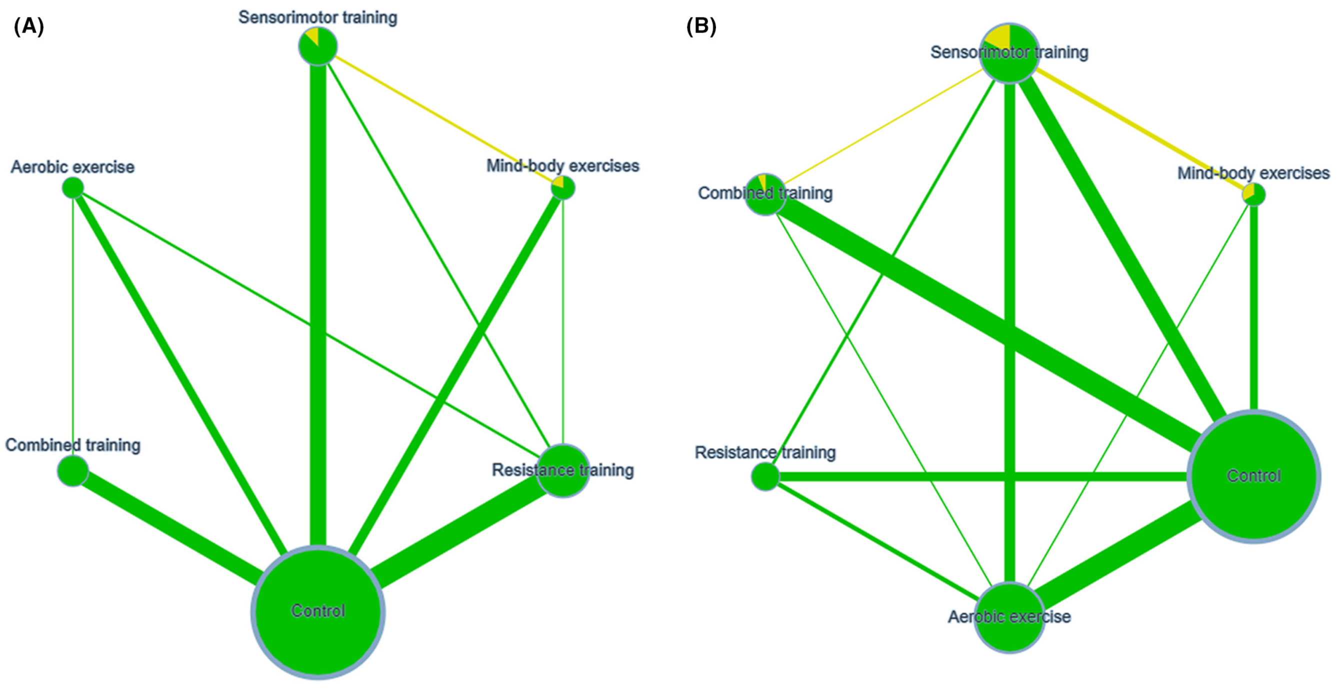

FIGURE 2 Network of available comparisons between different types of exercise interventions on fitness in multiple sclerosis: (A) muscular fitness; (B) cardiorespiratory fitness. The size of the nodes is proportional to the number of trials included of each intervention, and the line width corresponds to studies directly comparing the two interventions. Color area correspond with the proportion of studies of each node that meet transitivity assumptions, as follows: green for the four covariates (female [%], age, disease severity, and disease duration), yellow for two or three, and red for one or none.

TABLE 1 Absolute and relative effect size estimates (95% CI) on muscular fitness (i) and cardiorespiratory fitness (ii).

(i) Muscular fitness					
Control	**0.38 (0.14, 0.62)**	**0.66 (0.28, 1.04)**	**0.77 (0.44, 1.10)**	**0.33 (0.02, 0.64)**	**0.40 (0.02, 0.77)**
0.35 (−0.20, 0.91)	Aerobic exercise	0.18 (−0.14, 0.51)	0.00 (−0.18, 0.18)	na	na
0.93 (0.57, 1.29)	0.57 (−0.04, 1.19)	Resistance training	na	**−0.73 (−1.14, −0.32)**	−0.25 (−1.17, 0.68)
0.94 (0.47, 1.41)	0.59 (−0.10, 1.27)	0.01 (−0.57, 0.60)	Combined training	na	na
0.36 (−0.08, 0.79)	0.00 (−0.69, 0.70)	**−0.57 (−1.11, −0.03)**	−0.58 (−1.22, 0.06)	Sensorimotor training	0.25 (−0.22, 0.71)
0.49 (−0.05, 1.03)	0.13 (−0.64, 0.91)	−0.44 (−1.07, 0.19)	−0.45 (−1.17, 0.26)	0.13 (−0.51, 0.77)	Mind–body exercises
(ii) Cardiorespiratory fitness					
Control	**0.60 (0.28, 0.92)**	**0.32 (0.02, 0.62)**	0.27 (−0.21, 0.75)	**0.31 (0.08, 0.54)**	0.38 (−0.04, 0.80)
0.66 (0.34, 0.99)	Aerobic exercise	0.31 (−0.16, 0.78)	−0.03 (−0.53, 0.48)	−0.24 (−0.66, 0.18)	−0.32 (1.18, 0.54)
0.41 (−0.04, 0.86)	−0.25 (−0.74, 0.24)	Resistance training	na	0.14 (−0.30, 0.58)	na
0.53 (0.15, 0.90)	−0.14 (−0.61, 0.34)	0.12 (−0.46, 0.69)	Combined training	−0.51 (−1.03, 0.01)	na
0.32 (−0.05, 0.68)	−0.35 (−0.76, 0.06)	−0.10 (−0.61, 0.42)	−0.21 (−0.71, 0.29)	Sensorimotor training	0.05 (−0.25, 0.36)
0.38 (−0.13, 0.89)	−0.28 (−0.85, 0.28)	−0.03 (−0.69, 0.62)	−0.15 (−0.78, 0.48)	0.06 (−0.47, 0.60)	Mind–body exercises

Note: 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).

Abbreviations: CI, confidence interval; na, not available; 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 fitness compared to the second one.

Because of the lack of studies including patients at a severe level of MS (none, 1 or 2), subgroup analyses according to disease severity could only be conducted for the mild level of severity. The highest ESs in the mild category were for combined training versus the control (0.83, 95% CI 0.46, 1.20) and aerobic exercise versus the control (0.75, 95% CI 0.29, 1.21) for muscular fitness and CRF, respectively (Tables S11 and S12).

The highest ESs by maximal or submaximal CRF assessment were for aerobic exercise versus control in both cases (0.68; 95% CI 0.02–1.34 and 0.42; 95% CI 0.16–0.68, respectively) (Table S13).

Random-effects meta-regression models for muscular fitness indicated that the percentage of relapsing–remitting MS type was directly related to ES estimates of combined training versus control (β: 0.0051; $p=0.035$) and sensorimotor training versus control (β: 0.0209; $p=0.004$). Percentage of women was inversely related to combined training versus control (β: −0.0284; $p=0.001$). Adherence to intervention was directly related to combined training versus control (β: 0.0132; $p=0.046$). Finally, the duration of exercise in minutes was related to ES estimates for sensorimotor training versus control (β: −0.0512; $p=0.007$) and mind–body training versus control (β: 0.0447; $p=0.048$) for muscular fitness. Random-effects meta-regression analyses were not statistically significant for CRF (Table S14).

In the sensitivity analysis, the pooled ES estimates for the associations between physical exercise and muscular fitness and CRF were not significantly modified when removing individual studies from the analysis one at a time. By excluding studies with a high risk of bias from the pairwise comparison analysis, some comparisons changed the statistical significance because of a limited number of studies in the pairwise comparison (Table S15).

Resistance training, combined training, and mind–body exercises versus control showed considerable inconsistency for muscular fitness ($I^2=92.4\%$ and $t^2=0.5479$; $I^2=79.3\%$ and $t^2=0.2399$; and $I^2=79.3\%$ and

FIGURE 3 Rank-heat plot with SUCRA values for scoring in muscular fitness and cardiorespiratory fitness. CRF, cardiorespiratory fitness.

$t^2=0.1871$, respectively), and sensorimotor training versus control showed substantial inconsistency ($I^2=72.0\%$ and $t^2=0.1988$) (Table S16). Combined training versus control showed considerable inconsistency for CRF ($I^2=86.9\%$ and $t^2=0.7050$), and aerobic exercise versus control and aerobic exercise versus sensorimotor training showed substantial inconsistency ($I^2=72.7\%$ and $t^2=0.2466$; and $I^2=53.5\%$ and $t^2=0.1673$, respectively) (Table S17).

Finally, publication bias was found with Egger's test for both muscular fitness and CRF on the following comparisons: (i) aerobic exercise versus control ($p=0.036$ and $p=0.031$), (ii) combined training versus control ($p=0.040$ and $p=0.002$), and (iii) mind–body exercises versus control ($p=0.039$ and $p=0.069$), respectively. Funnel plots are shown in Figures S9 and S10.

4 | DISCUSSION

This NMA, based on 72 RCTs involving 2543 MS patients, was aimed at comparing the effectiveness of different types of physical exercise to improve muscular fitness and CRF in people with MS. Our results indicate that resistance and combined training for muscular fitness and aerobic exercise for CRF are the most effective exercise modalities. When analyzing the effect of different types of exercise according to disease severity, these interventions also reported the highest ES for their respective outcome in the mild category; however, for the other disease severity categories, no conclusive results could be obtained. The results of previous reviews showed the effect of physical exercise on improving fitness in people with MS,[5,10,104,105] and a recent NMA found that resistance training and aerobic exercise are the best for total fatigue[7] and physical quality of life,[8] respectively.

Regarding muscular fitness, our results show that the most effective types are resistance and combined training. The fact that muscular fitness is associated with walking capacity in people with MS[106] could explain why aerobic exercise added to resistance training is also beneficial to improve muscular fitness, as walking is mainly an aerobic exercise, and if walking capacity is improved, muscular fitness would also improve. Our data also indicated that the percentage of relapsing–remitting MS patients, which is the most prevalent type of MS,[107] and adherence to treatment could directly affect this association.

Regarding CRF, our results indicate that the best intervention is aerobic exercise. A previous meta-analysis also showed the beneficial effect of this type of exercise in improving CRF in people with MS, although no differences were observed when compared to the control.[11] This discrepancy may be because the previous review includes studies measuring CRF only with maximum oxygen uptake (VO_{2max}) or VO_2 peak. In the included studies in this NMA, CRF was assessed with maximal and submaximal outcomes, with the most commonly used VO_{2max} and the 6-min walk test (6MWT), respectively. The 6MWT is widely used to assess functional capacity.[108,109] However, due to the high cost of maximal cardiorespiratory assessment with VO_{2max}, the 6MWT is also used as a measure of fitness, with evidence supporting 6MWT as a valid parameter to classify CRFs compared to VO_{2max}.[110] Because of this controversy, subgroup analyses were conducted based on maximal or submaximal assessment of CRF. Most of the included studies measured CRF with submaximal tests, and our results were not substantially modified in the subgroup analysis, although some comparisons for maximal tests were missing due to the scarcity of studies. Furthermore, some of the studies included in this NMA measured fitness with both VO_{2max} and 6MWT.[37,55,71,86] In all of them, the results were in the same direction for maximal and submaximal assessment, although it seems that 6MWT underestimated CRF, as its results are generally lower than VO_{2max} in these studies.

Finally, the percentage of women, age, disease severity, and disease duration were similar between physical exercise categories, except for age and disease severity of patients who performed sensorimotor training. Sensorimotor training is characterized by the inclusion of balance or coordination. These components are important to avoid falls and could explain why patients who performed this type of exercise were older and had worse disease severity. Our data also showed that the percentage of relapsing–remitting MS patients could directly influence the effect of sensorimotor training, and the duration of each session also had an inverse relationship. As we could not consider the intensity of exercise, we cannot conclude that this effect is at the cost of higher intensity.

This NMA has some limitations that should be considered. First, we did not consider the intensity of exercise in our analysis because it was missing for most of the physical exercise modalities. However, we assessed the influence of adherence, minutes, frequency, and weeks in the meta-regression analysis. We also conducted a dose–response analysis based on the frequency of sessions and weeks of intervention; we could not consider the duration of each session because some studies did not report these parameters, or if they did, it was very heterogeneous between the studies. Second, despite the well-documented differences between men and women, it was not possible to conduct a stratified analysis by sex because the articles reported the data for the entire population. However, in general, meta-regression analysis by percentage of women showed no influence on the effect of physical exercise on improving fitness. Third, we only considered the main fitness variables (i.e., muscular fitness and CRF) for our analyses; however, other outcomes, such as speed-agility or walking ability, could act as confounders or mediators in the associations. Moreover, the instruments used to assess fitness varied between studies, which might have some influence on our estimates. However, we only selected studies using validated tests, and when CRF was separated by maximal or submaximal assessment, the results remained stable for submaximal tests, with few studies reporting maximal tests with no comparisons. Fourth, because of the scarcity of studies in the severe category, estimates by disease severity were only possible for the mild category. Fifth, a large proportion of studies were assessed as having a high risk of bias (51.39%), which could be attributed to lack of blinding, a moderate number of withdrawals in follow-up, and previous unpublished protocols. When sensitivity analysis was conducted excluding all these studies, the ES remained stable in their direction, although some comparisons lost statistical significance. When removing individual studies one at a time, the results also remained stable. Finally, aerobic exercise, combined training, and mind–body exercises versus control showed publication bias, so the results of this NMA could be modified by unpublished studies of those comparisons.

5 | PERSPECTIVE

The findings of this NMA show the therapeutic potential of exercise in the treatment of people with MS to improve muscular fitness and CRF. These results on the efficacy of exercise were similar to those demonstrated in previous systematic reviews. Nevertheless, the design of this NMA allowed us to assess other issues. We were able to compare the different types of physical exercise and detect which one has the highest effect for muscular fitness and CRF. Thus, healthcare professionals should consider resistance training and aerobic exercise when encouraging people with MS to improve muscular fitness and CRF, respectively.

6 | CONCLUSION

Physical exercise is a beneficial intervention to improve fitness in people with MS. Resistance training and aerobic exercise seem to be the types of exercise most effective in improving muscular fitness and CRF, respectively. Moreover, a combination of resistance and aerobic exercises has positive effects on muscular fitness. Our results are based on RCTs, represent an effort to synthetize the available evidence, and should be considered when designing programs for people with MS aimed at improving fitness.

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CONFLICT OF INTEREST STATEMENT

The authors have declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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