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The effect of exercise on dynamic balance and walking endurance in patients with relapsing remitting Multiple Sclerosis: A systematic review and meta-analysis

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Abstract

Background: Multiple Sclerosis (MS) affects 2-3 million people worldwide, with relapsing remitting MS (RRMS) accounting for 75% of new cases. Exercise has been proposed to alleviate symptoms and enhance quality of life. This meta-analysis aims to evaluate the effect of exercise on dynamic balance and walking endurance in RRMS patients.

Methodology: A comprehensive PubMed search identified exercise interventions that specifically measured walking endurance via the 6-minute walk test (6MWT) and dynamic balance through the timed up-and-go (TUG) test. Mean and standard deviation values at baseline and post-intervention were extracted for analysis. For subgroup comparisons, interventions were classified as either lower or higher intensity.

Results: Thirteen intervention groups were analysed. The 6MWT results showed a statistically significant improvement in distance covered post-intervention (MD, 29.11; 95% CI, 8.36–49.86; $p = 0.006$). In subgroup analysis, lower-intensity interventions produced a significant benefit (MD, 29.35; 95% CI, 5.21–53.49; $p = 0.02$), whereas higher-intensity interventions exhibited a trend (MD, 28.44; 95% CI, -12.18–69.05; $p = 0.17$). The TUG test demonstrated a significant reduction in test completion time (MD, -1.4; 95% CI, -1.69 to -1.10; $p < 0.00001$), with both lower- (MD, -2.00; 95% CI, -2.60 to -1.40; $p < 0.00001$) and higher intensity (MD, -1.20; 95% CI, -1.54 to -0.87; $p < 0.00001$) subgroups showing statistically significant improvements.

Conclusions: The results of this research reinforce the existing evidence that exercise significantly improves walking endurance and dynamic balance in RRMS patients. These findings support the recommendation for early, regular exercise as a non-pharmacological intervention.

Keywords: Multiple Sclerosis, Relapsing remitting, Exercise, Dynamic balance, Walking endurance, Timed up-and-go test, 6-minute walk test

Introduction

Multiple sclerosis (MS) is a chronic, debilitating, autoimmune disease of the central nervous system (CNS) characterised by demyelination and neurodegeneration. This is triggered by the immune system targeting the myelin sheath that surrounds nerve fibres. Clinical manifestations vary but are usually grouped into 3 types, primary progressive (PP), secondary progressive (SP), and relapsing remitting (RR), with the latter accounting for 75% of all new diagnoses (Khan and Hashim 2025). Symptoms vary between type but often include muscle weakness, fatigue, sensory deficits, cognitive dysfunction, walking difficulties, spasticity, and balance impairments (Giovannoni *et al.* 2016). Among these deficits, walking endurance and dynamic balance are particularly affected, leading to a significant impact on daily life (VanSwearingen *et al.* 2011).

Estimates place the global prevalence of MS between 2 and 3 million (Wallin *et al.* 2019), (Walton *et al.* 2020). However, these papers also highlighted the lack of available data for certain countries. As a result, this figure could be an underestimate. In the UK, recent estimates from the MS society (2024) place the prevalence of MS around 150,000 with 7,100 new yearly diagnoses. This is an increase from previous data in 2010 suggesting the figure to be around 125,000 (Mackenzie *et al.* 2013). MS places a financial strain not only on national health services but also personal finances with the estimated economic impact in the UK to be around £1.4 billion per annum (Nicholas *et al.,* 2020).

MS disproportionately affects females, with males comprising approximately 25% of the affected population (Coyle 2021). Despite this lower prevalence, males tend to experience a more severe disease course and earlier onset. This is characterised by reduced recovery following relapses, accelerated brain volume loss, greater overall disability, and a higher rate of cognitive decline (Rommer *et al.,* 2020). Notably, the incidence of MS among females is rising, with some research indicating a trend towards later disease onset (Koch-Henriksen *et al.,* 2018).

MS pathogenesis involves a complex interaction of genetic, environmental, and immunological factors. Genetic predisposition plays a key role in MS susceptibility, with the HLA-DRB1*15:01 allele being strongly linked to disease risk. Environmental factors such as vitamin D deficiency, smoking (Alfredsson and Olsson 2018) and Epstein-Barr virus infection (Bjornevik *et al.,* 2022) have been implicated in the development of MS. It is traditionally characterised as a T cell-mediated autoimmune disorder, with CD8+ T cells being more prevalent than other T-cell subsets, B-cells, or plasma cells. The disease is thought to originate from inflammation-driven lesions primarily composed of CD8+ and CD4+ T cells, alongside activated microglia and macrophages (Huang *et al.,* 2017). The cytotoxic effects of CD8+ T cells require interaction with target cells via major histocompatibility complex class I (MHC-1) expression, which is typically restricted in neurons. New research also implicates oligodendrocyte precursor cells (OPC's) in this process (Kirby *et al.,* 2019).

However, MHC-I molecules can be upregulated in response to potent danger signals, such as the pro-inflammatory cytokines interferon gamma (IFN-γ) and tumour necrosis factor (TNF) alpha, facilitating CD8+ T-cell-mediated neurotoxicity (Veroni and Aloisi 2021). Chronic demyelination results in axonal degeneration, which correlates with disability. Sustained CNS inflammation leads to microglial and astrocyte activation, promoting neurotoxic cytokine release and oxidative stress (El-Sayed *et al.,* 2025). This contributes to ongoing neurodegeneration and impairs remyelination. Remyelination is the process by which new myelin sheaths are restored to demyelinated axons, primarily mediated by OPC's in the CNS. These cells proliferate, migrate to lesion sites, and differentiate into mature oligodendrocytes that help generate new myelin. This process is crucial as effective remyelination preserves axonal integrity and restores conduction velocity (Cunniffe and Coles, 2019).

Diagnosis relies on a combination of clinical assessment, magnetic resonance imaging (MRI), cerebrospinal fluid analysis, and evoked potentials to detect CNS demyelination and exclude alternative conditions. Early and accurate diagnosis is crucial as delays can lead to irreversible neurological damage and poorer long-term outcomes (Ebers *et al.,* 2010). The 2017 revised McDonald criteria, which incorporate MRI-based lesion dissemination in space and time, is widely used to allow earlier diagnosis and enable rapid intervention (Thompson *et al.,* 2018). After diagnosis, a neurologist will often use the Expanded Disability Status Scale (EDSS) to measure disability progression. Originally developed by Kurtzke (1983), it provides a 0 to 10 rating, where 0 represents no symptoms and 10 signifies death due to MS-related complications. The EDSS primarily evaluates mobility and neurological function. On the scale, a 4.0 indicates the ability to walk ≥ 500 meters without aid or rest, while a score of 6.0 signifies the need for a unilateral walking aid to walk 100 meters with or without rest. The EDSS is widely used in both clinical and research environments to track disease progression and evaluate the effectiveness of interventions.

Disease-modifying therapies (DMTs) help reduce relapse rates and slow disease progression. Treatments range from immunomodulators like interferon-beta to more potent immunosuppressants such as natalizumab and ocrelizumab. Early initiation of high-efficacy DMTs has been linked to better long-term neurological outcomes (Giovannoni *et al.,* 2016). Given the lifelong nature of MS, a comprehensive, multidisciplinary approach is necessary to optimise patient outcomes.

Historically, vigorous exercise was not advised for people with MS due to the adverse effects related to fatigue and heat sensitivity (Petajan and White 1999). Evidence has since suggested that moderate exercise could be beneficial and should be included in treatment plans (Li *et al.,* 2022). It has been studied as a therapeutic treatment in MS for many years with some of the first papers published in the 1970's (Marcham 1974). It has now emerged as a promising intervention to improve the loss in function often seen in MS. In the absence of a definitive cure, therapeutic interventions and rehabilitation strategies represent one of the most effective means of alleviating symptoms, preserving functional mobility, and enhancing quality of life in individuals with MS.

Therapeutic and rehabilitation interventions often require quantitative measurements to assess the efficacy of the treatment while allowing for cross study analysis. Examples include the 9-hole peg test, timed 25-foot walk, Berg balance scale, timed up-and-go (TUG), and the 6-minute walk test (6MWT). With the latter two being analysed in this research. They help to explore the neurological deficit seen in MS patients while also assessing the efficacy of a treatment regime. Alongside clinical trials, neurologists use the results from these tests to evaluate disease progression in patients (Feys et al., 2017).

Deficits in dynamic balance often stem from impaired neuromuscular coordination and muscle weakness (Aungsumart and Apiwattanakul 2017). This coupled with the deterioration of proprioceptive feedback and reduced motor control causes challenges in adjusting to changes in posture (Dorche *et al.,* 2021). The TUG test measures the time taken to rise from a chair, walk 3 meters, turn 180^{o}, and return to a seated position (Valet *et al.,* 2019). The validity of the TUG test for assessing dynamic balance has been shown numerous times with a growing body of evidence supporting its use in clinical and research settings (Sebastião *et al.,* 2016; Kalron *et al.,* 2017).

Walking endurance is another critical component of functional mobility and independence. Factors such as fatigue, muscle weakness and cardiovascular fitness, all often diminished in MS patients, play a crucial role (Ghasemi *et al.,* 2022). The 6MWT is commonly used to assess walking endurance. Bennett *et al.* (2017) and Leone et al. (2015) show the validity of its use in research and clinical environments to assess patient progression as well as evaluate therapeutic interventions. Participants walk at a comfortable pace for 6 minutes and the total distance is recorded. In MS patients, this distance is often decreased compared to healthy individuals (Leone *et al.,* 2015). Recent papers have explored additional methods for assessing balance and endurance, including the 2-Minute Walk Test and the Berg Balance Scale (BBS). These studies have produced promising results with Veldkamp et al. (2021) indicating an increase in walking endurance while Ayvat et al. (2024) demonstrated an exercise intervention has clinically significant results when using the BBS. However, the TUG test and 6MWT have demonstrated strong validity and are particularly relevant to real-world activities, such as standing up from a seated position, exiting a vehicle, or walking short distances to access amenities. By reflecting functional mobility in everyday scenarios, they offer meaningful insights into potential improvements in independence and quality of life. As a result, these measures were selected for analysis.

Given the heterogeneity of MS symptoms and continued disease progression with DMT's, it is essential to systematically explore and evaluate evidence to determine the effectiveness of exercise interventions. The hypothesis is that exercise will increase the distance walked, therefore increasing walking endurance, of participants. The interventions should also reduce the time taken to complete the TUG test, indicating an increase to dynamic balance. The null hypothesis is that an exercise intervention has no effect on both tests. Accordingly, the aim of this systematic review and meta-analysis is to evaluate the effect of exercise on dynamic balance and walking endurance in RRMS patients.

Methodology

Search Strategy

This systematic review and meta-analysis were based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page *et al.,* 2021). A systematic search was conducted using the literature database PubMed, with a primary and a secondary search term. The primary search term was “Multiple sclerosis” AND “Exercise” between December 2022 and December 2024. The results were then filtered to only include “English language”, “involving humans”, “clinical trials” and “randomised control trials”.

The secondary search term was “Multiple sclerosis” AND “Exercise” AND “Relapsing remitting” between January 2015 and December 2022. With the same filters applied as the primary search term. The title and abstract of every paper were scrutinised, and full text articles were retrieved for further assessment.

Inclusion/Exclusion Criteria

Inclusion criteria: [1] experimental group receiving an exercise intervention, [2] at least 1 quantitative outcome measure used to assess participants, and [3] a RRMS diagnosis for all participants. For this paper an exercise intervention had to be planned, structured and repetitive with the objective of improving or maintaining physical fitness. This was based off Caspersen, Powell and Christenson’s (1985) definition of exercise which is widely used in the field. Investigators must also have reported the frequency and duration, type, and sets/repetitions (if applicable) of the exercise prescribed in the intervention to have met the eligibility criteria.

Exclusion criteria: [1] unrelated outcome measures to the aims of this research, [2] no defined exercise intervention, [3] contained only biomarker outcomes, [4] solely patient reported outcomes, [5] not accessible, [6] included novel drug regimes, [7] review articles, [8] did not include MS, and [9] participants <18 years old.

Data Collection

Information from the included studies was collected and characterised by one author (C.G.) into a standard table for each outcome. Information included, the author(s) and publication year (formatted as a reference), number of participants included in analysis, sex of the participants, the EDSS range used in the paper, brief description of the intervention, the frequency and duration of the research, and finally the intensity of the exercise performed (higher or lower intensity).

Methodological quality assessment

The included studies underwent methodological quality assessment by one author (C.G.). This was conducted using the Physiotherapy Evidence Database (PEDro) scale, the validity of this scale is detailed by Sherrington et al. (2009). Each included paper is evaluated using an 11-item scale in which the quality of the research is considered poor, average, good and excellent based on their score (<4, 4-5, 6-8 and >9 respectively) (Cashin and McAuley 2020).

Data and Statistical analysis

Cochrane Review Manager (RevMan) Web (version 8.17.0) was used for data analysis. Mean and standard deviation (SD) values were extracted from the papers for both the TUG test (in seconds) and 6MWT (in meters). Mean difference (MD) was then calculated, by RevMan, for each parameter. Continuous variables were selected as the aim was to assess the efficacy of the exercise interventions on quantitated outcome measures for MS patients.

Studies were divided into two subgroups by intensity of the exercise intervention; the groups were higher or lower intensity exercise. When both groups were combined this gave the overall effect for the outcome measure. Where possible, the calculated maximal heart rates of the participants were used to classify each exercise regime as higher or lower intensity. Where this information was not included, the NHS (2024) guidelines provided a framework of example activities classified as moderate or vigorous. This was used to define the subgroups. Heterogeneity was assessed using the I^2 value for each outcome. Cochrane Statistical Methods Group, (2023) provides a rough guide for interpreting the I^2 value with the following thresholds, 0% to 40%, 30% to 60%, 50% to 90%, 75% to 100% representing the respective categories; might not be important, may represent moderate heterogeneity, may represent substantial heterogeneity, and considerable heterogeneity. Results were deemed statistically significant if $p < 0.05$. Funnel plots were also created in RevMan to show risk of publication bias for each outcome.

Results

Identification and Selection

This process is detailed in figure 1. From the primary and secondary search terms a total of 161 papers were identified, 107 and 54 respectively. There were no duplicates and of the 161 screened, 131 were removed after the first stage, abstract and title screening. This is because they did not meet the eligibility criteria (unrelated outcomes to aims of this paper, no defined exercise intervention, contained only biomarker outcomes, solely patient reported outcomes, were not accessible, included novel drug regimes, review articles, did not include MS, participants <18 years old). Where the title and abstract were inconclusive to the eligibility criteria, full text articles were retrieved and assessed. A further 20 papers were eliminated following full text article assessment. Of these, 11 contained multiple or other types of MS rather than exclusively RR, while 9 contained different outcomes than those assessed in this analysis. Figure 1 below provides specific details of the identification and selection process.

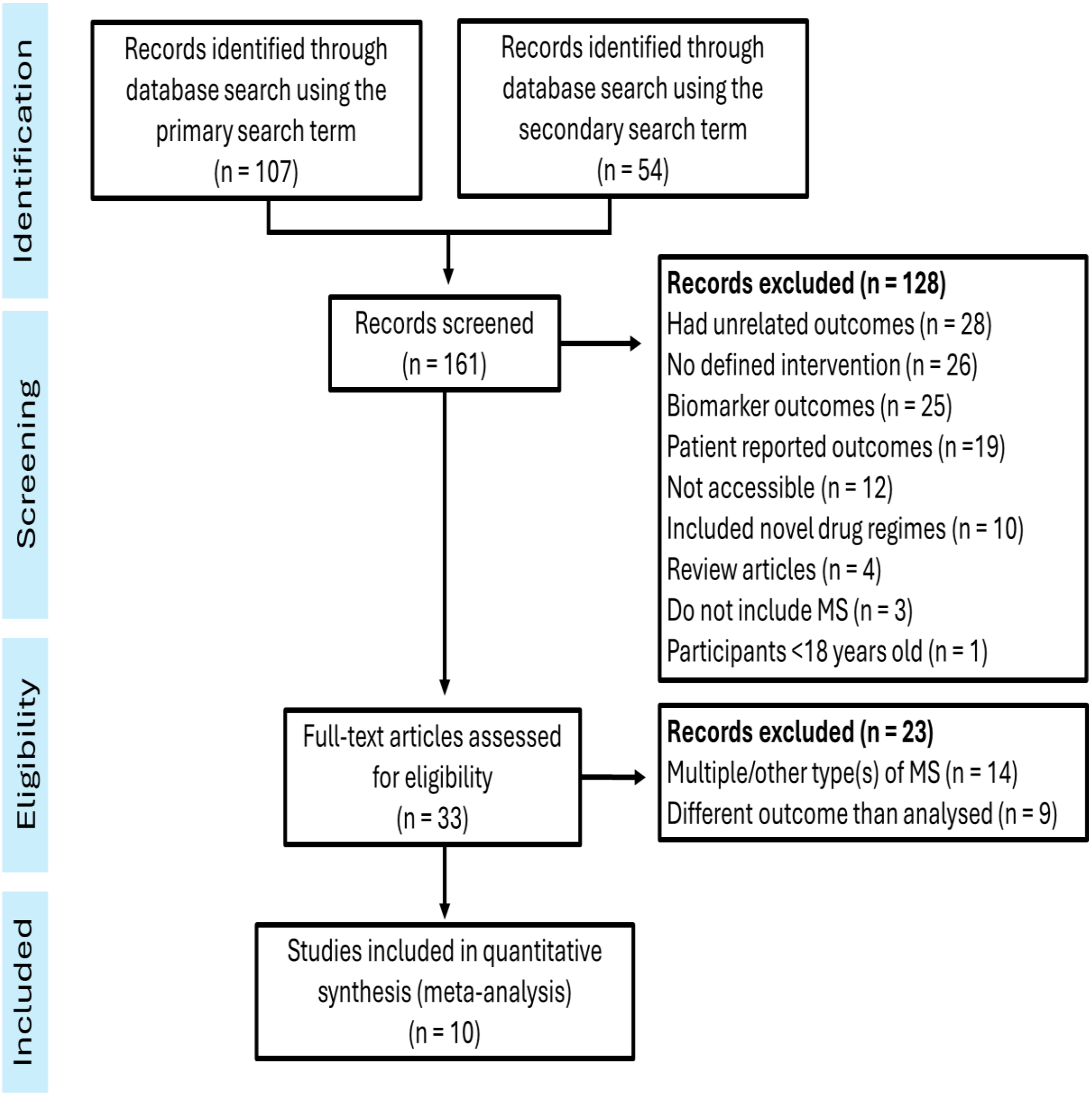


Figure 1: Consort figure showing the identification and selection process with reasons for exclusion.

Characteristics of the Included Papers

Timed Up-and-Go (TUG) Test

8 papers included the TUG test as one of their outcomes however 3 of these used active control groups. As a result, these can be treated as separate intervention groups, leading to a total of 11 intervention groups for the analysis. As previously described, the studies were characterised, this is shown below in Table 1.

Table 1: Characteristics of the included papers that used the 6MWT as an outcome measure. Abbreviations, M/F = Male/Female, EDSS = Expanded Disability Status Scale, HIIT = High intensity-interval training, VTP = virtual training programme. *This is the median EDSS score of the participants with an interquartile range of 2.3 as the paper did not include EDSS in the inclusion criteria. **Figures given were only at the start of the trial, the research excluded participants due to loss in follow ups but didn't state if they were male or female.

Paper	Total Participants Analysed	Sex (M/F)	EDSS Range	Brief Description of Exercise Intervention	Duration of Exercise	Intensity of Exercise
Amato *et al.*, (2024)	16	6/10	1.5-3.5	HIIT focussing on upper and lower limb movements	3x 30-minute sessions per week for 8 weeks	Higher
RostamiAnhar *et al.*, (2024)	20	0/20	< 4	Hip abductor muscle strengthening	3x 45-minute sessions per week for 8 weeks	Lower
Jazi, Rasti and Etemadifa, (2023) (Traditional)	15	15/0	2 - 5	Traditional balance exercises	3x 20–30-minute sessions per week for 8 weeks	Lower
Jazi, Rasti and Etemadifa, (2023) (VTP)	15	15/0	2 - 5	Traditional balance exercises alongside a VTP	3x 20-30 minutes per week for 8 weeks	Lower
Ghannadi *et al.*, (2022)	17	4/13	≤ 4	Respiratory muscle training using an inspiratory muscle training device	3x sets, 15x reps, 2x a day for 8 weeks	Lower
Kocica *et al.*, (2022)	23	4/19	≤ 4	Intensive circuit training focusing on whole body movements and balance	60 minutes per week for 12 weeks	Higher
Moghadasi *et al.*, (2020)	27	0/27	< 4	Total body resistance suspension training	3x 30 minutes per week for 8 weeks	Lower
Kalron *et al.*, (2016) (Pilates)	22	8/14	3 - 6	Pilates with a focus on trunk stability	1x 30-minute (instructor led) session per week and 1x 15-minute session (home based) per day, for 12 weeks	Lower
Kalron *et al.*, (2016) (Conventional)	23	8/15	3 – 6	Conventional therapy with a focus on trunk stability	1x 30-minute (led by a physiotherapist) session per week and 1x 15-minute session (home based) per day, for 12 weeks	Lower
Manca *et al.*, (2017) (Indirect)	13	4/11*	≤ 6	High intensity concentric training of the less affected ankle dorsiflexors	3x 25-minute sessions per week for 6 weeks	Higher
Manca *et al.*, (2017) (Direct)	12	2/13*	≤ 6	High intensity concentric training of the more affected ankle dorsiflexors	3x 25-minute sessions per week for 6 weeks	Higher

6-Minute Walk Test (6MWT)

5 papers used the 6MWT as an outcome measure, 2 of these had active control groups, therefore the total number of intervention groups was 7. These were characterised and are shown below in Table 2.

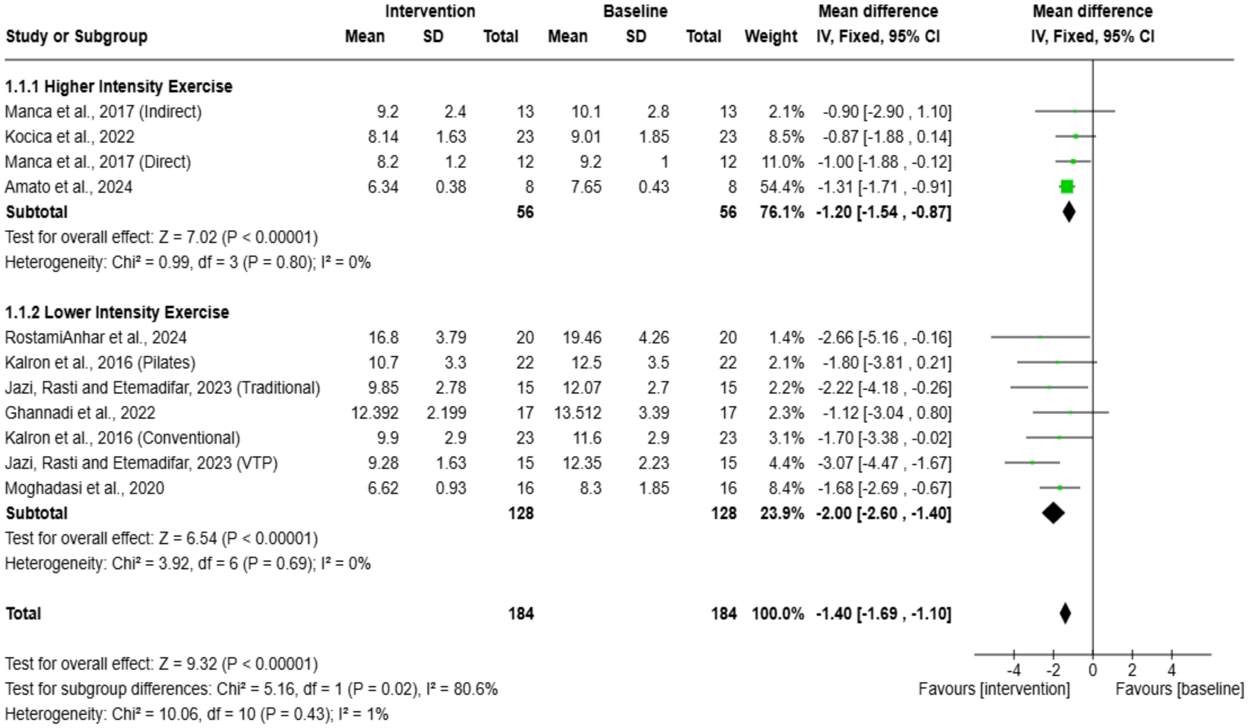
Table 2: Characteristics of included papers that used the 6MWT as an outcome measure. Abbreviations, M/F = Male/Female, EDSS = Expanded Disability Status Scale, HIIT = High intensity-interval training. *This is the median EDSS score of the participants with an interquartile range of 2.3 as the paper did not include EDSS in the inclusion criteria. **Figures given were only at the start of the trial, the research excluded participants due to loss in follow ups but didn't state if they were male or female.

Paper	**Total Participants Analysed**	**Sex (M/F)**	**EDSS Range**	**Brief Description of Exercise Intervention**	**Duration of Exercise**	**Intensity of Exercise**
Silveira *et al*., (2024)	14	2/12	5.5*	Individualised HIIT exercise regime	2 – 3x 30 minutes per week for 12 weeks	Higher
Ghannadi *et al*., (2022)	36	9/27	≤ 4	Respiratory muscle training using an inspiratory muscle training device	3x sets, 15x reps, 2x a day for 8 weeks	Lower
Kargarfard *et al.,* (2018)	17	0/32	≤ 3.5	Aquatic conditioning focused on joint mobility, functional exercises and balance	3x 60 minutes per week for 8 weeks	Lower
Kalron *et al*., (2016) (Pilates)	22	8/14	3 - 6	Pilates with a focus on trunk stability	1x 30-minute (instructor led) session per week and 1x 15-minute session (home based) per day, for 12 weeks	Lower
Kalron *et al.,* (2016) (Conventional)	23	8/15	3 – 6	Conventional therapy with a focus on trunk stability	1x 30-minute (physiotherapist led) session per week and 1x 15-minute session (home based) per day, for 12 weeks	Lower
Manca *et al*., (2017) (Indirect)	13	4/11**	≤ 6	High intensity concentric training of the less affected ankle dorsiflexors	3x 25-minute sessions per week for 6 weeks	Higher
Manca *et al.,* (2017) (Direct)	12	2/13**	≤ 6	High intensity concentric training of the more affected ankle dorsiflexors	3x 25-minute sessions per week for 6 weeks	Higher

Meta-analysis Results

Effect of Exercise on the Timed Up-and-Go (TUG) Test

The forest plot (figure 2) illustrates results from the analysis of 11 intervention groups with a total of 184 participants. The overall effect diamond is shifted to the left, favouring the post-intervention against the baseline mean values. This indicates after receiving an exercise intervention, the same groups of participants were able to reduce the time it took to complete the TUG test by a MD of -1.4 seconds (95% CI, -1.69 to -1.10) across all types of exercise interventions. This is a statically significant reduction as demonstrated by the p value ($p < 0.00001$). The I^2 value was 1%, using Cochrane Statistical Methods Group (2023) guide this would fall into the category of 'might not be important'. As it did not meet the 30% threshold for 'may represent moderate heterogeneity' regression analysis was not conducted.



	Intervention			Baseline				Mean difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
1.1.1 Higher Intensity Exercise								
Manca et al., 2017 (Indirect)	9.2	2.4	13	10.1	2.8	13	2.1%	-0.90 [-2.90 , 1.10]
Kocica et al., 2022	8.14	1.63	23	9.01	1.85	23	8.5%	-0.87 [-1.88 , 0.14]
Manca et al., 2017 (Direct)	8.2	1.2	12	9.2	1	12	11.0%	-1.00 [-1.88 , -0.12]
Amato et al., 2024	6.34	0.38	8	7.65	0.43	8	54.4%	-1.31 [-1.71 , -0.91]
Subtotal			**56**			**56**	**76.1%**	**-1.20 [-1.54 , -0.87]**
Test for overall effect: Z = 7.02 (P < 0.00001)								
Heterogeneity: Chi² = 0.99, df = 3 (P = 0.80); I² = 0%								
1.1.2 Lower Intensity Exercise								
RostamiAnhar et al., 2024	16.8	3.79	20	19.46	4.26	20	1.4%	-2.66 [-5.16 , -0.16]
Kalron et al., 2016 (Pilates)	10.7	3.3	22	12.5	3.5	22	2.1%	-1.80 [-3.81 , 0.21]
Jazi, Rasti and Etemadifar, 2023 (Traditional)	9.85	2.78	15	12.07	2.7	15	2.2%	-2.22 [-4.18 , -0.26]
Ghannadi et al., 2022	12.392	2.199	17	13.512	3.39	17	2.3%	-1.12 [-3.04 , 0.80]
Kalron et al., 2016 (Conventional)	9.9	2.9	23	11.6	2.9	23	3.1%	-1.70 [-3.38 , -0.02]
Jazi, Rasti and Etemadifar, 2023 (VTP)	9.28	1.63	15	12.35	2.23	15	4.4%	-3.07 [-4.47 , -1.67]
Moghadasi et al., 2020	6.62	0.93	16	8.3	1.85	16	8.4%	-1.68 [-2.69 , -0.67]
Subtotal			**128**			**128**	**23.9%**	**-2.00 [-2.60 , -1.40]**
Test for overall effect: Z = 6.54 (P < 0.00001)								
Heterogeneity: Chi² = 3.92, df = 6 (P = 0.69); I² = 0%								
Total			**184**			**184**	**100.0%**	**-1.40 [-1.69 , -1.10]**

Test for overall effect: Z = 9.32 (P < 0.00001)
Test for subgroup differences: Chi² = 5.16, df = 1 (P = 0.02), I² = 80.6%
Heterogeneity: Chi² = 10.06, df = 10 (P = 0.43); I² = 1%

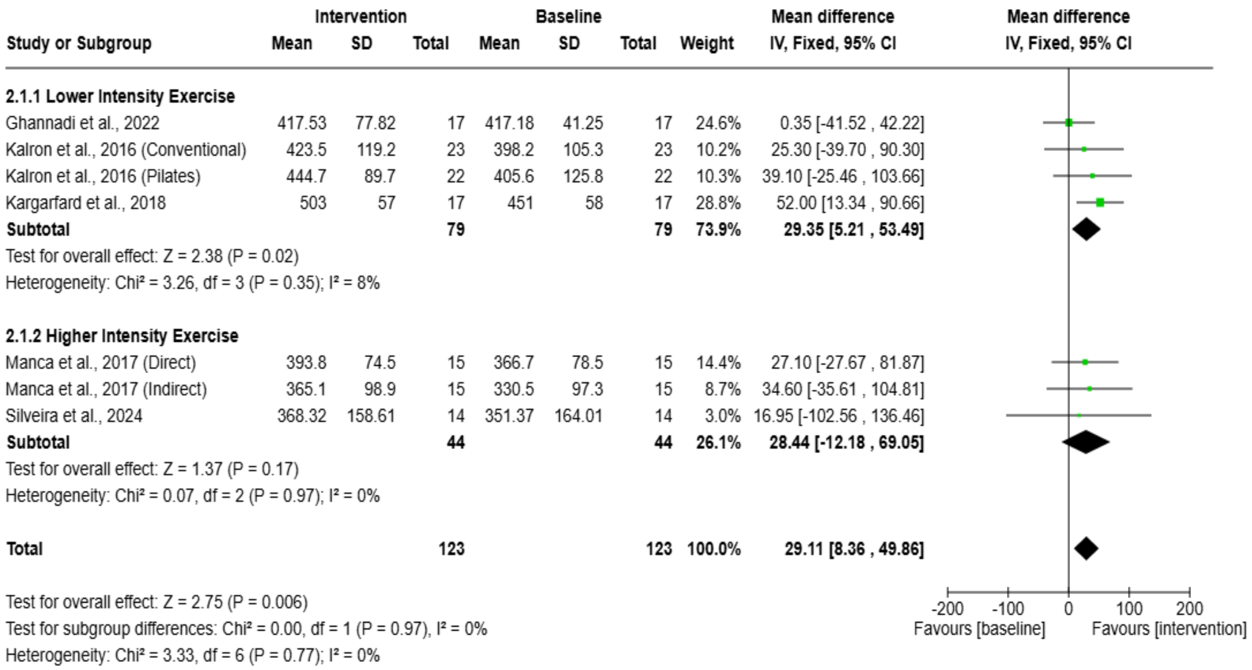
Figure 2: Forest plot showing results of the TUG test analysis. The combined effect of all exercise interventions showed a reduction in time taken to complete the TUG test when comparing baseline mean values with post-intervention mean values, with statistical significance ($p < 0.00001$). MD for overall effect was -1.40 (95% CI, -1.69 to -1.10). Subgroup analysis revealed both groups had a statically significant reduction in time taken to complete the TUG test ($p < 0.00001$). MD for high intensity was -1.20 (95% CI, -1.54 to -0.87) while the low intensity MD was -2.00 (95% CI, -2.60 to -1.40).

Also shown in figure 2 are the results from the subgroup analysis. The higher intensity subgroup comprised 4 intervention groups with 56 participants while the lower intensity groups had 7 intervention groups with 128 participants. Both groups diamond effect is shifted to the left, favouring the post-intervention mean values over the baseline mean values. This suggests both groups were able to reduce the time taken to the complete the TUG test. Both results were statistically significant ($p < 0.00001$) however the lower intensity group reduced the MD by -2.00 seconds (95% CI, -2.60 to -1.40) while the higher intensity group only reduced the MD by -1.20 seconds (95% CI, -1.54 to -0.87).

Effect of Exercise on the 6-Minute Walk Test (6MWT)

The forest plot (figure 3) shows results from the 6MWT analysis, comprising 7 interventions groups with a total of 123 participants. The overall effect diamond is shifted to the right favouring the post-intervention mean values rather than the baseline mean values. This suggests after receiving an exercise intervention, the same participants were able to walk further in 6 minutes. MD for overall effect was 29.11 (95% CI, 8.36 to 49.86) suggesting that on average, participants were able to walk 29.11 meters further in post intervention testing. This is a statistically significant result ($p = 0.006$). All I^2 values in figure 3 did not meet the 30% threshold for ‘may represent moderate heterogeneity’ suggested by Cochrane Statistical Methods Group (2023). As a result, regression analysis was not conducted.

Subgroup analysis concluded that in both the lower and higher intensity subgroup participants were able to walk further post intervention compared to pre intervention (baseline). The higher intensity subgroup MD was 28.44 (95% CI, -12.18 to 69.05) while the lower intensity subgroup MD was 29.35 (95% CI, 5.21 to 53.49). This suggests, on average, participants were able to walk 28.44 and 29.35 meters further in post-intervention testing compared to their baseline mean values respectively. However, only a statistically significant result was observed in the lower intensity subgroup ($p = 0.02$). The higher intensity subgroup did not meet the threshold for significance ($p = 0.17$), although a trend was observed in increasing the distance walked in post-intervention testing.



Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Baseline Mean	Baseline SD	Baseline Total	Weight	Mean difference IV, Fixed, 95% CI
2.1.1 Lower Intensity Exercise								
Ghannadi et al., 2022	417.53	77.82	17	417.18	41.25	17	24.6%	0.35 [-41.52 , 42.22]
Kalron et al., 2016 (Conventional)	423.5	119.2	23	398.2	105.3	23	10.2%	25.30 [-39.70 , 90.30]
Kalron et al., 2016 (Pilates)	444.7	89.7	22	405.6	125.8	22	10.3%	39.10 [-25.46 , 103.66]
Kargarfard et al., 2018	503	57	17	451	58	17	28.8%	52.00 [13.34 , 90.66]
Subtotal			**79**			**79**	**73.9%**	**29.35 [5.21 , 53.49]**
Test for overall effect: Z = 2.38 (P = 0.02)								
Heterogeneity: Chi² = 3.26, df = 3 (P = 0.35); I² = 8%								
2.1.2 Higher Intensity Exercise								
Manca et al., 2017 (Direct)	393.8	74.5	15	366.7	78.5	15	14.4%	27.10 [-27.67 , 81.87]
Manca et al., 2017 (Indirect)	365.1	98.9	15	330.5	97.3	15	8.7%	34.60 [-35.61 , 104.81]
Silveira et al., 2024	368.32	158.61	14	351.37	164.01	14	3.0%	16.95 [-102.56 , 136.46]
Subtotal			**44**			**44**	**26.1%**	**28.44 [-12.18 , 69.05]**
Test for overall effect: Z = 1.37 (P = 0.17)								
Heterogeneity: Chi² = 0.07, df = 2 (P = 0.97); I² = 0%								
Total			**123**			**123**	**100.0%**	**29.11 [8.36 , 49.86]**

Test for overall effect: Z = 2.75 (P = 0.006)
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%
Heterogeneity: Chi² = 3.33, df = 6 (P = 0.77); I² = 0%

Figure 3: Forest plot showing results of the 6MWT analysis with an overall effect for all exercise interventions and subgroup analysis split by the intensity of the exercise intervention (higher or lower). Overall effect diamond is shifted to the right with statistical significance (p = 0.006). Noted increased in distance walked when comparing pre-intervention (baseline) against post-intervention mean values (MD, 29.11; 95% CI, 8.36 to 49.86). Subgroup analysis indicated an increase to the distance walked when comparing pre- and post-intervention mean values for the lower intensity subgroup with statistical significance (p = 0.02). Only a trend was observed in the higher intensity subgroup (p = 0.17). MD indicated an average increase to the distance walked by 29.35 meters (95% CI, 5.21 to 53.49) for lower and 28.44 meters (95% CI, -12.18 to 69.05) for the higher intensity subgroup. As RevMan assumes the lower value is significant, the axis titles for baseline and post-intervention were adjusted accordingly. A higher score on the 6MWT is deemed significant.

Risk of Bias

The included papers underwent quality and risk of bias assessment, shown in table 3. The PEDro scale results indicated 9 of the included papers were considered good quality while 1 paper (Silveira *et al.,* 2024) was not suitable for assessment. This is because the PEDro scale requires the research to be randomised control trials, as this was a pre-post clinical trial it did not meet this requirement. However, when assessed against this scale it scored 6, deeming the quality to be good, hence why it was included.

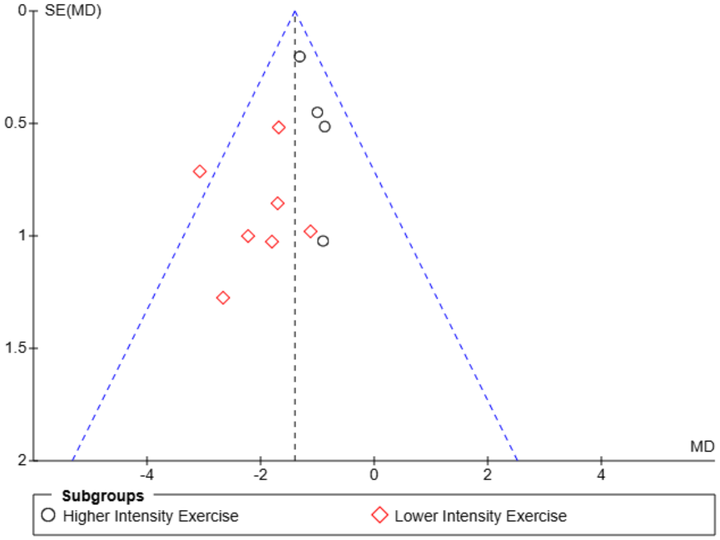
Table 3: Result of the methodological assessment of included papers using the PEDro scale. A = eligibility criteria and source, B = randomised allocation, C = concealed allocation, D = baseline comparability, E = blinding of subjects, F = blinding of therapists, G = blinding of assessors, H = adequate follow-up, I = intention-to-treat, J = between group comparisons, and K = point estimates and variability. The total score represents the score of the PEDro scale. Item A is not scored. Y = yes.

Paper	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**Score**
Amato *et al.*, (2024)	Y	1	1	0	0	1	0	1	1	1	1	7/10
Ghannadi *et al.*, (2022)	Y	1	1	1	0	0	1	1	1	1	1	8/10
Jazi, Rasti and Etemadifar, (2023)	Y	1	0	1	0	0	0	1	1	1	1	6/10
Kalron *et al.*, (2016)	Y	1	1	1	0	0	1	1	1	1	1	8/10
Kargarfard *et al.*, (2018)	Y	1	1	1	0	0	1	0	1	1	1	7/10
Kocica *et al.*, (2022)	Y	1	1	1	0	0	0	1	1	1	1	7/10
Manca *et al.*, (2017)	Y	1	1	1	0	0	0	0	1	1	1	6/10
Moghadasi *et al.*, (2020)	Y	0	1	1	0	0	1	0	1	1	1	6/10
RostamiAnhar *et al.*, (2024)	Y	1	1	1	0	0	0	1	1	1	1	7/10

Publication Bias

Publication bias was assessed through visual examination of the created funnel plots for the TUG and 6MWT (figure 4). Both indicated symmetry for overall effect with no significant publication bias as noted by Sterne *et al.* (2011).

***A.** TUG Test*



***B.** 6MWT*

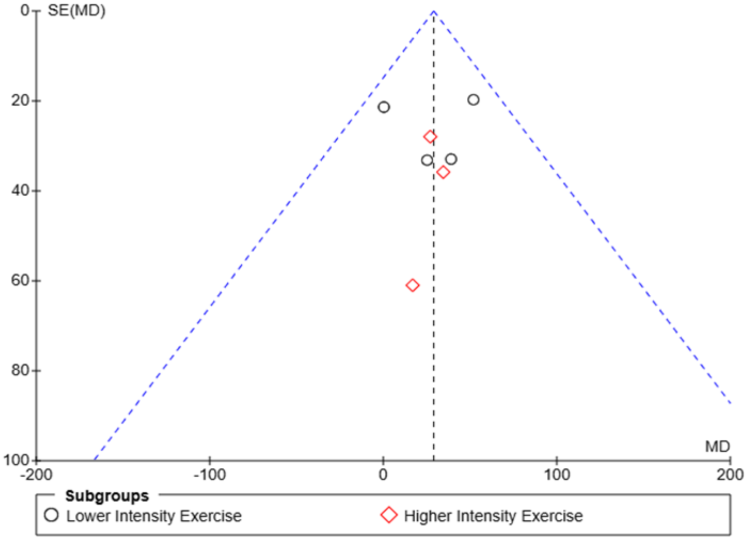


Figure 4: Funnel plots to assess risk of publication bias for (A) papers that used the TUG test (B) papers that used the 6MWT. No significant publication bias is noted.

Discussion

This research identified a gap in the literature of meta-analyses as many studies grouped all types of MS rather than focusing on just one. This made selection challenging however through a comprehensive search, a total of 10 papers were analysed. These comprised 13 intervention groups that used either the TUG test or the 6MWT to assess the exercise intervention. As previously described these tests represent real world activities and results can have lasting impacts on participants, enabling greater independence. Overall, promising results were observed, and the specifics are detailed below.

Summary of Key Findings

Results from the TUG test analysis indicate a reduction in time taken to complete the test with statistically significant results observed in the lower and high groups as well as the overall effect. This reduction in time suggests an increase to the dynamic balance of participants following an exercise intervention.

Although overall results indicate an exercise intervention increases the distance walked in 6 minutes, and therefore a suggested increase to walking endurance, the higher intensity subgroup failed to meet statistical significance. A suggested reason is the small sample size either from the number of intervention groups (n = 3) or number of participants (n = 44). Moreover, the type of exercise intervention may not have been conclusive to improving walking endurance. Additionally, given the nature of MS symptoms previously described, participants may have experienced increased fatigue on the day of testing, which could have skewed the results.

Comparison with Existing Literature

Hao, Zhang and Chen, (2022) compared different exercise interventions to assess the effect on the TUG test in all types of MS. They found that although all exercise interventions reduced the time taken to complete the TUG test, aquatic training was superior. Only one paper in this analysis (Kargarfard *et al.*, 2018) used aquatic training however they assessed the 6MWT not the TUG test, similar results were observed though as aquatic training resulted in the highest MD of 52.00 meters (95% CI, 13.34 to 90.66) compared to the other papers. These findings suggest that aquatic training should be investigated further as it has the potential to have the greatest effect on patients. A large recent meta-analysis (Du *et al.*, 2024) of over 2,000 MS patients detailed similar findings to this research, that exercise improves walking endurance and dynamic balance. However, this meta-analysis included participants <18 years of age and grouped all types of MS without reporting what types each paper contained.

Pearson, Dieberg and Smart, (2015) noted no statistically significant improvement to dynamic balance (MD= −1.05s; 95% CI, –2.19 to 0.09; p = 0.07) merely a trend. These results comprised 5 intervention groups with 74 participants, this is a small sample size and not representative of the wider population. There were also limitations in the eligibility criteria as they did not accept adapted forms of exercise. Considering some MS patients may not safely be able to complete exercise without adaptations, this does not reflect real world implications of the research.

Focusing on higher intensity exercise and walking endurance this meta-analysis noted only a trend. Langeskov-Christensen *et al.*, (2021) detailed minor improvements in distance walked following a high intensity exercise intervention however, just as in this meta-analysis, no statistically significant results were observed. Further investigation is warranted to identify the mechanisms behind this apparent lack of improvement.

Physiological Mechanisms

Although some of the exact cellular and molecular pathways are yet to be elucidated, key physiological mechanisms are suggested to result from exercise (Langeskov-Christensen *et al.*, 2017). One such mechanism is the increase in brain-derived neurotrophic factor (BDNF) levels could promote neuroplasticity and reduce long-term disability. Exercise is suggested to increase DNA demethylation in the BDNF promoter region leading to increased production of neurogenesis promoting signalling modules. Increased BDNF sensitivity is linked with increased TrkB receptor sensitivity (a BDNF receptor in astrocytes). This reduces BDNF synthesis and indicates release following exercise (Shobeiri *et al.*, 2022). Garavito *et al.*, (2025) notes that following exercise, BDNF levels are increased suggesting exercise improves neuronal function.

Improvements to cardiovascular fitness play a vital role in the increase to walking endurance noted by this research. Exercise improves cardiac output, enhancing oxygen delivery to muscles, which boosts oxygen utilisation at the cellular level. It also increases stroke volume and cardiac output which allows more efficient blood flow to skeletal muscles. Additionally, exercise improves vascular health by improving endothelial function to promote better vasodilation and circulation (Motl *et al.*, 2017). Furthermore, bilateral symmetry may also be increased reducing the time lower limbs are supported by the ground (Jensen *et al.*, 2016), overall, leading to improved walking endurance.

Exercise improves muscle strength and coordination resulting from increased motor unit recruitment and better synchronisation. This contributes to more effective movement patterns thus reduces energy expenditure. As a result, enhancements in walking endurance could be noted alongside increased postural control directly supporting improvements to dynamic balance (Du *et al.*, 2024). Although unrelated to MS, Zech *et al.* (2009) notes certain neuromuscular exercises improve dynamic balance more than static balance suggesting an underlying mechanism. It is suggested adaptations arise in the feedback mechanism of mechanoreceptors following exercise. This leads to reorganisation of CNS processes in sensorimotor integration of learning. As a result, changes are found in motor responses connected to neuromuscular control (Rahnama *et al.,* 2021).

Clinical and Policy Implications

Current treatments often prioritise pharmacological intervention, such as DMTs (Giovannoni *et al.* 2016), however this research highlights the importance of early structured exercise alongside this. As the EDSS scores in the papers were low this suggests participants were in the early stages of the disease (Kurtzke, 1983) reinforcing the need for early intervention to retain their mobility.

This research supports the need for more options regarding exercise in MS patients, however many patients face barriers to exercise. A recent meta-analysis (Bozkurt, Unal and Salci, 2024) concluded the main barriers were fatigue, false beliefs regarding the benefit of exercise, financial constraints, and lack of time. This highlights the need for further education regarding the benefits of exercise to not only patients, but clinicians and governments to improve the access to exercise. Examples of this could include more funding for community-based exercise programmes and specialised physiotherapy clinics. However, due to the individualised symptoms experienced in MS, many patients might find it difficult to attend in person sessions. The rise in telerehabilitation was seen throughout the pandemic and earlier research (Learmonth *et al.*, 2017) have suggested an increased adherence when using virtual workouts compared to in person regimes. This should be a consideration when designing future research. Multi-disciplinary teams should also prioritise patient-centred approaches, ensuring that interventions are tailored to the individual's specific needs and disease progression.

Strengths and Limitations

The papers included in this meta-analysis did not specially target individuals with impaired dynamic balance or walking endurance, rather they used these measurements to assess the overall efficacy of the intervention. While these symptoms are frequently reported among RRMS patients, symptom presentation varies, with some patients experiencing upper limb deficits rather than lower limb impairments. Moreover, several of the included studies did not use these measurements as their primary outcomes, instead reporting them as secondary outcomes alongside qualitative data. Future research should consider addressing these limitations by expanding the search criteria or refining the eligibility criteria.

The average EDSS range in the papers was between 4-5, given the progressive nature of the disease these finding could not be extrapolated to other patients with different EDSS scores or other subtypes such as PPMS or SPMS. This reduces the generalisation of the findings to primarily ambulant patients with RRMS. Similar limitations are noted by Heine *et al.*, (2015).

Although all the research papers had independent assessors for the measurements of the outcomes, there was no blinding of participants to the intervention as it was obvious they were performing exercise. As a result, the placebo effect could not be measured. Therefore, the validity of these findings are limited in comparison to results from double blinded research. Future research could compare results to control groups however the main limitation of blinding will always be present in the RCTs.

Although RRMS accounts for 75% of MS patients, many RCTs have eligibility criteria allowing for all types of MS. This resulted in several studies being excluded as the results were not split by subtype. Further RCT's should focus solely on one type as the nature of MS symptoms can be vastly different between them.

This research however demonstrates several key strengths. Following a comprehensive search on PubMed, it is thought to be the only meta-analysis specifically investigating the effects of exercise on walking endurance and dynamic balance in individuals solely with RRMS. This highlights a significant gap in the existing literature, providing a foundation for future research to expand upon. Furthermore, by focusing on research published within the past 10 years, this meta-analysis incorporates the most up-to-date evidence available. Additionally, the findings support exercise as a cost-effective, non-pharmacological intervention, demonstrating statistically significant improvements in dynamic balance and walking endurance among individuals with RRMS.

Future research

Considering the previously discussed limitations, future research should focus on translating these findings into clinical practice with larger samples sizes, refining eligibility criteria, and targeting patients with reduced walking endurance and dynamic balance. Additionally, further investigation is needed to explore the relationship between high intensity exercise and walking endurance.

Conclusions

This research achieved its aim of evaluating current research on exercise interventions and their effects on walking endurance and dynamic balance in RRMS patients. The findings of this paper led to the rejection of the null hypothesis for the overall impact exercise has on the TUG test and for both the higher and lower intensity subgroups. Similarly, the null hypothesis was also rejected when analysing the overall effect exercise has on the 6MWT and for the lower intensity subgroup. However further research is required to determine the effect high intensity exercise has on walking endurance.

While this research details significant gaps in the literature, particularly concerning design, sample sizes, and clinical implications, the broader consensus within the field remains that exercise is a powerful and essential tool in mitigating the decline in mobility observed in RRMS patients. Future research should focus on refining intervention protocols, optimising exercise intensity, and exploring long-term functional outcomes to further enhance clinical recommendations. Overall, these findings reinforce the critical role of structured exercise programs in improving mobility and overall quality of life for individuals living with RRMS.

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