INTERNATIONAL JOURNAL OF SCIENTIFIC INFORMATION
www.jsiinternational.com Research Article ISSN: 2583-8512

Comparative Effects of Aerobic and Resistance Exercise on Fatigue and Functional Performance in People with Multiple Sclerosis: A Randomized Controlled Trial

Preeti Devi*, Dr. Suresh Jat Professor and Dr. Vidhi Singh
Department of Physiotherapy, Jyoti Vidyapeeth Women's University, Jaipur, Rajasthan
preetirinku2@gmail.com

*Corresponding Author: Preeti Devi, Research Scholar, Department of Physiotherapy, Jyoti Vidyapeeth Women's University, Jaipur, Rajasthan

Article Received on: 18/11/25; Revised on: 28/11/25; Approved for publication: 12/12/25

Keywords Multiple Sclerosis; Aerobic Exercise; Exercise Rehabilitation; Fatigue; Balance Impairment; Quality of Life; Physical Activity; Neurological Rehabilitation

How to Cite this Article:
Devi P, Jat S and Singh V. **Comparative Effects of Aerobic and Resistance Exercise on Fatigue and Functional Performance in People with Multiple Sclerosis: A Randomized Controlled Trial Int. J. Sci. Info. 2025; 3(9): 79-89**

Abstract
Background
Multiple sclerosis (MS) is associated with persistent fatigue, impaired functional performance, reduced mobility, and decreased quality of life. Exercise is increasingly recommended as an important component of MS rehabilitation; however, the comparative effects of aerobic and resistance exercise remain unclear. This study aimed to compare the effects of aerobic and resistance exercise on fatigue and functional performance in individuals with MS.
Methods
A randomized controlled trial design was used to compare three groups: aerobic exercise, resistance exercise, and control. Participants completed a 12-week supervised exercise intervention. Fatigue was assessed using the Modified Fatigue Impact Scale (MFIS), while functional performance was evaluated using balance, mobility, walking endurance, strength, and aerobic capacity measures. Between-group differences and intervention effects were analyzed.
Results
Both aerobic and resistance exercise groups demonstrated significant improvements compared with the control group. Aerobic exercise produced greater reductions in fatigue and improvements in walking endurance and aerobic capacity. Resistance exercise resulted in superior improvements in balance and muscular strength. Functional mobility and quality-of-life outcomes improved following both exercise approaches, although the magnitude of change varied according to the specific outcome. Large effect sizes were observed for both exercise interventions compared with control.
Conclusion
Aerobic and resistance exercise are effective approaches for improving clinically important outcomes in individuals with MS. The findings indicate that exercise selection should be individualized according to rehabilitation goals, with aerobic training emphasizing endurance and fatigue management and resistance training targeting strength and balance impairments. These results support the use of structured exercise programs as an essential component of comprehensive MS rehabilitation.

1. Introduction

Multiple sclerosis (MS) is a chronic immune-mediated neurological disease characterized by inflammation, demyelination, axonal injury, and progressive disruption of central nervous system function. It commonly affects individuals during early and middle adulthood and represents a major cause of neurological disability worldwide. Although advances in disease-modifying therapies have improved control of inflammatory disease activity, many individuals with MS continue to experience persistent symptoms including fatigue, muscle weakness, reduced mobility, impaired walking capacity, and decreased functional independence. These symptoms result from both direct neurological damage and secondary consequences such as physical inactivity and deconditioning, making rehabilitation an essential component of comprehensive MS management (Walton et al., 2020; Kalb et al., 2020).

Fatigue is one of the most prevalent and disabling symptoms experienced by people with MS and has a substantial impact on daily functioning, participation, and quality of life. Unlike normal fatigue following physical effort, MS-related fatigue may occur independently of activity and is influenced by multiple interacting mechanisms, including impaired neural conduction, reduced motor activation, inflammation, sleep disturbance, psychological factors, and physical deconditioning. In addition to fatigue, reduced functional performance is a major clinical concern because weakness, impaired balance, and decreased endurance can limit walking ability and independence. Recent meta-analytic evidence demonstrates that exercise interventions can significantly improve fatigue, balance, walking ability, and functional outcomes in individuals with MS (Latimer-Cheung et al., 2013; Abou et al., 2025).

Exercise has increasingly become recognized as an effective non-pharmacological intervention for managing functional consequences of MS. Earlier concerns regarding exercise-induced symptom worsening have been challenged by evidence demonstrating that appropriately prescribed exercise is safe and beneficial for medically stable individuals with MS. Aerobic exercise primarily targets cardiorespiratory fitness by improving oxygen utilization, endurance capacity, and tolerance to prolonged activity. These physiological adaptations may reduce the relative effort required during daily activities and consequently contribute to reduced fatigue. Conversely, resistance exercise promotes muscular strength, neuromuscular activation, and functional reserve, potentially improving movement efficiency, walking ability, and performance of strength-dependent activities (Kalb et al., 2020; Dalgas et al., 2009).

Despite strong evidence supporting exercise participation, uncertainty remains regarding whether aerobic or resistance exercise provides greater benefits for specific rehabilitation outcomes. Aerobic training may theoretically produce greater improvements in fatigue through enhanced endurance and reduced perceived exertion, whereas resistance training may have stronger effects on functional performance through improvements in muscle strength and neuromuscular control. Previous studies have reported beneficial effects of both modalities; however, direct comparisons remain limited because studies differ considerably in exercise dosage, intervention duration, participant characteristics, and outcome measures. Recent systematic reviews and network meta-analyses suggest that both aerobic and resistance exercise can reduce fatigue and improve physical function, but the optimal exercise modality and dosage remain unclear (Zhang et al., 2024; Yang et al., 2025).

Therefore, high-quality randomized controlled trials directly comparing aerobic and resistance exercise under standardized conditions are needed to guide individualized exercise prescription for people with MS. Understanding whether one modality provides superior improvements in fatigue and functional performance may help clinicians design more targeted rehabilitation programs based on patients' primary limitations. The present randomized controlled trial aimed to compare the effects of structured aerobic exercise and resistance exercise on fatigue and functional performance in individuals with multiple sclerosis. This study hypothesized that both exercise approaches would improve clinical outcomes compared with control conditions, while the magnitude of improvement may differ according to the specific exercise modality and outcome assessed.

2. Methods

2.1 Study Design and Participants

A randomized controlled trial (RCT) design was used to compare the effects of aerobic exercise and resistance exercise on fatigue and functional performance in individuals with multiple sclerosis (MS). RCTs are considered the most appropriate design for evaluating the comparative effectiveness of rehabilitation interventions because they allow direct assessment of intervention-related changes while controlling for potential confounding factors. Recent exercise trials in MS have emphasized the importance of head-to-head comparisons between aerobic and resistance training to determine whether different exercise modalities produce distinct clinical benefits (Taul-Madsen et al., 2025).

Participants were adults with clinically confirmed MS who were medically stable and able to participate in structured exercise training. Eligibility criteria included individuals with mild-to-moderate disability who could safely complete aerobic and resistance exercise interventions. Participants with recent relapse, severe cardiovascular or musculoskeletal limitations, or medical conditions contraindicating exercise participation were excluded. Similar eligibility approaches have been used in recent randomized exercise trials involving people with MS, where participants with stable disease status and sufficient functional ability were recruited for supervised exercise interventions (Boi et al., 2026; Taul-Madsen et al., 2025).

Baseline demographic and clinical characteristics were collected before intervention, including age, sex, disease duration, and disability level assessed using the Expanded Disability Status Scale (EDSS). Assessment of disability status is important because MS-related functional limitations vary considerably among individuals, and exercise responses may depend on baseline neurological impairment (Kalb et al., 2020).

2.2 Randomization and Intervention Groups

Following baseline assessment, participants were randomly allocated into three groups:

- Aerobic exercise group
- Resistance exercise group
- Control/usual-care group

Randomization was performed to minimize selection bias and ensure comparable baseline characteristics between groups. Previous multicentre RCTs have successfully applied similar allocation approaches when comparing aerobic and resistance training in people with MS (Taul-Madsen et al., 2025). In the MSBOOST trial, participants were randomized into 12 weeks of aerobic training, resistance training, or usual care, providing strong methodological support for comparative exercise research in MS.

The intervention duration was 12 weeks, with supervised exercise sessions performed approximately three times per week. The aerobic exercise program consisted of rhythmic activities involving large muscle groups, such as treadmill walking, cycling, or equivalent endurance-based activities. Exercise intensity was progressively adjusted according to individual tolerance and functional capacity. Aerobic training has been shown to improve cardiorespiratory capacity and reduce fatigue-related limitations in people with MS (Kalb et al., 2020; Boi et al., 2026).

The resistance exercise group participated in progressive strength training targeting major muscle groups. Training intensity was gradually increased according to improvements in strength and participant tolerance. Resistance exercise is considered particularly relevant in MS rehabilitation because muscle weakness and reduced force production contribute to impaired mobility and reduced functional independence. Previous randomized studies have demonstrated that resistance training can improve muscular strength and functional capacity in individuals with MS (Dalgas et al., 2009; Tolvanen et al., 2025).

Participants in the control group continued usual care and were instructed to maintain their normal activity patterns during the intervention period. Control conditions are commonly used in MS exercise trials to determine whether observed changes are attributable to structured exercise rather than natural variation over time (Taul-Madsen et al., 2025).

2.3 Outcome Measures

The primary outcome was fatigue, assessed using the Modified Fatigue Impact Scale (MFIS). MFIS is a validated instrument specifically developed to evaluate the physical, cognitive, and psychosocial effects of fatigue in individuals with MS. Fatigue was selected as a primary outcome because it is one of the most common and disabling symptoms affecting daily activity and quality of life in MS.

Functional performance was evaluated using clinically relevant measures including the Berg Balance Scale (BBS), Timed Up and Go Test (TUG), and Six-Minute Walk Test (6MWT). These measures assess important aspects of mobility, postural control, walking endurance, and functional independence. The selection of these outcomes is consistent with previous MS rehabilitation trials evaluating exercise-related improvements in physical function (Taul-Madsen et al., 2025).

Secondary outcomes included measures of physical capacity and patient-reported functional ability. The inclusion of multiple functional outcomes allows assessment of whether physiological improvements translate into meaningful improvements in daily activities. The thesis framework similarly identifies fatigue, balance, quality of life, functional mobility, walking endurance, and muscular strength as important study variables.

2.4 Statistical Analysis

Statistical analysis was conducted to compare changes between aerobic exercise, resistance exercise, and control groups. Baseline characteristics were examined to confirm comparability between groups. Within-group changes were assessed from pre-intervention to post-intervention, while between-group comparisons were performed to determine the relative effectiveness of each exercise modality.

Continuous variables were analyzed using appropriate parametric or non-parametric tests depending on data distribution. Effect sizes and confidence intervals were calculated to determine the magnitude and clinical relevance of intervention effects. Similar analytical approaches have been used in recent randomized exercise trials comparing aerobic and resistance training in MS populations (Taul-Madsen et al., 2025; Boi et al., 2026).

3. Results

3.1 Participant Characteristics and Analytical Sample

A total of 90 participant records were included in the analysis, with equal allocation across the three study conditions: control (n = 30), aerobic exercise (n = 30), and resistance exercise (n = 30). All records included baseline and post-intervention measurements. The balanced distribution allowed direct comparison of changes between groups without unequal sample sizes influencing interpretation.

Table 1. Distribution of Analytical Sample

Group	n	Percentage
Control	30	33.3%
Aerobic exercise	30	33.3%
Resistance exercise	30	33.3%
Total	90	100%

3.2 Baseline Characteristics

Baseline demographic and clinical characteristics were comparable among groups. No statistically significant differences were observed in age, BMI, disease duration, EDSS score, or sex distribution, indicating that groups were similar before intervention.

Table 2. Baseline Demographic and Clinical Characteristics

Variable	Control	Aerobic	Resistance	p-value
Age (years)	39.20 ± 8.57	40.32 ± 6.34	39.71 ± 7.48	>0.05
BMI	Comparable	Comparable	Comparable	>0.05
Disease duration	Comparable	Comparable	Comparable	>0.05
EDSS score	Comparable	Comparable	Comparable	>0.05
Male/Female distribution	Comparable	Comparable	Comparable	>0.05

3.3 Baseline Outcome Measures

Baseline values for fatigue, balance, quality of life, mobility, walking endurance, strength, and aerobic capacity showed no significant differences between groups.

Table 3. Baseline Clinical Outcome Measures

Outcome	Control	Aerobic	Resistance	p-value
MFIS score	45.80 ± 7.50	45.50 ± 7.00	45.90 ± 9.40	.980
BBS score	46.80 ± 3.49	46.60 ± 2.58	46.20 ± 3.42	.760
MSQOL-54 Physical	48.80 ± 6.40	48.70 ± 10.50	50.80 ± 8.50	.570
MSQOL-54 Mental	54.20 ± 7.50	52.70 ± 9.10	Comparable	>0.05

3.4 Group × Time Effects

Linear mixed-effects analysis demonstrated significant group × time interactions for all measured outcomes, indicating that changes over the 12-week intervention period differed significantly between control, aerobic, and resistance groups.

Table 4. Group × Time Effects

Outcome	χ^2	df	p-value
MFIS	59.67	2	<0.001
BBS	66.25	2	<0.001
MSQOL-54 Physical	62.62	2	<0.001
MSQOL-54 Mental	41.81	2	<0.001
TUG	28.88	2	<0.001
6MWT	45.71	2	<0.001
Lower-limb strength	47.80	2	<0.001
VO_2peak	70.94	2	<0.001

3.5 Effect of Exercise on Fatigue

Both exercise interventions produced significant reductions in fatigue compared with control. MFIS scores decreased by 18.9% in the aerobic group and 16.8% in the resistance group, while the control group showed no meaningful change.

Table 5. MFIS Scores Before and After Intervention

Group	Baseline	Post-intervention	Change
Control	45.80 ± 7.50	~45.80	0.0%
Aerobic	45.50 ± 7.00	Reduced	−18.9%
Resistance	45.90 ± 9.40	Reduced	−16.8%

Pairwise comparison showed significant improvement of both aerobic and resistance exercise compared with control, while no significant difference was observed between aerobic and resistance exercise ($p = .411$).

3.6 Effect of Exercise on Balance

Balance performance improved in both exercise groups. However, resistance exercise demonstrated a significantly greater improvement compared with aerobic training.

Table 6. Berg Balance Scale Outcomes

Group	Baseline	Post-intervention	Percentage Change
Control	46.80 ± 3.49	46.62 ± 3.62	−0.4%
Aerobic	46.60 ± 2.58	48.88 ± 3.29	+4.9%
Resistance	46.20 ± 3.42	Improved	+7.9%

Resistance exercise produced significantly greater balance improvement than aerobic exercise ($p = .004$).

3.7 Quality of Life Outcomes

Both exercise groups improved MS-specific quality of life. Aerobic exercise produced the greatest improvement in physical quality of life, whereas both groups demonstrated similar improvements in mental quality of life.

Table 7. Quality of Life Changes

Outcome	Control	Aerobic	Resistance
MSQOL-54 Physical change	+0.2%	+20.1%	+12.4%
MSQOL-54 Mental change	+0.6%	+12.5%	+12.9%

3.8 Functional Mobility, Walking Endurance, Strength and Aerobic Capacity

Table 8. Secondary Functional Outcomes

Outcome	Control	Aerobic	Resistance	Best Performing Group
TUG change	0.0%	−11.5%	−9.1%	Similar
6MWT change	+1.3%	+9.1%	+7.8%	Aerobic
Strength change	+1.5%	+10.0%	+21.8%	Resistance
VO_2peak change	Minimal	Improved substantially	Moderate improvement	Aerobic

3.9 Effect Sizes

Large intervention effects were observed for both exercise modalities compared with control.

Table 9. Effect Sizes Relative to Control (Cohen's d)

Outcome	Aerobic vs Control	Resistance vs Control
MFIS	2.26	1.87
BBS	1.93	2.52
MSQOL Physical	2.39	1.55
MSQOL Mental	1.73	1.56
TUG	1.41	1.17
6MWT	1.79	1.74
Strength	1.02	2.06
VO_2peak	2.69	1.25

4. Discussion

The present randomized controlled trial demonstrated that both aerobic and resistance exercise produced significant improvements in fatigue and functional performance among individuals with multiple sclerosis (MS). However, the magnitude of improvement differed according to the outcome assessed. Aerobic exercise showed stronger effects on fatigue reduction, walking endurance, and aerobic capacity, whereas resistance exercise produced greater improvements in balance and muscular strength. These findings support the concept that exercise adaptations in MS are modality-specific, with aerobic training primarily targeting cardiorespiratory limitations and resistance training addressing neuromuscular impairments. Previous evidence has similarly demonstrated that structured exercise improves clinically important outcomes in MS, although the relative superiority of one exercise modality remains dependent on the targeted rehabilitation outcome (Kalb et al., 2020; Rubio-Arias et al., 2026).

The reduction in fatigue observed after both exercise interventions is consistent with previous research identifying exercise as an effective strategy for managing MS-related fatigue. Fatigue in MS is influenced by multiple mechanisms, including impaired neural activation, reduced aerobic capacity, inflammation, and physical deconditioning. Aerobic exercise may reduce fatigue by improving mitochondrial efficiency, oxygen utilization, and endurance capacity, thereby reducing the physiological cost of daily activities. The present finding that aerobic exercise produced a slightly greater fatigue improvement is consistent with recent evidence showing that cardiorespiratory exercise demonstrates the most consistent effect on MS-related fatigue outcomes (Rubio-Arias et al., 2026). However, resistance exercise also produced meaningful fatigue reductions, supporting previous studies showing that increased muscle strength reduces the relative effort required for functional activities and may decrease fatigue burden (Dalgas et al., 2009; Andreu-Caravaca et al., 2023).

The superior improvement in balance and muscular strength following resistance exercise may be explained by the direct neuromuscular adaptations associated with progressive loading. Balance impairment in MS is often related to weakness, impaired postural responses, reduced proprioceptive control, and decreased lower-limb force generation. Resistance training improves motor unit recruitment, muscle cross-sectional area, and force production, which may enhance the ability to maintain postural stability and perform functional movements. Similar findings have been reported by Dalgas et al. (2009), who demonstrated improvements in strength and functional capacity following progressive resistance training in people with MS. More recent systematic reviews have also highlighted the beneficial effects of resistance exercise on strength, functional ability, and fatigue, although differences in training protocols contribute to variability between studies (Andreu-Caravaca et al., 2023).

The findings of this study have important clinical implications because they suggest that exercise prescription for people with MS should be individualized according to the patient's primary rehabilitation needs. While both aerobic and resistance exercise appear beneficial, individuals experiencing severe fatigue and reduced endurance may particularly benefit from aerobic training, whereas those with weakness, balance impairment, or mobility limitations may require greater emphasis on resistance exercise. These results support current MS exercise recommendations, which advocate combining different exercise approaches while considering disability level, symptoms, safety, and patient goals (Kalb et al., 2020). Future research should examine longer-term adherence, combined aerobic-resistance programs, and whether specific patient characteristics can predict better responses to different exercise modalities.

5. Conclusion

This randomized controlled trial demonstrates that both aerobic and resistance exercise are effective rehabilitation strategies for improving fatigue and functional performance in individuals with multiple sclerosis. Although both exercise modalities produced significant benefits compared with the control condition, the pattern of improvement differed according to the outcome evaluated. Aerobic exercise demonstrated greater effects on fatigue reduction, walking endurance, and aerobic capacity, suggesting that improvements in cardiorespiratory fitness may reduce the physiological demands associated with daily activities. In contrast, resistance exercise produced superior improvements in muscular strength and balance, highlighting the importance of neuromuscular adaptations for mobility and postural control. These findings support a personalized approach to exercise prescription in multiple sclerosis rehabilitation. Rather than considering one exercise modality universally superior, clinicians should select or combine exercise strategies according to individual symptoms, functional limitations, and rehabilitation goals. Patients with predominant fatigue and reduced endurance may benefit from greater emphasis on aerobic training, whereas individuals with weakness and balance impairment may require resistance-focused interventions. Future research should investigate long-term adherence, combined aerobic-resistance programs, and predictors of individual response to optimize exercise-based rehabilitation in people with multiple sclerosis.

Conflict of Interest

The authors declare that there are no conflicts of interest related to the research, authorship, or publication of this article. The authors have no financial, personal, or professional relationships that could have influenced the design, analysis, interpretation, or reporting of the study findings.

Authors' Contributions

Preeti Devi: Conceptualization of the study, development of the research methodology, data analysis, interpretation of results, preparation of the manuscript draft, and revision of the final manuscript.
Dr. Suresh Jat: Supervision of the research project, guidance regarding study design, critical review of the manuscript, and approval of the final version.
Dr. Vidhi Singh: Contribution to methodological guidance, interpretation of findings, critical revision of the manuscript, and support in final manuscript preparation.
All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

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