



## Review article

# The effect of exercise training in adults with multiple sclerosis with severe mobility disability: A systematic review and future research directions



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## ARTICLE INFO

## Abbreviations:

2MWT2-min walk test  
6MWT6-min walk test  
ABCactivities-specific balance confidence scale  
BBSBerg Balance Scale  
BWSTbody-weight support treadmill training  
DGIDynamic Gait Index  
EDSSExpanded Disability Status Scale  
ESACElectrical stimulation assisted cycling  
FWSfast walking speed test  
HRQOLhealth-related quality of life  
MFISmodified fatigue impact scale  
MMTmanual muscle test  
MSmultiple sclerosis  
MSIS-29Multiple Sclerosis Impact Scale  
NNewtons  
PEDphysiotherapy evidence database  
RCTrandomized control trial  
SSWSelf-selected walking speed test  
TBRSTtotal body recumbent stepper training  
T25FWTtimed 25-foot walk  
TUGTimed Up-and-Go  
VO<sub>2</sub>volume of oxygen consumption

## Keywords:

Multiple sclerosis  
Exercise training  
Disability  
Mobility impairment

## ABSTRACT

**Introduction:** There is evidence for the benefits of exercise training in persons with multiple sclerosis (MS). However, these benefits have primarily been established in individuals with mild-to-moderate disability (i.e., Expanded Disability Status Scale [EDSS] scores 1.0–5.5), rather than among those with significant mobility impairment. Further, the approaches to exercise training that have been effective in persons with mild-to-moderate MS disability may not be physically accessible for individuals with mobility limitations. Therefore, there is a demand for an evidence-base on the benefits of physically accessible exercise training approaches for managing disability in people with MS with mobility impairment.

**Objective:** To conduct a systematic review of the current literature pertaining to exercise training in individuals with multiple sclerosis (MS) with severe mobility disability.

**Methods:** Four electronic databases (PubMed, EMBASE, OvidMEDLINE, and PsychINFO) were searched for relevant articles published up until October 2016. The review focused on English-language studies that examined the effect of exercise training in people with MS with severe mobility disability, characterized as the need for assistance in ambulation or EDSS score  $\geq 6.0$ . The inclusion criteria involved full-text articles that: (i) included participants with a diagnosis of MS; (ii) included primarily participants with a reported EDSS score  $\geq 6.0$  and/or definitively described disability consistent with this level of neurological impairment; and (iii) implemented a prospective, structured exercise intervention. Data were analyzed using a descriptive approach and summarized by exercise training modality (conventional or adapted exercise training), and by outcome (disability, physical fitness, physical function, and symptoms and participation).

**Results:** Initially, 1164 articles were identified and after removal of duplicates, 530 articles remained. In total, 512 articles did not meet the inclusion criteria. 19 articles were included in the final review. Five studies examined conventional exercise training (aerobic and resistance training), and thirteen studies examined adapted exercise modalities including body-weight support treadmill training (BWSTT), total-body recumbent stepper training (TBRST), and electrical stimulation cycling (ESAC). Outcomes related to mobility, fatigue, and quality of life (QOL) were most frequently reported. Two of five studies examining conventional resistance exercise training reported significant improvements in physical fitness, physical function, and/or symptomatic and participatory outcomes. Nine of 13 studies examining adapted exercise training reported significant improvements in disability, physical fitness, physical function, and/or symptomatic and participatory outcomes.

**Conclusions:** There is limited, but promising evidence for the benefits of exercise training in persons with MS with severe mobility disability. Considering the lack of effective therapeutic strategies for managing long-term disability accumulation, exercise training could be considered as an alternative approach. Further research is necessary to optimize the prescription and efficacy of exercise training for adults with MS with severe mobility disability.

## 1. Introduction

Multiple sclerosis (MS) is a chronic, neurological disease that affects 1 in 1000 people in the United States making it the most common non-

traumatic cause of neurological disability in young adults (Freeman, 2001). The disease is characterized by inflammation, demyelination and neurodegeneration within the central nervous system (CNS), and this damage results in functional impairments and symptomatic

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experiences. Unfortunately, these impairments and symptoms worsen as neurological disability increases (Motl and Learmonth, 2014).

An EDSS score of 6.0 (i.e., use of assistive device for ambulation) (Kurtzke, 1983) is a commonly reported benchmark of disease progression and disability (Confavreux et al., 2000, 2003). It is well documented that individuals with MS with an EDSS score of  $\geq 6.0$  have greater impairments in muscular fitness, aerobic fitness, mobility, and balance compared to individuals with lower disability scores (Motl and Learmonth, 2014; Pilutti et al., 2015; Sandroff et al., 2013; Motl et al., 2010; Sosnoff and Sung, 2015; Bakshi et al., 2000). Additionally, symptoms of fatigue, spasticity, depression and cognitive impairment become more severe with increasing disability (Amato et al., 2001; Bakshi et al., 2000; Benito-León et al., 2003; Flachenecker et al., 2014; Motl and McAuley, 2010; Sandroff et al., 2015). Physiological deconditioning induced by lower levels of physical activity likely contributes to these impairments with disability progression (Motl, 2010). Indeed, lower levels of physical activity have also been reported in individuals with MS with higher disability scores (Klaren et al., 2013).

Current disease-modifying agents have limited efficacy in preventing the accumulation of long-term disability in MS (Confavreux et al., 2003). Consequently, alternative strategies for disease management in persons with MS with severe mobility disability should be considered. One potential strategy is exercise training. There is evidence for the benefits of exercise training for improving walking performance, fitness, cognition, fatigue, anxiety, and depressive symptoms in persons with MS (Ensari et al., 2014; Pilutti et al., 2013; Platta et al., 2016; Sandroff et al., 2015; Snook and Motl, 2009). Despite these benefits, much of the current literature pertaining to exercise training in people with MS has focused on individuals with mild-to-moderate disability (i.e., EDSS scores 1.0–5.5) (Latimer-Cheung et al., 2013). This is problematic as individuals with MS with severe mobility disability are often excluded from studies of exercise training, limiting the evidence to those with mild-to-moderate MS disability. Furthermore, the exercise approaches that have been effective in persons with mild-to-moderate disability may not be physically accessible for individuals with MS with severe mobility limitations. Therefore, there is a demand for a comprehensive review of exercise training strategies that have been implemented for managing disability for people with MS with severe mobility disability.

Herein, we conducted a systematic review of exercise training interventions in persons with MS with severe mobility disability (EDSS  $\geq 6.0$ ) to: (i) evaluate and summarize the current evidence for the effects of exercise training on disability, physical fitness, physical function, symptoms, and participatory outcomes; (ii) evaluate the exercise training modalities and approaches applied; and (iii) identify current limitations and future research directions for exercise training in persons with MS with severe mobility disability. This review will provide a summary of the potential benefits of exercise training in persons with MS with severe mobility disability, and a future research agenda for developing effective strategies for managing disability through exercise training.

## 2. Methods

### 2.1. Article inclusion criteria and search strategy

This review focused on English-language studies that examined the effect of exercise training on disability, physical fitness, physical function, symptoms, and participatory outcomes in individuals with MS with severe mobility disability. Exercise training is defined as “planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness” (Bouchard et al., 1994). We conducted a search of four electronic databases (PubMed, EMBASE, OvidMEDLINE, and PsychINFO) using the search terms “multiple sclerosis” AND “exercise” OR “physical activity” OR “fitness” AND “advanced disability” OR “severe mobility disability” OR

“progressive” OR “robot”. This search was supplemented by an additional hand-search of the authors’ personal databases and relevant reviews and meta-analyses involving exercise training in persons with MS.

The inclusion criteria involved full-text articles that: (i) included participants with a diagnosis of MS; (ii) included primarily participants with a reported EDSS score  $\geq 6.0$  and/or definitively described disability consistent with this level of neurological impairment (e.g., use of an assistive device for ambulation); and (iii) implemented a prospective, structured exercise intervention per the definition of exercise previously described. For the purpose of this review, we selected an EDSS score of  $\geq 6.0$  as this is considered a robust disability landmark characterized by the need for assistance in ambulation (e.g., cane, walker) (Confavreux et al., 2000, 2003; Kurtzke, 1983). We included randomized and nonrandomized controlled trials, and pre-post intervention designs.

### 2.2. Article quality assessment

The quality of each article was determined using the Physiotherapy Evidence Database (PEDro) (Verhagen et al., 1998) scale for randomized control trials (RCTs) and the Downs and Black scale for non-RCTs (Downs and Black, 1998). The PEDro scale has a maximum possible score of 11 points, while the Downs and Black scale has a maximum possible score of 28 points. For both scales, a higher score is indicative of better methodological quality. Articles were independently evaluated by each of the authors. Scoring discrepancies between the authors were resolved by re-examining the articles and through discussion. The level of evidence of each article was categorized using the Spinal Cord Injury Rehabilitation Evidence (SCIRE) system (Eng et al., n.d.), a 5-level system that distinguishes between studies of differing quality and incorporates the types of research designs commonly used in rehabilitation research (Table 1). These scales have been used in several published systematic reviews and meta-analyses of exercise training in persons with MS (Ensari et al., 2014; Platta et al., 2016; Pilutti et al., 2013; Latimer-Cheung et al., 2013).

### 2.3. Descriptive approach and data summary

Considering the limited number of studies that were retrieved and the variability in the outcomes included across studies, we did not attempt a meta-analytic approach. After review of the articles for inclusion, relevant data was extracted from each manuscript. Data were extracted by one member of the research team (TAE), and verified by a

**Table 1**

Level of evidence and criteria applied to studies included in the review based on the Spinal Cord Injury Rehabilitation Evidence (SCIRE) system.

Level of evidence	Criteria
Level 1 (n = 5)	<ul style="list-style-type: none"> <li>• <b>RCT:</b> PEDro Score &gt; 6. Includes cross over design with randomized experimental conditions and within-subjects comparison.</li> </ul>
Level 2 (n = 0)	<ul style="list-style-type: none"> <li>• <b>RCT:</b> PEDro Score <math>\leq 6</math>.</li> <li>• <b>Prospective controlled trial:</b> non-randomized.</li> <li>• <b>Cohort:</b> longitudinal study using two (minimally) similar groups with one group being exposed to a condition.</li> </ul>
Level 3 (n = 0)	<ul style="list-style-type: none"> <li>• <b>Case-control studies:</b> retrospective study comparing controls conditions.</li> </ul>
Level 4 (n = 13)	<ul style="list-style-type: none"> <li>• <b>Pre-post:</b> trial with a baseline measure, intervention and a post-test using a single group of subjects.</li> <li>• <b>Post-test:</b> post-test with 2 or more groups using a single group (intervention followed by a post-test with no retest or baseline assessment).</li> </ul>
Level 5 (n = 0)	<ul style="list-style-type: none"> <li>• <b>Observational:</b> study using cross sectional analysis to interpret relations.</li> </ul>

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