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# Rationale and design of a randomized controlled, clinical trial investigating a comprehensive exercise stimulus for improving mobility disability outcomes in persons with multiple sclerosis

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ABSTRACT

This randomized controlled trial (RCT) examines the effect of a comprehensive exercise training stimulus on physiological function and mobility disability (i.e., problems walking) in individuals with multiple sclerosis (MS) who have walking impairment. This trial will recruit 30 persons with MS across central Illinois who have an Expanded Disability Status Scale score between 4.0 and 6.0, and those persons will be randomized into either the intervention or control arm of the study; the participants will not be blinded regarding group assignment. The intervention will incorporate equal amounts of aerobic, resistance, and balance modes of training delivered 3 times/week with a gradual progression of duration and intensity across a 6-month period. The control will involve stretching along with minimal muscle strengthening stimuli and will be delivered on the same frequency and duration. The primary outcomes will be clinical, kinematic, patient-rated, and physiological measures of mobility disability. The secondary outcomes will be measures of physiological function including aerobic capacity, muscle strength, and balance. This study will lay the foundation for the design of a subsequent Phase II or Phase III RCT by (a) providing effect sizes that can be included in a power analysis for sample size estimation and (b) investigating whether aerobic capacity, muscle strength, and balance are possible factors associated with the beneficial effect of exercise training on walking outcomes. Taken as a whole, the proposed study and our subsequent research agenda has the potential for advancing the management of mobility disability using exercise training in the 2nd stage of MS.



## 1. Introduction and background

Multiple sclerosis (MS) has an estimated prevalence of 1 per 1000 persons in the United States [1,2]. This disease typically begins with intermittent bursts of focal inflammation in the central nervous system (CNS) [3] and results in the demyelination and transection of axons in the brain, optic nerves, and spinal cord [4]. The axonal damage results in conduction delay and conduction block of electrical potentials along CNS pathways [5]. This disease process results in progressive mobility disability and might be exacerbated by physiological deconditioning brought about by physical inactivity that is often observed in MS [6–8].

Mobility disability (i.e., impairment of ambulation) is a ubiquitous and life altering feature of MS [9], and the rate and predictors of its progression vary based on the stage of this disease [10]. The median time from onset of MS until reaching an initial benchmark of mobility disability, characterized by an Expanded Disability Status Scale (EDSS) score of 4.0 (i.e., limited walking ability, but able to walk more than 500 m without aid or rest), is approximately 10 years [10–12]. The rate of progression

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in this "1st stage of MS" has been predicted by sex, age, symptoms and course at onset of disease, degree of recovery from the 1st relapse, time to a second neurological episode, and number of relapses in the 1st 5 years of the disease [10–12]. By comparison, the median time for further progression of mobility disability, characterized by the transition from an EDSS score of 4.0 to an EDSS score of 6.0 (i.e., ability to walk with unilateral support no more than 100 m without rest), is approximately 5 years. The rate of progression in this "2nd stage of MS" is usually considered irreversible as it is invariant with respect to baseline characteristics, course, signs and symptoms assessed at the onset of disease [10–12]. Importantly, the attainment of an EDSS of 4.0–6.0 in persons with MS typically involves severe disability in one or more of the Functional Systems, particularly pyramidal and cerebellar [13], and gait limitations presumably involve contributions from aerobic deconditioning, muscle weakness and spasticity, and balance problems [14–16].

There are 5 disease modifying agents developed over the past 2 decades that represent first-line treatments for slowing disease progression in MS [17]. For example, the early use of disease modifying agents (e.g., Interferons) has decreased the number of lesions seen through magnetic resonance imaging and the rates of both relapses and disease progression [18,19]. Unfortunately, disease modifying agents delivered in clinical practice often yield suboptimal response regarding treatment efficacy, perhaps because of side effects and poor patient compliance [17]. Disease modifying agents are only modestly effective in slowing the eventual progression of disability in the 2nd stage of MS [10–12,20]. Indeed, the long-term course of MS is characterized by progression in mobility disability—despite ongoing treatment with disease-modifying therapies [19,20]; there are insufficient data indicating that more recently developed oral medications will demonstrate better efficacy rates over time [17]. This limited long-term efficacy might be explained, in part, by disease-modifying agents having minimal effect on physiological deconditioning as one potential latent contributor to mobility disability.

Physiological deconditioning plays an important role in the accumulation of mobility disability in persons with chronic disease conditions [6], including MS [14,21]. There is substantial evidence for deconditioning in MS, including reductions in aerobic capacity, muscle strength, and balance [22–24]. Those parameters of physiological function, in turn, are major influences of mobility disability in senescence [25,26] and neurological disease conditions [27]. Physiological deconditioning often results from physical inactivity [28], and there is evidence that exercise training improves physiological function, attenuates mobility disability, and increases physical activity in persons with MS [8,29].

Exercise training has a variety of beneficial consequences in persons with MS, including positive effects on physiological function and mobility disability [24,29–32]. One meta-analysis has supported a small, but clinically meaningful, improvement in walking mobility after exercise training in persons with MS [33]. Of note, the majority of previous exercise training research has been conducted in samples with minimal disability (e.g., EDSS scores $< 4.0$) rather than among those in the 2nd stage of MS who have reached a benchmark of ambulatory impairment (e.g., EDSS scores $\geq 4.0$) [24,29,31,33]. Additional concerns include the lack of focus on factors such as physiological function that might account for an improvement in mobility disability; general inclusion of a single mode of training rather than a comprehensive regimen that includes multiple modes of training (e.g., aerobic, resistance, & balance training) [24,29]; relatively brief (e.g., 2–3 months) rather than longer (e.g., 6 months) intervention periods [24,29]; and lack of a credible control condition that accounts for attention, social contact, and participant expectations [29,33].

We further base the development of an exercise training program for MS on previous randomized controlled trials (RCTs) in neurological diseases such as stroke; this body of literature is more advanced than that of MS and might be useful for informing the proposed work. For example, a recent Cochrane review examined the effects of exercise training (i.e., cardiorespiratory, strength, or both) on primary outcomes of death, dependence, and disability, along with secondary outcomes of physical fitness, mobility, and physical function, in stroke patients [34]. The review located 32 trials with 1414 participants with exercise regimens comprising cardiorespiratory (14 trials), resistance (7 trials), and mixed training (11 trials). The overall conclusions were that cardiorespiratory training that involved walking was associated with improved maximum walking speed, walking endurance, and reduced dependence on an assistive device during walking. The literature was characterized by too few resistance training and mixed training trials for conclusions about changes in mobility outcomes; lack of credible attention control conditions that involve minimal physical activity; and few studies of long-term training effects. Some of the recommendations for future work on exercise training in stroke included examinations of the optimal regimen for improving mobility and fitness outcomes; trials lasting longer than 12-weeks; and matching the exposure of training in the intervention and control conditions. Collectively, research in stroke largely paralleled the conclusions and recommendations for research in advanced stages of MS and further informed the development of the exercise training regimen in this application.

This RCT involves a "proof of concept" investigation of a 6 month, comprehensive (i.e., aerobic, resistance, & balance) exercise training intervention versus a minimal exercise (i.e., stretching along with minimal muscle strengthening stimuli for maintaining participant interest), attention control condition on physiological function and mobility disability among persons in the 2nd stage of MS (i.e., EDSS score of 4.0 – 6.0). This study will lay the foundation for the design of a future Phase II or Phase III RCT by (a) providing effect sizes that can be included in a power analysis for sample size estimation and (b) investigating whether aerobic capacity, muscle strength, and balance (i.e., physiological function) are possible factors accounting for the beneficial effect of exercise training on mobility disability.

## 2. Methods

### 2.1. Study design, overview, and hypotheses

The proposed study, data collection, and intervention will take place in the Exercise Neuroscience Research Laboratory on the University of Illinois at Urbana-Champaign located in central Illinois. The study will use a two-arm RCT design to examine the effect of a comprehensive exercise training stimulus versus a minimal exercise, attention control condition on physiological function and mobility disability in individuals with MS who