# Gait Rehabilitation and Monitoring in Multiple Sclerosis; Optimal Rehabilitation Interventions, Longitudinal Changes, Sex Differences and the Protective Role of Cardiorespiratory Fitness

By

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# Abstract

Multiple sclerosis (MS) is a chronic demyelinating and autoimmune disease of the central nervous system, characterized by episodes of new or worsening neurologic symptoms, followed by partial or complete recovery. Despite an expanding body of literature on the effectiveness of exercise in MS, the optimal approaches to improve gait are lacking. Notably, people with MS often have low levels of cardiorespiratory fitness, limiting their exercise capacity. Furthermore, covert gait changes precede clinical signs, often not detectable on observation, and measurement of subtle changes in gait, such as variability, could be a potential biomarker of covert neurodegeneration. Both cognition and fitness could influence changes in gait variability over time. The purpose of my doctoral work was to systematically review the optimal interventions to improve gait speed, the intricate relationship between cardiorespiratory fitness, and gait variability—a potential longitudinal biomarker of covert gait changes.

The first study critically synthesized randomized controlled trials, consolidating knowledge on optimal rehabilitation interventions to improve gait speed in individuals with MS. Lower limb resistance and treadmill training emerged as the most effective interventions. Overall, there was a positive albeit small effect of interventions on gait speed in individuals with MS. The second study focused on the early detection of covert gait changes in clinically stable people with MS and highlighted gait variability as a sensitive longitudinal biomarker. Notably, it proposed the protective role of cardiorespiratory fitness against covert worsening of gait variability over two years in individuals with MS. The third study assessed cardiorespiratory fitness and examined its association with self-reported moderate to vigorous physical activity, with an emphasis on sex-related differences. The findings showed that males and females had low levels of

cardiorespiratory fitness. Furthermore, there was an agreement between self-reported physical activity and aerobic fitness only in females, indicating potential over-reporting by males. This comprehensive thesis contributes valuable insights into treatments and monitoring of gait in MS, specifically identifying optimal rehabilitation interventions, identifying gait variability as a potential longitudinal biomarker for covert neurodegeneration, the protective role of cardiorespiratory fitness and sex differences in fitness and reporting of physical activity.

Keywords: Cardiorespiratory Fitness; Gait variability; Multiple sclerosis; Rehabilitation; Sex differences

Word count- 342/350

## General Summary

Multiple sclerosis (MS) is a chronic progressive disease that leads to walking problems. There is a large body of literature related to exercise in people with MS. Because of that, rehabilitation providers face challenges in determining and understanding the most effective options for improving walking function in people with MS. Also, the capacity to exercise is low in people with MS. Furthermore, silent walking changes occur before visible symptoms appear in people with MS. Early identification of those changes is important to halt the disease progression. In my doctoral work, I addressed these gaps by reviewing the existing literature related to rehabilitation interventions, assessed walking changes over time and the factors that could predict those changes, and investigated fitness levels in both males and females with MS.

In my first study, I reviewed the existing literature, using a systematic approach with meta-analysis, and showed that exercise has a positive effect on walking speed and notably, lower limb resistance and treadmill were the most effective approaches in people with MS. In my second study, I investigated the changes in walking over two years in clinically stable people with MS and showed that walking changes occur even before the patient or physician notices it. I also showed that higher fitness levels appeared to protect against worsening of walking over time, indicating the protective role of fitness in maintaining walking function.

Building on this second study, in my third study, I assessed the fitness levels and self-reported physical activity levels in both males and females with MS. Both males and females had low levels of fitness, while the agreement between self-reports and objectively measured fitness was significant in females only, indicating the need for considering sex differences in fitness appraisal tests and the interventions to improve fitness in people with MS. The results of

my doctoral work identify optimal rehabilitation to improve gait speed and support the potential use of walking changes as a marker of disability progression and the role of fitness in preserving walking function in MS. More importantly, these findings contribute to our understanding of MS management and may inform personalized approaches to improve walking for people with MS.

Word count- 347/350

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# Table of Contents

# List of Tables

# List of Figures

## List of Symbols, Nomenclature, or Abbreviations

| | |
|---|---|
| CV | Coefficient of Variation |
| CI | confidence interval |
| EDSS | Expanded Disability Status Scale |
| MS | Multiple Sclerosis |
| mWT | meter Walk Tests |
| PEDro | Physiotherapy Evidence Database |
| PIRA | Progression independent of relapse activity |
| PT | Physiotherapy |
| PMS | Primary progressive MS |
| PwMS | People with Multiple Sclerosis |
| RCT | Randomized controlled trial |
| RRMS | Relapsing-remitting MS |
| SPMS | Secondary progressive MS |
| STV | Stride Time Variability |
| T1 | Time point 1 |
| T2 | Time point 2 |
| VR | Virtual Reality |
| $VO_{2max.}$ | maximal oxygen uptake |
| WBV | Whole body vibration |

# Chapter 1 Introduction

## 1.1 Prevalence of Multiple Sclerosis

Multiple sclerosis (MS) is a chronic demyelinating and autoimmune disorder affecting the central nervous system. MS affects individuals in their career-building years, most commonly between the ages of 20 and 40 years [1]. The global prevalence of MS has been on the rise since 2013, affecting approximately 2.8 million people worldwide [2]. Canada has one of the world's highest rates of MS, with over 90,000 individuals affected, equating to 1 in every 400 people [3]. Approximately 4,377 Canadians are diagnosed with MS annually, at an average age of 43 years, with 75% of those affected being women and 90% initially diagnosed with relapsing-remitting forms of MS [3]. Future projections suggest an increase in MS prevalence to 430 cases per 100,000 population by 2031, corresponding to 133,635 Canadians living with MS by 2031 [4]. The anticipated annual healthcare costs are projected to reach $2.0 billion [4]. Since MS impacts young people's lives and poses a considerable economic burden, there is an urgent need to develop better treatments to reduce gait disability and test the efficacy and safety of the existing treatments to reduce the disease burden.

While the exact cause of MS remains unknown, evidence shows that genetic predisposition, along with environmental and lifestyle factors, contributes significantly to MS susceptibility. An umbrella review of 44 meta-analyses with 416 studies investigating risk factors for MS susceptibility reported compelling and consistent evidence that anti-Epstein-Barr virus nuclear antigen IgG seropositivity, smoking, and infectious mononucleosis are the strongest associated factors in the development of the disease [5].

### 1.2 Incidence of Multiple Sclerosis

Population-based studies show that MS incidence varies in racial-ethnic minorities, with a higher incidence rate in black people (10.2) and lower in Hispanics (2.9) and Asians (1.4) than whites (6.9) [6] . The incidence rate is higher among women than men, with a progressively increasing female-to-male ratio of 3:1 [6]. The primary risk factor for MS is linked to the gene HLA-DRB1 *15 with an odds ratio of developing MS >3 and >6 for heterozygotes and homozygotes, respectively [7]. However, the mechanism is not clear.

Other factors, such as exposure to sunlight and vitamin D levels [8], adolescent obesity [9], geographical latitudes at the population level [10], and Epstein Barr virus [11] have been strongly associated with MS, indicating a complex interplay between genetic and environmental factors. Recent migration studies reveal a noteworthy trend where adults relocating from low-risk countries to high-risk countries exhibit a lower risk of developing MS [12]. Conversely, children who migrate to high-risk countries at a young age are at an increased risk of developing MS [12]. This evidence underscores the substantial impact of environmental factors compared to genetics on MS susceptibility, indicating the significance of preventive studies to mitigate the risk of developing MS [13].

### 1.3 Pathophysiology of MS

In a healthy brain, the blood-brain barrier functions as a tight junction, imposing significant restrictions on the entry of leukocytes (immune cells) and contributing to maintaining homeostasis within the central nervous system. In MS, the blood-brain barrier disrupts, allowing infiltration of the leukocytes [14]. This dysregulated immune response plays a crucial role in the onset and progression of MS [14]. The infiltrating leukocytes damage the oligodendrocytes

(myelin-producing cells) through the secretion of cytotoxic mediators. Cells from both the innate and adaptive immune systems, particularly CD4+ T helper cells, including T helper cells1 and 17 , along with CD8+ T cytotoxic cells, B cells, monocytes, macrophages, and natural killer cells, have been responsible for the pathogenesis of MS [15]. The plasma cells produce antibodies that attack oligodendrocytes and break down myelin, further forming scars. As described by Charcot, the pathological hallmark of MS is the formation of scars *'sclerose en plaques'* [16]. These sclerosed plaques are commonly seen in periventricular areas of the brain [15]. Later, T-regulatory cells control the inflammatory process, and anti-inflammatory cytokines such as IL-10, IL-27, and interferon beta are thought to act on lymphocytes and suppress the inflammation [17]. Neurodegeneration in MS is likely due to damage to oligodendrocytes, while premature oligodendrocytes are abundant, they often fail to differentiate into mature oligodendrocytes, leading to inefficient remyelination[18]. Therefore, targeting remyelination is considered one of the neuroprotective strategies in MS.

MS disease course significantly varies, with relapsing-remitting MS (RRMS), the most common form (about 80%), which may transition to secondary progressive MS (SPMS) in some individuals while other people present with primary progressive MS (about 10%; PPMS) [19]. In all forms of MS, inflammation is a common factor; however, RRMS primarily involves the peripheral immune compartment and loss of BBB integrity, while progressive forms exhibit compartmentalized infiltrates in the meninges and perivascular space, along with slowly expanding and smouldering lesions [15,20].

### 1.4 Covert Neurodegeneration in Multiple Sclerosis

Focal white matter lesions are detected on magnetic resonance imaging scans in people with MS; however, evidence shows a limited correlation between the lesion load and clinical disability [21]. This may be due to the covert neurodegeneration, evidenced by clinically silent lesions, even in newly diagnosed MS patients or those with mild disability [21]. The silent disease progression is thought to be attributed to diffuse axonal injury in the normally appearing white matter [22]. Another determinant of disease accumulation is the progression independent of relapse activity (PIRA), commonly seen in RRMS [23]. Researchers argue that PIRA is associated with slowly expanding brain lesions and highlights the need to identify the subtle changes and covert neurodegeneration in patients with RRMS [24]. Due to the heterogeneity of MS disease course, assessing silent progression is challenging. Structural biomarkers such as MRI [24-26] , optical coherence tomography [27] and serum biomarkers, such as neurofilament light chain [28] and glial fibrillary acid protein [29], are being tested to identify subtle disease progression. Despite the significance of these biomarkers, the clinical evaluation of functional limitations related to walking, including spatiotemporal parameters such as gait variability, helps in the early detection of disease progression [30]. Moreover, longitudinal analysis, which involves tracking changes over time, is important in understanding the natural evolution of disease progression. This approach enables healthcare professionals to identify covert neurodegeneration even in individuals with MS who may appear clinically stable [31].

### 1.5 Gait problems in people with MS

Over 70% of people with MS report gait impairments, which typically occur in early adulthood (20-40 years), than in other neurological diseases such as [32] stroke [33] or Parkinson's disease [34]. Consequently, the potential negative impacts of gait impairments in MS are

substantial. Gait impairment often results in reduced community participation, physical inactivity and poor quality of life [32]. Various clinical, performance, physiological, and kinematic measures have been used to document the extent of walking impairment in people with MS [35]. Expanded Disability Status Scale (EDSS) is a widely used clinical tool to quantify and monitor walking disability and progression [36]. EDSS scores of 4.0 (able to walk >500m without aid or rest) and 6.0 (able to walk no more than 100 meters without rest with the use of unilateral aid) are the most common clinical disability benchmarks [36]. Approximately 50% of people with MS reach these benchmarks within 10-20 years of disease onset [37]. Other performance tools used to quantify walking impairment are short walk tests (10-meter walk test-10MWT), timed 25-foot walk test -T25WT) and long walk tests (6-minute walk tests) [35]. The timed walking tests estimate walking speed while the distance walked in a specified time estimates walking endurance. Deteriorations in walking speed and endurance suggest disability progression in MS [37]. Physiological measures of walking quantify the energetic or oxygen ($O_2$) cost of walking measured in millilitres of oxygen per one kilogram of body weight per one meter walked. The oxygen cost of walking is significantly higher in people with MS than in healthy peers [38]. Furthermore, the oxygen cost of walking was strongly associated with subjective reports of walking difficulty estimated using Multiple Sclerosis Walking Scale-12 scores, indicating that people with MS require greater energy and walking is inefficient [39]. Other kinematic measures of walking [40], such as spatial and temporal parameters of the gait cycle, help determine walking impairments and are important endpoints in rehabilitation trials. Evidence showed reduced speed, cadence, stride and step length, and increased gait variability in people with mild MS than age and sex-matched controls [40-42]. These findings allude to the degree of walking impairment and the breadth of measurement tools in MS.

Notably, walking impairments in MS result in physical inactivity, leading to physiological deconditioning [43]. Deconditioning, in turn, reduces cardiorespiratory fitness, muscle strength and balance, further affecting physical functioning and leading to sedentary behaviours [43]. A growing body of evidence supports that exercise helps to decrease physiological deconditioning and walking disability in chronic neurological conditions, including MS [44].

### 1.6 Rehabilitation interventions to improve gait in MS

MS, with no known cause and cure, is treated with disease-modifying drugs, corticosteroids for acute exacerbations and symptomatic treatment [13]. Although pharmacological treatments aim to reduce relapse rate and lesion load, their effectiveness in managing common symptoms such as gait impairment and preventing disability progression is limited [45-47]. Non-pharmacological interventions such as exercise were shown to effectively address gait impairments [48]. Currently, various interventions such as resistance training [49-51], task-specific training such as treadmill training with and without body weight support [34,52-55], aquatic exercises [56], yoga [57,58], Pilates [59-64], intervention combined with robotic gait [65-70], virtual reality [54,55,71-74], and exergaming [75-77] are commonly tested to improve gait in MS. A key point of discussion arises from the variability in intervention dosages across different studies. For instance, one study demonstrated that 36 sessions of body weight support treadmill training resulted in a significant increase in gait speed from 0.31m/s to 0.44 m/s, with a mean change of 18% from baseline on the T25FWT [78]. In contrast, another study reported a notable decrease in the time taken to complete the T25FWT, a 31% improvement in gait speed after only twelve sessions of body weight support treadmill training [68]. Additionally, after 15 sessions of robotic-assisted gait training, gait speed increased from 0.21m/s to 0.27 m/s [79]. These findings allude to the fact that there exists a knowledge gap about optimal rehabilitation interventions to improve gait in MS.

This leaves rehabilitation providers with inadequate knowledge about intervention dosage that works best for people with MS. Hence, it is important to determine the effectiveness of these interventions through further research and meta-analyses, considering factors such as intervention duration, modality (conventional or adapted) and mode of delivery (in-person or virtual) to better inform rehabilitation providers and optimize interventions for improving gait in MS. Furthermore, early detection of subtle gait changes and factors that could predict those changes over time is also important. This helps to identify disease progression and disability in people with MS.

### 1.7 Rationale/Objectives of the studies

The ultimate goal of my doctoral work is to advance the understanding of MS management by elucidating effective gait rehabilitation interventions, identifying the factors that could predict covert gait changes and highlighting the association between objective and self-reports of physical activity in males and females with MS.

The rationale was to address critical gaps in understanding and improving the management of gait problems in MS, a common clinical manifestation of MS. Therefore, the first stage of my doctoral work was to consolidate existing evidence on rehabilitation interventions to enhance gait speed, recognizing the importance of mobility for their overall well-being in people with MS [80,81]. All the randomized controlled trials (RCT) published before June 2023 were reviewed and finally 90 RCTs were included. The studies were categorized into 10 groups based on the type of intervention tested. I also computed effect sizes for 77 RCTs to determine the effectiveness of rehabilitation interventions in improving gait speed. The findings of this comprehensive systematic review and meta-analysis would provide rehabilitation clinicians with adequate

knowledge about the optimal rehabilitation interventions to improve gait speed in people with MS.

My second study investigated covert gait changes in people with MS with no to mild walking disability (EDSS<4.0). Subtle gait changes may not be evident on observation. The covert neurodegeneration in the brain might cause changes in the gait, which was evident as 'gait variability.' I also assessed whether cardiorespiratory fitness or cognition could predict the change in gait variability over two years in clinically stable people with MS. This included determining predictors of gait change while controlling for age, sex, time between assessments, and gait variability at year one. The findings of this study paved the path for my third study to assess cardiorespiratory fitness levels and their association with subjective reports of moderate to vigorous physical activity in males and females with MS.

### 1.8 Specific objectives of the studies

The three stages of my thesis are described separately in Chapters 2, 3, and 4. Chapter 1 is the thesis Introduction, and Chapter 5 is the thesis Discussion.

Chapter 2. The aim of this study was to systematically review tested rehabilitation interventions and determine their effectiveness through a quantitative synthesis, specifically focusing on determining the optimal approaches to improve gait speed in people with MS. This study has been submitted to the Journal of Neurologic Physical Therapy.

Chapter 3. The aim of this study was to evaluate the longitudinal changes in gait among clinically stable individuals with MS and determine whether baseline levels of fitness or cognition could predict covert gait changes. At year one (T1), gait (gait speed and stride time variability) was assessed using an instrumented walkway (1.2 × 4.3 m, Protokinetics, Havertown,

USA), cardiorespiratory fitness ($VO_{2max}$) during exercise on a whole-body recumbent stepper (NuStep, Ann Arbor, Michigan, USA) and cognition using Montreal Cognitive Assessment (MoCA). At year 2 (T2), gait was reassessed using the same instrumented walkway. Finally, I assessed the changes in stride time variability and the factors that predicted the change when controlling for baseline characteristics such as age, sex, time between assessments and stride time variability at T1. This study has been submitted to the Gait & Posture Journal.

Chapter 4. Based on my findings demonstrating that cardiorespiratory fitness is important in predicting the gait variability over two years in clinically stable people with MS, my next study investigated cardiorespiratory fitness levels in people with MS and their association with self-reported moderate to vigorous physical activity (MVPA). I focused on the relationships between self-reported MVPA, $VO_{2max}$, and disability status (EDSS), with an emphasis on potential sex differences. Lastly, I also determined whether self-reported MVPA could predict $\dot{V}O_{2max}$ in females and males with MS. This study has been accepted in the MS International Journal and will be published soon.

**Co-authorship statement**

Chapter 1 Introduction

Author. Syamala Buragadda

Author contributions: SB contributed to all aspects of Chapter 1 and had main responsibility for writing this chapter. Michelle Ploughman edited this Chapter.

Chapter 2 Optimal rehabilitation interventions to improve gait speed in people with MS: A systematic review and meta-analysis

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Author contributions: SB designed and contributed to all aspects of the study and had main responsibility for writing the manuscript. KR contributed to the literature search. SR, AB, AC, EM, SH, LP, and HM contributed to screening, quality assessment and data extraction. JM contributed to cleaning and data visualization. MP supervised the study and edited the manuscript. This study has been submitted to the Journal of Neurologic Physical Therapy and is under review.

Chapter 3: Cardiorespiratory fitness protects against covert worsening of gait variability over two years in people with multiple sclerosis

Syamala Buragadda and Michelle Ploughman

Author contributions: SB designed the study, collected, cleaned, analyzed the data, interpreted the findings, wrote, edited, and submitted the manuscript. MP supervised the study, funding acquisition and edited the manuscript. This study has been submitted to the Gait & Posture Journal and is under review.

Chapter 4: Incongruence between cardiorespiratory fitness and subjective reports of physical activity in multiple sclerosis: A focus on sex differences

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Author contributions: SB designed the study, collected, cleaned, analyzed the data, interpreted the findings, and wrote the manuscript. NJS contributed to analysis, visualization, reviewing and edited the manuscript. AG and JNM contributed to the investigation and data curation. CJN administered the project and data curation. MP conceptualized and supervised the study, funding acquisition, and edited the manuscript. This study has been accepted in the MS International Journal.

Chapter 5 Discussion

Author. Syamala Buragadda

Author contributions: SB contributed to all aspects of Chapter 5 and had main responsibility for writing this chapter. Michelle Ploughman edited this Chapter.

# Chapter 2 Optimal rehabilitation interventions to improve gait speed in multiple sclerosis: A systematic review and meta-analysis


## Abstract

**Background and Purpose:** Despite an expanding body of literature on the effectiveness of rehabilitation interventions in multiple sclerosis (MS), optimal approaches to improve walking are lacking for rehabilitation providers.

**Methods:** We systematically searched articles from electronic databases published before June 2023. We included rehabilitation interventions that were ≥ 3 weeks in duration, with gait speed assessed as an outcome. Independent reviewers screened and extracted data and Physiotherapy Evidence Database (PEDro) scale to assess study's methodological quality. We calculated effect sizes as standardized difference in means (Cohen's d) using a random effects model.

**Results:** The initial search identified 5,447 studies, with 90 RCTs meeting the inclusion criteria. Based on type of rehabilitation interventions tested, studies were categorized into lower limb resistance, treadmill, whole body vibration, overground and robotic gait, home exercises, Pilates and yoga, individualized in-person and virtual physiotherapy, balance, aerobic and resistance groups. The overall effect size (77 articles; 3,276 participants) indicated a positive impact of interventions on gait speed (d=0.23; 95% confidence interval (CI), 0.1, 0.36; P<0.001). Sub-group analysis showed that lower limb resistance (d=0.70; 95% CI, 0.42, 0.98; P<0.001) and treadmill training (d=0.52; 95% CI, 0.23-0.81; P<0.001) were most effective. Heterogeneity analysis revealed variation in the effect size across studies (Q=210.8; df-76; p<0.001) with a variance ($I^2$) of 64%. Most studies (72.2%) exhibited good methodological quality (PEDro score 6 to 10).

**Discussion and Conclusions:** Despite heterogeneity across studies, our review showed an overall positive but small effect of rehabilitation interventions on gait speed in individuals with MS. Notably, lower limb resistance and treadmill training emerged as the most effective interventions.

Keywords: exercise; multiple sclerosis; gait; rehabilitation; systematic review

## 2.1 Introduction

Over 70% of people with multiple sclerosis (MS) report walking problems. Maintaining an adequate gait speed is essential for independent community ambulation [82]. Although disease-modifying medications can reduce relapse rates and slow disability progression, clinical neurological disability persists in the absence of relapse [83]. Multiple approaches to manage gait difficulties include task-specific training, strengthening, or using novel devices such as robotics or whole body vibration [84, 85, 86, 87, 71]. Gait speed is often considered a clinical endpoint in trials evaluating the efficacy of pharmacological and rehabilitation interventions. Despite significant advances in the field of rehabilitation, clinicians encounter challenges in navigating the multitude of available options due to a lack of robust evidence to guide their decisions. Lack of comprehensive systematic reviews further compounds these difficulties, leaving rehabilitation providers with insufficient guidance on determining the most effective approaches for their patients. For instance, a recent systematic review of exercise interventions by Taul-Madsen et al., (2021) included limited studies, with five focusing on resistance training and three on aerobic training to improve gait speed [49]. Moreover, previous systematic reviews have also been limited in scope as they either included small number of studies [88, 89], or focused on specific interventions without examining the effect sizes [90]. This highlights the need for a more comprehensive and quantitative synthesis of gait rehabilitation interventions that work or may not work for people with MS. Therefore, the aim of our study was to conduct a comprehensive review of tested rehabilitation interventions and determine their effectiveness through a quantitative synthesis, specifically focusing on determining the optimal approaches to improve gait speed in people with MS.

## 2.2 Methods

Guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [91], the study protocol was registered on PROSPERO (#CRD42021261776: https://www.crd.york.ac.uk/prospero/#myprospero)

### 2.2.1 Eligibility and Study Selection

**Type of studies:** We included RCTs published in English in peer-reviewed journals, testing any rehabilitation intervention that was at least 3 weeks with gait speed assessed as the primary or secondary outcome. Conference abstracts, animal studies, interventions to improve language, mood, or cognitive impairments and tested drugs such as Fampridine were excluded. Comparison or control group involved another exercise intervention, sham/ placebo, conventional therapy, usual care, or no intervention.

**Participants:** People with MS over 18 years of age, any type of MS (relapsing-remitting, primary or secondary progressive) with any level of disability on expanded disability status scale (EDSS 0-9) who have received inpatient or outpatient physical rehabilitation therapies at any time since onset.

**Outcomes:** Studies report gait speed as short walk tests or using instrumented walkway, such as the 10-meter walk test (10MWT), 20-meter walk test (20MWT), 25-foot walk test (25FWT), measured in seconds or cm/s (centimetres/second), m/s (meters/second) or km/hr (kilometres/hour). Studies assessing walking endurance (6-minute walk tests or 10-minute walk tests) were excluded.

### 2.2.2 Study selection and Trial registration

Electronic databases (Ovid MEDLINE, PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane, Physiotherapy Evidence Database (PEDro) and Web of Science) were searched for titles and abstracts up to June 2023. Trial registers (ClinicalTrials.gov and the World health organization international clinical trials registry)were also searched. Reference lists of all included studies were examined for additional studies. A librarian (KR) developed the initial search strategy for Ovid MEDLINE in consultation with members of the review team (SB, MP) and translated the search for the additional information sources listed above.

After removing duplicates, the citations were exported to Covidence systematic review software for screening (Veritas Health Innovation, Melbourne, Australia www.covidence.org). Reviewers received training and discussed the eligibility criteria and management of potential disagreements. Six reviewers screened articles independently at the title and abstract level, followed by full-text screening. In case of disagreement, a third reviewer resolved the conflicts. Data was extracted from all articles that passed the full-text screening.

### 2.2.3 Methodological quality assessment

We assessed the quality and risk of bias of the included studies using the Physiotherapy Evidence Database (PEDro) scale [92]. The total score was 10 since we excluded external validity. Study quality was rated poor (0-3), fair (4-5), or good quality (≥6) [93].

### 2.2.4 Data extraction

We created data extraction sheets in Covidence and extracted information as outlined in Box 2.1. After pilot testing the data extraction forms, the reviewers extracted the required data, and an independent reviewer (SR) verified the extracted data (Box 2.1). The principal investigator (SB) contacted the reviewers for any unreported/missing or additional data.

**Box 2.1 Data Items extracted**

**Study Characteristics:** Study authors, year of publication, study location, type of study, and sample size.

**Participant characteristics:** Mean age of the participants (for the total sample unless it is specified separately for each group), level of disability (EDSS, Patient Determined Disease Steps (PDSS), or Guy's Neurological Disability Scale score or Hauser Ambulation Index), type of MS.

**Intervention characteristics:**

a) Frequency of rehabilitation - number of days per week and number of weeks
b) Intensity of rehabilitation- perceived exertion, maximal heart rate, one-repetition maximum test
c) Time/duration of rehabilitation - number of minutes of each session
d) Type of rehabilitation-whole body vibration, aerobic exercise, gait training, balance training, resistance training, adapted training using specialized exercise training equipment such as body-weight support treadmill training, total-body recumbent stepper training, or electrical stimulation assisted cycling, virtual reality, robotic training devices, yoga, Pilates, group/home/hospital/community/web-based exercises, tele rehabilitation.

**Comparison:** Control group or no treatment or sham/placebo

**Outcome:** Gait speed measured by 6MWT, 10MWT,20MWT, T25FWT, GAITRite walkway

6MWT-6 meter walk test; 10MWT-10 meter walk test; 20MWT-20 meter walk test; T25FWT-timed 25 foot walk test; GAITRite-instrumented walkway

### 2.2.5 Statistical analysis

Effect sizes were computed as the mean change of gait speed pre- to post-intervention of the exercise intervention group minus the change in the mean of the control group divided by the pooled standard deviation (SD) of the baseline gait speed, expressed as Cohen's d [94]. We considered effect sizes as small (d=0.14), moderate (d= 0.31), and large (d=0.61) based on novel empirically based effect size guidelines for rehabilitation studies [95] and reported 95% confidence intervals (CI). A positive effect size indicated that gait speed improved with intervention, while a negative effect size indicated improvement in favor of the control group.

We used a random effects model as the true effect might vary based on the sample characteristics, and the effect sizes also vary between studies. We also tested the heterogeneity of the mean effect size (all studies and for subgroups based on the type of intervention) and computed 95% CI. We imputed the intervention group as a moderator to examine the effect of an intervention on the overall effect size. Heterogeneity was indicated as Q-statistic, I-squared ($I^2$) and prediction interval at a significance level $p \leq 0.05$. Q-tests indicate if there is any variation in effects between studies, $I^2$ indicates the proportion (%) of variance in observed effects, and how much the effect size varies is indicated by the prediction interval [96]. The Q should be equal to the degrees of freedom (number of studies minus one), and in case of deviation, we assumed that all the studies included in the analysis do not share a common effect size. We interpreted $I^2$ as statistical heterogeneity (>50%) and limited heterogeneity (<50%). We interpreted the prediction interval and assumed that true effects are normally distributed and 95% of all comparable effects fall in this interval [96].The analyses were done using Comprehensive Meta-Analysis (Version 4.0; Biostat, Englewood, New Jersey) [97]. All the included studies' methodological quality (PEDro scores) was summarized.

## 2.3 Results

### 2.3.1 Included studies and participant characteristics

After removing duplicates, 4821 articles remained for screening (Figure 2.1) (refer to supplementary file 2.1). The final screening resulted in 90 articles (PRISMA 2020 guidelines) [98] (Figure 2.2). The characteristics of the included studies were heterogenous, so we categorized the studies based on the type of intervention: Lower limb resistance (n=9), Treadmill (n=13), Whole body vibration (n=6), Overground and Robotic gait (n=12), Home exercises (n=10), Individualized virtual Physiotherapy (PT) (n=8), Pilates and yoga (n=4), Individualized in-person PT (n=12), Balance (n=10), and Aerobic and Resistance (n=6). (Box 2.2 and Table 2.1)

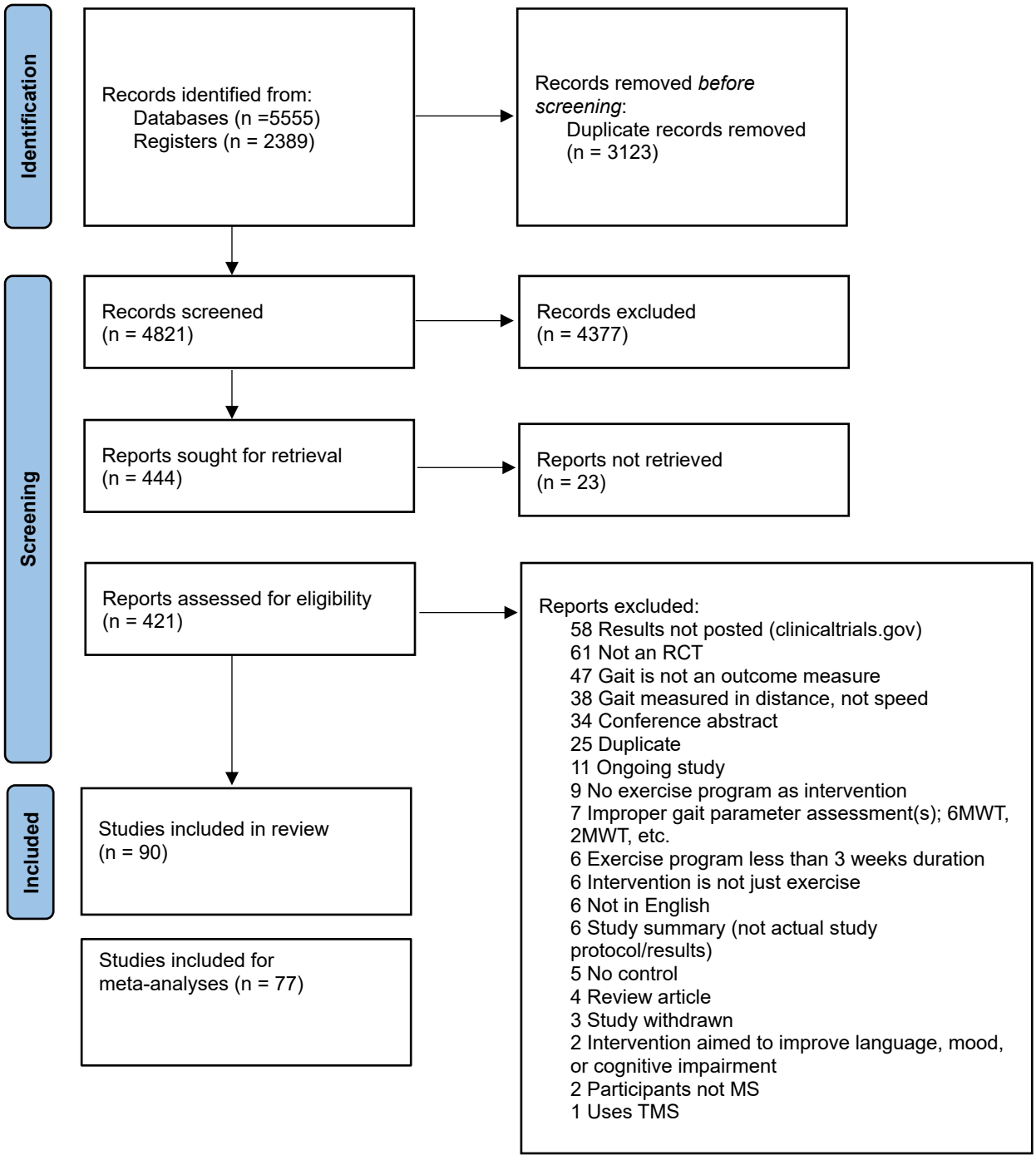


**Figure 2.1: PRISMA flow chart for search strategy**

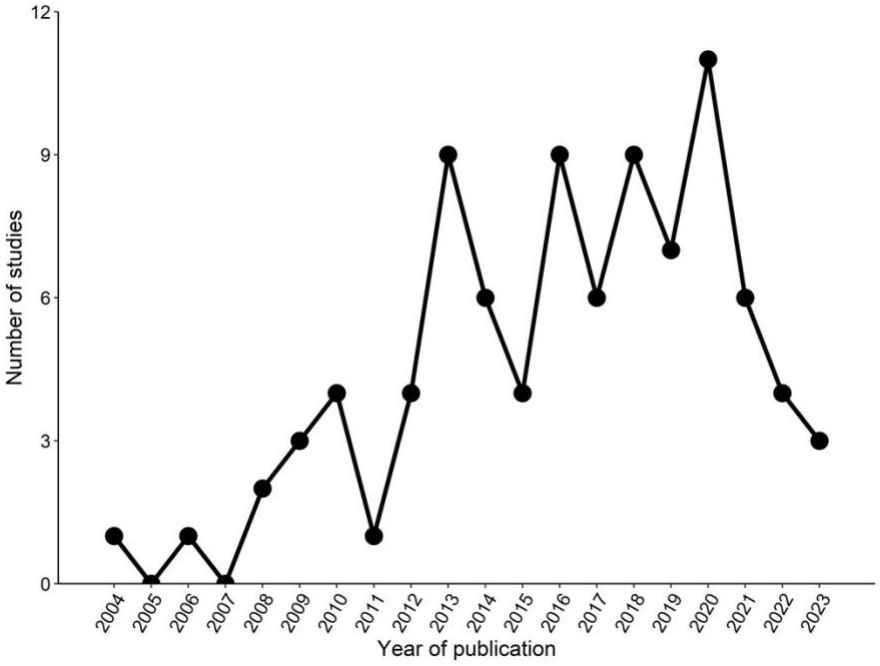


**Figure 2.2: Included trials by the year of publication**

### 2.3.2 Overall effect of interventions on gait speed

The meta-analysis of 77 trials with 3,276 participants showed an overall positive, but small, effect of intervention on gait speed (Cohen's d=0.23; 95% CI: 0.10, 0.365; P=0.001). We found significant heterogeneity across intervention groups ($I^2$=64%; Q=210.84; df=76; p<0.001). The prediction interval is -0.68,1.15, indicating that the true effect size in 95% of all comparable populations falls in this interval.

**Box 2.2 Interventions included under each group**

| Intervention group | Examples of interventions included in each category |
|---|---|
| Lower limb resistance | • Progressive Resistance Training [51,99]<br>• Lower limb fast-velocity concentric resistance training [85]<br>• Progressive Resistance Training on a Bicycle Ergometer [100]<br>• Resistance exercise via negative eccentrically induced work [101]<br>• Direct strength training of more affected dorsiflexors [102]<br>• Total body resistance exercise [103]<br>• Bilateral ankle exercise program combined with neuromuscular electrical stimulation with mirror therapy [104] |
| Treadmill | • Walking on a treadmill [105]<br>• Downhill walking on the treadmill [106]<br>• High-intensity aerobic exercise on treadmill [107]<br>• Body weight support treadmill training with a robot-driven gait orthotic [68]<br>• Treadmill Training combined with Virtual reality [54,55]<br>• Dual-task training on the treadmill [108] |
| Whole body vibration (WBV) | • Squatting exercise with whole body vibration [109]<br>• Whole body vibration with strengthening and stretching exercises for the lower limbs [110]<br>• Whole body vibration on a multidirectional Stochastic platform [111]<br>• WBV during circuit exercises [112] |
| Overground and Robotic gait | • Robot-assisted gait training [67,69,79,113,114]<br>• Robot-assisted gait training with physiotherapy [115]<br>• Robot-assisted gait training on a lokomat [70,116]<br>• Progressive gait training using overground robotic training [66]<br>• Robot-assisted gait training combined with virtual reality [73]<br>• Gait training with rhythmic auditory stimulation and by listening to the metronome beat [117]<br>• Task-oriented and multicomponent walking training and education program [118] |

| | |
|---|---|
| Home exercises | • Home based Functional electrical stimulation combined with exercises at home [119,120]<br>• Tele-management home exercise [121]<br>• Home-based step training [122]<br>• Home-Based Neurofunctional Exercise [123]<br>• Home based task-specific program [124] and balance training [125,126]<br>• Home based ergometry training [127]<br>• Home-based music- and verbally cued motor imagery [128] |
| Individualized virtual PT | • Pilates training via videoconference [62]<br>• Telephone-Delivered Exercise Therapy [129]<br>• Supervised exercises via audio/visual real-time telecommunication [130]<br>• Telerehabilitation-based motor imaging training [131]<br>• Web based physiotherapy (Videos, Text, Audio Description) [132-135] |
| Pilates and yoga | • Pilates [61,63,64] and yoga [58] |
| Individualized in-person PT | • Inpatient multidisciplinary rehabilitation therapy [136,137]<br>• Group program led by a physiotherapist at a local community centre [138-141] and in hospital [142,143]<br>• Hippotherapy [144] |
| Balance | • Balance and eye-movement exercises [145]<br>• Balance training with- virtual reality [72] cognitive tasks [86,146], exergaming [76,77,147], postural control exercises [148]<br>• Vestibular rehabilitation [149] |
| Aerobic and Resistance | • Strength training and aerobic training [150-153]<br>• Pool therapy including strength training and aerobic training [56,154] |

**Table 2.1: Participant characteristics, interventions tested, and the effects of intervention on gait speed**

| Author name, publication year Study location | Study design sample (n) | MS type [EDSS; Age: Mean (SD) (years)] | Intervention vs Control | Intervention parameters | Gait speed measure | Effect of intervention on gait speed | Follow up (retention of effects) |
|---|---|---|---|---|---|---|---|
| Lower limb resistance (n=9) | | | | | | | |
| Moradi M et al, 2015 [99] Iran | RCT IG (n)=8 CG (n)=8 | PwMS (only males) [EDSS 1-6; Age: 34.05 (7.8)] | Progressive resistance training program vs No intervention | F: 3x/wk for 8wks I: 50% to 80% of 1 RM (progressively increased) T: 30 min/session | Fast walking 10MWT (sec) | NS | No |
| Caravaca L et al, 2022 [155] Spain | RCT IG (n)=18 CG (n)=12 | RRMS/SPMS [EDSS 1-6; Age: 46.21 (10.43)] | Lower limb fast-velocity concentric resistance training vs No intervention | F: 3x/wk for 10wks I: 50% to 80% of 1 RM (progressively increased) T: 30 min/session | Fast walking 10MWT (sec) | S | No |
| Cakt BD et al, 2010 [100] Turkey | Randomized controlled crossover trial IG-1(n)=14 IG-2 (n)=10 CG (n)=9 | RRMS/SPMS [EDSS 0-6; Age: IG-1:36.4 (10.5). IG-2: 43.4 (10.2)] CG-35.5 (10.9) | IG-1: Progressive resistance training on a bicycle ergometer and balance exercise IG-2: Home-based lower limb strengthening and balance exercises. vs No intervention | F: 2x/wk for 8wks I:16 sets of 2 mins high intensity on bike (40% TMW and a 20-25 mins balance exercises T: 1 hr /session | Fast walking 10MWT (sec) | S (IG-1) | No |
| Callesen J et al, 2019 [50] Denmark | RCT (three arm; multicenter trial) IG-1 (n)=24 IG-2 (n)=17 CG (n)=18 | PwMS [EDSS 2-6.5; Median age 52] | IG-1: Balance and motor control training IG-2. Progressive resistance training vs Usual care | F: 2x/wk for 10wks I: level of participants' difficulty T: 1 hr/session | T25FWT (m/sec) | S (IG-1) | No |
| Hayes H et al, 2011 [101] United States | RCT IG (n)=10 CG (n)=9 | PwMS [EDSS 0-6; Age: 49 (11)] | Resistance exercise via negative, eccentrically induced work vs Standard exercises | F: 3x/wk for 12wks I: high-intensity resistance training utilizing a customized eccentric ergometer T: 45-60 min/session | Fast walking 10MWT (m/sec) | NS | No |
| Kjølhede T et al, 2013 [51] Denmark | RCT IG (n)=17 CG (n)=12 | RRMS [EDSS 2-5.5; Age: 43.2 (8.1)] | Progressive resistance training vs Waitlist | F: 2x/wk for 24wks I:10 reps, 3 sets, 15 RM to 6 reps, 5 sets, 6 RM T: not specified | T25FWT (m/sec) | S | 6 months (effects not retained) |
| Manca A et al, 2020 [102] Italy | RCT IG (n)=12 CG (n)=13 | RRMS [EDSS 0-6; Age: IG-49.2 | Direct strength training of more | F: 3x/wk for 6wks I: 3 sets of 4 maximal efforts at | Self-pace 10MWT (m/sec) | S | No |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | (9.1); CG-42.8 (15.3)] | affected dorsiflexors vs Contralateral strength training of the less affected dorsiflexors. | 10 degrees/s and 45 degrees/s on isokinetic device. T: 25 min/session | | | |
| Moghadasi A et al, 2020 [103] Iran | RCT IG (n)=16 CG (n)=11 | RRMS (only females) [EDSS 0-4; Age: IG-37.62 (4.58); CG-34.72 (5.01)] | Total body resistance exercise (TRX) program vs Usual care | F: 3x/wk for 8wks I: TRX suspension training program including 8 TRX whole-body workouts with 4 levels of difficulty for every exercise. T: 30 min/session | Fast walking 10MWT (m/sec) | S | No |
| Tekeoglu T et al, 2021 [104] Turkey | RCT IG (n)=13 CG (n)=13 | PwMS [EDSS 4-6.5; Age: IG-41.77(9.7) CG:42.38 (11.32)] | Bilateral ankle exercise and neuromuscular electrical stimulation with mirror therapy at hospital and at home vs Exercise program without mirror box | F: 3x/wk in hospital and 2x/wk at home for 6 weeks and only exercise for next 6weeks I: individually tailored exercise program+ biphasic current width of 400 msn, and at a frequency of 100 Hz T: 35min/session | T25FWT (sec) | S | No |
| Treadmill (n=13) | | | | | | | |
| Ahmadi A et al,, 2010 [58] Iran | RCT IG (n)=10 CG (n)=10 | PwMS (Only females. [EDSS 1-4; Age: 36.75 (9.0)] | Treadmill training vs No intervention | F: 3x/wk for 8 wks I: 40 - 75% of HRmax T:30 min/session | Fast walking 10MWT (sec) | S | No |
| Jonsdottir J et al, 2018 [108] Italy | RCT IG (n)=26 CG (n)=12 | PwMS [EDSS 0-7; Age: IG- 51.4 (10.7); CG-56.7 (5.7)] | Treadmill Dual Task Training vs strength training | F: 4-5x/wk for 4 wks I: RPE on the Borg Scale (6–20) T: 30 min/session | Self-pace 10MWT (m/s) | S | No |
| Lasheen Y et al, 2022 [156] Egypt | RCT IG (n)=15 CG (n)=15 | RRMS [EDSS 0-5; Age: IG-30.06 (4.77); CG-29.4 (6.37)] | Conventional medical treatment, vitamin D supplements, and aerobic exercise vs Conventional medical treatment and vitamin D supplements | F: 2 to 3x/wk for 6 wks I: 60-80% of HRmax T: 30 min/session | T25FWT (sec) | S | No |
| Mahler A et al, 2016 [157] Germany | RCT IG (n)=17 CG (n)=17 | RRMS | Training under hypoxia (hypoxic chamber) | F: 3x/ wk for 4 wks I: 65% of HRmax T: 60 min/session | Fast walking 10MWT (cm/s) | NS | No |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | [EDSS 0-4.5; Age: IG- 49 (9); CG-51 (10)] | vs Training under normoxia | | | | |
| Samaei A et al, 2016 [106] Iran | RCT IG (n)=18 CG (n)=15 | RRMS [≥3 on the Guy's Neurological Disability Scale; Age: IG- 33.9 (7.3) CG-32.1 (7.6)] | Downhill walking on a treadmill vs Uphill treadmill walking | F: 3x/wk for 4 wks I: 10% positively or 10% negatively sloped treadmill T: 30 min/session | T25FWT (sec) | S | 4 weeks (effects retained) |
| VandenBerg M et al, 2006 [158] UK | RCT (cross-over pilot study) IG (n)=8 CG (n)=8 | PwMS [EDSS not reported; Age range 30-65 years] | Supervised aerobic treadmill training vs no training | F: 3x/wk for 4 wks I: 55–85% of HRmax T: 30 min/session | Fast walking 10MWT (sec) | NS | 12 weeks (effects not retained) |
| Ahmadi et al., 2013 [57] Iran | RCT (only females) IG-1 (n)=10 IG-2 (n)=11 CG (n)=10 | PwMS [EDSS 1-4; Age: 35.16 (9.01)] | Treadmill training, yoga practice (considered third group here) vs no intervention | F: 3x/wk for 8 wks I: 40-75% of HRmax T: 30 min/session | Fast walking 10MWT (sec) | S (IG-1) | No |
| Straudi S et al, 2014 [105] Italy | RCT (feasibility study) IG (n)=12 CG (n)=12 | PwMS [EDSS 4-5.5) Age: 52.58 (11.21)] | Task-oriented circuit training vs usual care | TOCT F: 5x/wk for 2 wks I: treadmill speed 0.9-2.9 km/h. T: 120 min/session Home based: F: 3x/wk for 12 wks T: 60 min/session. | Fast walking 10MWT (m/s) | NS | 3 months (effects not retained) |
| Riemenschneider et al, 2023 [107] Denmark | RCT (multicenter) IG (n)=42 CG (n)=42 | RRMS [EDSS 1-4; Age: 37.4 (9.8)] | High-intensity aerobic exercise vs Health education | F: 2x/wk for 3wks I: 30% to 40% body weight support and an initial treadmill speed of 1.5 km/h T:40 min/session | T25FWT (sec) | NS | 6 months (effects not retained) |
| Lo A et al, 2008 [68] United States | Randomized Cross over pilot Trial IG (n)=6 CG (n)=7 | PwMS [EDSS-4.9 (1.2); Age: 49.8 (11.1)] | BWSTT alone (T) followed by BWSTT + robot-driven gait orthotic (R) vs BWSTT + robot-driven gait orthotic (R) followed by BWSTT alone (T) | F: 2x/wk for 8wks I: 40% body weight support and treadmill speed of 1.5 km/h T:40 min/session | T25FWT (sec) | NS | No |
| Ruiz J et al, 2013 [159] United States | RCT IG (n)=3 CG (n)=4 | PwMS [EDSS 3-6; Median age: 47] | Robot-Assisted and conventional BWSTT vs Waitlist | F: 2x/wk for 8wks I: 40% body weight support and treadmill speed of 1.5 km/h T:40 min/session | T25FWT (cm/sec) | NS | No |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Peruzzi A et al, 2017 [74]<br>Italy | RCT<br>IG (n)=14<br>CG (n)=11 | RRMS<br>(EDSS 3-5.5;<br>Age:<br>IG-43.6 (10.2);<br>CG-42.0 (12.0)] | Treadmill training +VR<br>vs Treadmill training | F: 3x/wk for 6wks<br>I: 80% of the subject's overground gait speed<br>T:45 min/session | Fast walking 10MWT (m/sec) | NS | No |
| Galperin I et al, 2023 [54]<br>Germany | RCT<br>(multicenter)<br>IG (n)=51<br>CG (n)=53 | RRMS<br>[EDSS 2-6)<br>Age: 49.0 (9.8)] | Treadmill training +VR<br>vs Treadmill training | F: 3x/wk for 6wks<br>I: tailored for each participant.<br>T: 15-45 min/session | T25FWT (cm/sec) | NS | 3 months (effects retained) |
| Whole body vibration (n=6) | | | | | | | |
| Broekmans T et al, 2010 [160]<br>Belgium | RCT<br>IG (n)=11<br>CG (n)=12 | PwMS<br>[EDSS 1.5-6.5; Age 47.9 (1.9)] | WBV with leg muscle training programme<br>vs Normal living habits | F: 5 x/in 2wk cycle for 20 wks<br>I: 25–45 Hz, 2.5 mm amplitude<br>T: 50 min/session | T25FWT (sec) | NS | No |
| Hilgers C et al, 2013 [109]<br>Germany | RCT<br>IG (n)=37<br>CG (n)=45 | PwMS<br>[EDSS 2-7;<br>Age: 43.3 (8.3)] | Squatting exercise set with whole body vibration<br>vs Squatting exercise set without whole body vibration | F: 3x/wk for 3 wks<br>I: 3 series of 60-second moderate squats while standing on the vibration platform vibrating at 30 Hz.<br>T: 12 min/session | Self-pace 10MWT (sec) | NS | No |
| Eftekhari E et al, 2012 [161]<br>Iran | RCT<br>(only females)<br>IG (n)=12<br>CG (n)=12 | RRMS<br>[EDSS 2-4;<br>Age:<br>IG-35.08 (6.89);<br>CG-33.75 (5.32)] | Progressive resistance training and WBV<br>vs No intervention | F: 3x/wk for 8 wks<br>I: a set of 5-12 reps at %50-70 MVC and six 30-second vibration postures; Vibration frequency set to 2-5 Hz and gradually increased to 20 Hz.<br>T: not specified | Fast walking 10MWT (m/min) | S | No |
| Schyns F et al, 2009 [110]<br>UK | RCT<br>(cross-over pilot study)<br>IG (n)=5<br>CG (n)=7 | PwMS<br>[1-6 on the Hauser Ambulation Index)<br>Age:<br>IG-45.8 (8.4);<br>CG-49.5 (6.14)] | WBV + exercise (4weeks),<br>no intervention (2weeks), exercise alone (4 weeks)<br>vs<br>Exercise alone (4 weeks),<br>no intervention (2 weeks)<br>and WBV + exercise (4 weeks) | F:3 x/wk for 4 wks<br>I: 30, 40 or50 Hz frequency and the amplitude between 2 -4 mm)<br>T:11min/session | Self-pace 10MWT(sec) | NS | No |
| Wolfsegger T et al., 2014 [111]<br>Austria | RCT<br>IG (n)=9<br>CG (n)=8 | RRMS<br>[EDSS 0-5;<br>Age:<br>IG-43.0 (13.4); | Whole body vibration<br>vs<br>Placebo group | F: 3 wks (sessions x/wk-not specified)<br>I: 2.5–3.0 Hz<br>T: 14.45 min/session | Self-pace 20MWT (km/hr) | NS | 2 weeks (effects not retained) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | CG-39.3 (10.6)] | | | | | |
| Escudero-Uribe 2017 [112] Spain | RCT IG (n)=16 CG (n)=18 | RRMS [EDSS 0-4.5; Age: IG- 43.1 (10.2); CG-40.3 (8.9)] | Aerobic, body weight, coordination, and balance exercises with either WBV vs Standard exercise programme | F:2x/wk for 12 wks I: Borg scale (11–12 [light]); 3 mm and average frequency of 4Hz/ second. T: 1hr/session | Self pace walking on GAITRite (cm/sec) | S | No |
| Overground and Robotic gait (n=12) | | | | | | | |
| Sconza C et al, 2021 [115] Italy | RCT cross over trial IG (n)=9 CG (n)=9 | PwMS (EDSS 3.5-7) Age range 36-74 | Robot-assisted gait training with physiotherapy treatment vs Physiotherapy treatment | F: 5x/ wk for 5 wks I: 40% body weight support and an initial treadmill speed of 1.5 km/h; T: 1.5 hr/ session | T25FWT (sec) | S | No |
| Straudi S et al, 2020 [116] Italy | RCT IG (n)=34 CG (n)=30 | PPMS/SPMS [EDSS 6-7; Age: IG-56.0 (11.0); CG-55.0 (11.0)] | Robot-assisted gait training on a Lokomat treadmill vs Conventional therapy | F: 3x/wk for 4wks I: 50% body weight T: 2 hr/session | T25FWT (sec) | NS | 3 months (effects not retained) |
| Gandolfi M et al, 2014 [67] Italy | RCT IG (n)=12 CG (n)=10 | RRMS/SPMS [EDSS 1.5-6.5) Age: IG-50.83 (8.42); CG-50.1 (6.29)] | Robot-assisted gait training vs Sensory integration balance training | F: 2x/ wk for 6 wks 6 weeks I: 20% of supported body weight and 1.3 km/h speed; 2nd session at 10% of supported body weight and 1.6 km/h of speed T: 50 min/ session | Self selected walking on GAITRite (cm/sec) | NS | 1 month (effects not retained) |
| Vaney C et al, 2012 [70] Switzerland | RCT IG (n)=26 CG (n)=23 | PwMS [EDSS 3-6.5; Age: IG-58.23 (9.42); CG-54.22 (11.28)] | Robot-assisted gait training on a Lokomat vs Strengthening exercises, horseback riding, pool exercises and occupational therapy and over ground walking | F: 3x/ wk for 3 wks I: 50% of the body weight T: 30 min/ session | Fast walking 10MWT (m/s) | S (CG) | 8 weeks (effects not retained) |
| Berriozabalgoitia R et al, 2021 [66] Spain | RCT IG (n)=18 CG (n)=14 | PwMS [EDSS 4.5-7; Age: 50.48] | Individualized and progressive gait training using over ground robotic training. | F: 3x/ wk for 12 wks I: tailored to each participant. | Fast walking 10MWT (sec) | NS | No |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | vs<br>Physical therapy treatment | T:1 hr PT session + 40 min/gait training session | | | |
| Martini D et al, 2018 [118]<br>United States | RCT<br>IG (n)=20<br>CG (n)=20 | PwMS<br>[EDSS 0-6; Age: IG-56.0 (9);<br>CG-54.8 (1.4)] | Multicomponent walking training and education program<br>Vs<br>Usual medical care | F: 1x/wk for 6 wks<br>I: tailored to participant's mobility level.<br>T: 40 min/sessions | T25FWT (sec) | NS | 3 months (effects not retained) |
| Munari D et al, 2020 [73]<br>Canada | RCT<br>(Pilot study)<br>IG (n)=8<br>CG (n)=7 | PwMS<br>[EDSS 3-6; Age: IG-57.0 (5.83); CG-51.7 (10.24] | Robot-assisted gait training combined with virtual reality<br>vs<br>Robot-assisted gait training | F: 2x/wk for 6 wks<br>I: 2 wks at 30% of body weight, 2 weeks at 20%, and 2 weeks at 10% of body weight support<br>T: 40 min/ session | Fast walking 10MWT (sec) | S | 1 month (effects not retained) |
| Straudi S et al, 2013 [113]<br>Italy | RCT<br>(Pilot study)<br>IG (n)=8<br>CG (n)=8 | PwMS<br>[EDSS 4.5-6.5; Age: IG-49.6 (12.0); CG-61.0 (8.8)] | Robot-assisted gait training<br>vs<br>Conventional physiotherapy | F: 2x/ wk for 6 wks<br>I: speed of the treadmill between 0-3 km/h (0-100% body weight support)<br>T: 1 hr/ session | walkway using motion capture system (m/s) | S | 3 months (effects retained) |
| Straudi S et al, 2016 [114]<br>Italy | RCT<br>(multicenter)<br>IG (n)=27<br>CG (n)=25 | PPMS/SPMS<br>[EDSS 6-7; Age: IG-52.26 (11.11); CG-54.12 (11.44)] | Robot-assisted gait training<br>vs<br>Conventional physiotherapy | F: 2x/ wk for 6 wks<br>I: speed of the treadmill between 0.1-3 km/h (100% guidance and 50% body weight support)<br>T: 1 hr/ session | Fast walking 10MWT (m/s) | NS | 3 months (effects not retained) |
| Schwartz I et al, 2012 [69]<br>Israel | RCT<br>IG (n)=12<br>CG (n)=16 | PwMS<br>[EDSS 1-6.5; Age: IG-46.8 (12.0); CG-50.5 (11.0)] | Robot-assisted gait training<br>vs<br>Conventional walking | F: 2-3x/wk for 4 wks<br>I: speed of the treadmill between 0-3 km/h (40% body weight support)<br>T: 30 min/ session | Fast walking 10MWT (m/s) | S (CG) | 3 and 6 months (effects not retained) |
| Beer S et al, 2008 [79]<br>Switzerland | RCT<br>IG (n)=14<br>CG (n)=15 | PwMS<br>[EDSS 6-7.5; Age: IG-49.7 (11.0); CG-51.0 (15.5)] | Robot-assisted gait training<br>vs<br>Conventional walking training | F: 5x/wk for 3 wks<br>I:4 speed of the treadmill between 1-1.5 km/h (40-80% body weight support)<br>T: 1 hr/ session | 20MW test (Pace not specified)(m/s) | NS | 6 months (effects not retained) |
| Shahraki M et al, 2017 [117]<br>Iran | RCT<br>IG (n)=9<br>CG (n)=9 | PwMS<br>(EDSS 3-6; Age: IG-40.3(6.6)<br>CG:38.11 (12.12)] | Rhythmic auditory stimulation<br>vs<br>Gait training without auditory stimulation | F: 3x/wk for 3 weeks<br>I: metronome output beat set at 10% higher than the | Self-pace 10MWT(m/s) | S | No |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | preferred cadence of each subject.<br>T: 30min/session | | | |
| Home exercises (n=10) | | | | | | | |
| Taylor P et al, 2014 [120]<br>UK | RCT<br>(cross over trial)<br>IG (n)=9<br>CG (n)=11 | SPMS<br>(EDSS ≤6.5;<br>Age: IG-54.6 (9.4) CG:56.9 (7.8)] | FES followed by FES + PT<br>vs<br>PT followed by FES + PT | F: 2x/day for 24wks<br>I: Tailored to individual abilities.<br>T: 30min/session | Fast walking 10MWT (m/sec) | S (FES group) | No |
| Barrett CL et al, 2009 [119]<br>UK | RCT<br>IG (n)=20<br>CG (n)=24 | SPMS<br>[EDSS 4-6.5;<br>Age: IG-56.6 (9.0) CG:52.1 (6.7)] | Physiotherapy home exercises<br>vs<br>FES | F: 2x/day for 18wks<br>I: Tailored to individual abilities<br>T: 30min/session | Self pace 10MWT (m/sec) | S | No |
| Conroy S et al, 2018 [121]<br>United States | RCT<br>IG (n)=16<br>CG (n)=18 | PwMS<br>(PDDS 4-6.5)<br>Age: IG-51.0 (8.1) | Tele-management home exercise: Internet-based instructions<br>vs<br>Routine home-based exercise: Paper instructions | F: 24wks<br>I: Personalised based on individual abilities and expressed goal.<br>T: not specified | T25FWT (sec) | NS | No |
| Hoang P et al, 2016 [122]<br>Australia | RCT<br>IG (n)=23<br>CG (n)=21 | PwMS<br>[EDSS 2-6;<br>Age: IG-53.4 (10.7)<br>CG:51.4 (12.8)] | Home based step training<br>vs<br>usual physical activity | F: 2x/wk for 12wks<br>I: Personalised based on individual abilities.<br>T: 30 min/session | Fast walking 10MWT (sec) | S | No |
| Mardaniyan Ghahfarrokhi M et al, 2022 [123]<br>Iran | RCT<br>(pilot, feasibility trial)<br>IG (n)=15<br>CG (n)=15 | PwMS<br>[EDSS <6;<br>Age: 38.85 (8.76)] | Home-based neurofunctional training program<br>vs<br>Home-based resistance training | F: 3x/wk for 8wks<br>I: RPE; of 2-6<br>T: 90-120 min/session | T25FWT (sec) | NS | No |
| Miller L et al, 2009 [124]<br>UK | RCT<br>IG (n)=15<br>CG (n)=15 | PPMS and SPMS<br>[EDSS 6.5-8;<br>Age: IG-56.3 (9.0) CG:52.9 (6.3)] | Home based PT<br>vs<br>Usual Care | F: 2x/wk for 8wks<br>I: Personalised based on individual abilities.<br>T: 1 hr/session | Self pace 10MWT (sec) | NS | 8 weeks (effects not retained) |
| Prosperini L et al, 2013 [125]<br>Italy | RCT<br>(cross over pilot trial)<br>IG (n)=17<br>CG (n)=17 | RRMS/SPMS<br>[EDSS ≤5.5;<br>Age: IG-35.3 (8.6) CG:37.1 (8.8)] | Home-based balance training using the Nintendo Wii Balance Board System<br>vs<br>No intervention | F: 5x/wk for 12wks<br>I: Personalised based on individual abilities.<br>T: 30 min /session | T25FWT (sec) | S | No |
| Heinrich I et al, 2021 [127]<br>Germany | RCT<br>IG (n)=17<br>CG (n)=22 | PPMS<br>(EDSS 4-6.5;<br>Age: IG-51.9(7.9) CG:50.3 (6.9)] | Arm ergometry exercise training at home<br>Vs<br>waitlist | F: multiple sessions/day for 12 wks | T25FWT (sec) | NS | No |

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| | | | | I: Borg Scale <15 and individually tailored.<br>T: 1 hr/session | | | |
| Seebacher B et al, 2018 [128]<br>Austria | RCT<br>(three arm trial)<br>IG (n)=19<br>CG (n)=20 | PwMS<br>[EDSS 1.5-4.5; median age: IG-45.3; CG:43.3; IG-2:44.5] | IG-1. music- and verbally cued MI:<br>IG-2. Music-cued MI<br>vs MI | F: 6x/wk for 4 weeks<br>I: individually tailored.<br>T: 17min/session | T25FWT (sec) | S (IG-1) | No |
| Novotna K et al, 2019 [126]<br>Czech Republic | RCT<br>(feasibility)<br>IG (n)=23<br>CG (n)=16 | PwMS<br>[EDSS 1.5-7; Age: IG-39.39 (9.68); CG-42.56 (10.63)] | Home-based balance exercise program using<br>vs<br>Wait list | F: 7x/wk for 4wks<br>I: tailored to suit each participant's ability and preference.<br>T: 15 min/session | Fast pace GAITRite walkway (cm/s) | NS | 1 month (effects not retained) |
| Individualized Virtual PT (n=8) | | | | | | | |
| Eldemir K et al, 2023 [62]<br>Turkey | RCT<br>IG (n)=15<br>CG (n)=15 | PwMS<br>[EDSS 0-5; Age: IG-41.0 (7.8) CG:38.4 (10.86)] | Pilates training via videoconference<br>vs<br>No treatment | F: 3x/wk for 6wks<br>I: 20 repetitions with resistance bands<br>T: 60 min /session | Fast walking 10MWT (m/sec) | S | No |
| Kratz A et al, 2020 [129]<br>United States | RCT<br>(pilot, feasibility trial)<br>IG (n)=9<br>CG (n)=10 | PwMS<br>[PDDS 1-4; Age: 48.3 (7.9)] | Telephone-delivered exercise therapy<br>vs<br>In-person delivered exercise therapy | F: 2x/wk for 8wks<br>I: 60-70% of HR max<br>T: 30 min/session | T25FWT (sec) | NS | No |
| Fjeldstad-Pardo C et al, 2018 [130]<br>United States | RCT<br>(three arm trial)<br>IG-1 (n)=7<br>IG-2 (n)=7<br>CG (n)=6 | PwMS<br>[EDSS 0-6; Age: 54.7 (12.3)] | IG-1:Remote PT supervised via audio/visual real-time telecommunication<br>IG-2: in-person PT at the medical facility<br>vs<br>Customized unsupervised home-based exercise program | F: Telerehab-2x/wk; (HEP) 5x/wk; in-person PT 2x/wk for 8wks<br>I: not specified.<br>T: not specified. | T25FWT (sec) | NS | No |
| Kahraman T et al, 2020 [131]<br>Turkey | RCT<br>IG (n)=20<br>CG (n)=15 | PwMS<br>[EDSS 0-4; median age: IG- 34.5; CG-36] | Telerehabilitation-based motor imaging training (Tele-MIT)<br>vs<br>Wait list | F: 2x/wk for 8wks<br>I: Personalised based on individual abilities.<br>T: 20-30 min/session | T25FWT (sec) | NS | No |
| Donkers S et al, 2020 [132]<br>Canada | RCT<br>(Pilot Study)<br>IG (n)=32<br>CG (n)=16 | PwMS<br>[PDDS 2-7; Age: 54.3 (11.9)] | Web based group. Contains exercises (videos, text, audio description) | F: 2x/wk for 24wks<br>I: Individually tailored session<br>T: not specified | T25FWT (sec) | NS | No |

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| | | | vs Usual Care | | | | |
| Flachenecker P et al, 2020 [133] Germany | RCT IG (n)=34 CG (n)=30 | PwMS [EDSS ≤6; Age: IG-47.6 (9.2) CG:46.4 (12.2)] | Internet-based physical activity promotion PT supervised vs No intervention | F: 1-2x/wk for 3 months I: Borg Scale from 6 (no exertion) to 20 (maximum exertion) T: 10-60mins/session | Fast walking 10MWT (sec) | S | No |
| Paul L et al, 2014 [134] UK | RCT (Pilot Study) IG (n)=15 CG (n)=14 | PwMS [EDSS 5-6.5; Age: IG-51.7 (11.2)] | Individualised web-based physiotherapy vs Usual care | F: 2x/wk for 12wks I: Individually tailored session T: not specified | T25FWT(m/sec) | NS | No |
| Paul L et al, 2019 [135] UK | RCT (multicenter; feasibility trial) IG (n)=45 CG (n)=45 | PwMS [EDSS 4-6.5; Age: IG-55.6 (10.2) CG:56.5 (9.1)] | Web-based physiotherapy (home exercise program) vs Sheet of exercises | F: 2x/wk for 26 wks I: Individually tailored session T: not specified | T25FWT (ft/sec) | NS | 3 months (effects not retained) |
| Pilates and Yoga (n=4) | | | | | | | |
| Eftekhari E and Etemadifar M, 2018 [61] Iran | RCT (only females) IG (n)=13 CG (n)=12 | PwMS [EDSS 2-6; Age: IG-33.0(8.08)] | Pilates training vs No intervention | F:3x/wk for 8 weeks I:core stability exercises low to moderate intensity. T: 1hr /session | Fast walking 10MWT (min) | S | No |
| Fox E et al, 2016 [63] UK | RCT (three arm; multicenter trial) IG (n)=33 CG (n)=29 | PwMS [EDSS 4-6.5; Age: IG-53.97(9.19);IG-2: 54.6(11.54); CG:53.78 (9.72)] | IG-1: Pilates Training IG-2: Standardized exercises vs Relaxation | F:1x/wk for 12 weeks I: individually tailored. T: 30 min/session | Fast walking 10MWT (sec) | S | 1 month (effects not retained) |
| Kalron A et al., 2017 [64] Israel | RCT IG (n)=22 CG (n)=23 | RRMS (EDSS 3-6; Age: IG-42.9(7.2) CG:44.3 (6.6)] | Pilates training+ home exercises vs Standardized physical therapy | F:1x/wk for 12 weeks I: individually tailored. T: 45 min/session | Self pace on Treadmill (km/hr) | NS | No |
| Ahmadi A et al, 2010 [58] Iran | RCT (only females) IG (n)=11 CG (n)=10 | PwMS [EDSS 1-4; Age: 34.38 (5.68)] | Yoga intervention vs Waitlist | F: 3x/wk for 8 weeks I: Individually tailored. T: 45-60 min | Fast walking 10MWT (sec) | S | No |
| Individualized in-person PT (n=12) | | | | | | | |
| Aydin T et al, 2014 [162] Turkey | RCT IG (n)=16 CG (n)=20 | RRMS [EDSS 0-4.5; Age: 32.83 (3.64)] | Hospital based calisthenic exercises for 3 weeks and relaxation exercises for 2 weeks. vs | F: 5x/wk for 12wks I: Intensive training T: 1 hr/session for 3 days and 20 min/session for 2 days | Fast walking 10MWT (sec) | NS | No |

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|---|---|---|---|---|---|---|---|
| | | | Home based calisthenic exercises 3 days a week and relaxation exercises 2 days a week. | | | | |
| Salhofer-Polanyi S et al, 2013 [137] Austria | RCT<br>IG (n)=10<br>CG (n)=9 | PwMS [EDSS 3.5-6.5; Age: IG-53.8 (7.3); CG-52.9 (8.0)] | Inpatient multidisciplinary rehabilitation therapy<br>vs<br>Wait list | F: 4-5x/wk for 3wks<br>I: individualized intensity<br>T: 1 hr/session (30 min PT+30 min functional gait and balance training + 2–3 minutes training with a Galileo device. | T25FWT (sec) | NS | No |
| Tarakci Et al, 2013 [142] Turkey | RCT<br>IG (n)=51<br>CG (n)=48 | PwMS [EDSS 2-6.5; Age: IG-41.49 (9.37); CG-39.65 (11.18)] | Group exercise program<br>vs<br>Wait list | F: 3x/wk for 12wks<br>I: 1 set of 8–12 repetitions, increase gradually to 12–20 repetitions.<br>T: 1 hr/session. | Fast pace 10MWT (sec) | S | No |
| Arntzen E et al, 2020 [163] Norway | RCT<br>IG (n)=39<br>CG (n)=40 | PwMS [EDSS 1-6.5) Age: IG-52.2 (12.9); CG-48 (8.75)] | Group-based comprehensive core stability and balance training<br>vs<br>Standard care | F: 3x/wk for 6wks<br>I: core muscle activation was also obtained indirectly during optimal alignment and adjustment to the base of support.<br>T: 1 hr/session. | Fast walking 10MWT (sec) | S | 12 weeks (effects retained) |
| Learmonth YC et al, 2012 [139] UK | RCT<br>IG (n)=17<br>CG (n)=11 | PwMS [EDSS 5-6.5; Age: IG-51.4 (8.06); CG-51.8 (8.0)] | Physiotherapist delivered centre-based exercise class with mobility, balance and resistance exercises<br>vs<br>Usual care | F: 2x/wk for 12wks<br>I: self-regulated pace; 8–12 different exercises for 1 minute each<br>T: 1 hr/session. | T25FWT (sec) | NS | No |
| Louie J et al, 2015 [140] Australia | RCT (feasibility trial)<br>IG (n)=10<br>CG (n)=5 | PwMS [EDSS 0-6.5; Age: 48.6 (11.7)] | Physiotherapist delivered self-management program, involving group-based exercise, education and community integration<br>vs<br>Wait list | F: Exercise session-2x/wk for 6wks; education session-1x/wk for 6wks. Community integration and sustaining exercise behaviours for next 6 wks.<br>I: Self-regulated pace<br>T: 1 hr/session. | Fast 6 MWT (m/sec) | S | 12 weeks (effects retained) |
| Sandroff B et al, 2017 [141] | RCT<br>IG (n)=32 | PwMS | Supervised multimodal exercise | F: 3x/wk for 24wks | T25FWT (ft/sec) | NS | No |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| United States | CG (n)=30 | [EDSS 4-6; Age: IG-49.8 (8.5); CG-51.2 (8.7)] | training (aerobic, resistance, and balance) vs Stretching and toning | I: Aerobic: 40-60% $VO_2$ peak Resistance: 8-15 reps at 40-70% of 1 RM T: 30-60 min/session. | | | |
| Williams K et al, 2021 [138] Australia | RCT (multicenter) IG (n)=23 CG (n)=24 | PwMS (EDSS not reported; Age: IG-52.7 (11.9); CG-51.3 (8.9)] | Physiotherapist delivered community center-based functional and balance training vs Home-based functional and balance training | F: 2x/wk for 8wks I: >7/10 on the modified Borg scale T: 1 hr/session | Fast walking 10MWT (m/sec) | NS | 8 weeks (effects not retained) |
| Moraes A et al, 2020 [144] Brazil | RCT IG (n)=17 CG (n)=16 | RRMS [EDSS ≤6; Age: IG-45.5(9.7) CG:44.8 (8.8)] | Hippotherapy vs No intervention | F: 2x/wk for 8 weeks I: participant´s physical and emotional limits. T:30 min/session | T25FWT (sec) | S | No |
| Barclay A et al, 2019 [164] UK | RCT (feasibility trial) IG (n)=8 CG (n)=3 | PwMS [EDSS 6-8.5; Age: IG-54.9 (2.6) CG:53.6 (2.7)] | Lower limb active passive trainer + usual care vs Usual care | F: 5x/wk for 4 weeks I: RPE 12 -14 T: 30min/session | T25FWT (sec) | NS | No |
| Sangelaji B et al, 2016 [143] Iran | RCT (four arm trial) IG (n)=10 CG (n)=10 | RRMS [EDSS 0-5; Age: IG 1-35.80 (8.42), IG 2- 31.33 (8.21), IG 3- 33.91 (7.94), CG 3-33.63 (6.92)] | IG-1: One aerobic exercise training and 3 resistance exercise training sessions per week IG- 2: 2 aerobic exercise training and 2 resistance exercise training sessions per week vs No intervention | F: 4x/wk for 8wks I:40-70% HRmax and 50% of 1RM T: 30 min/session | Fast walking 10MWT (sec) | S (IG-1) | No |
| Sepehri Far S et al, 2022 [165] Iran | RCT IG (n)=34 CG (n)=13 | RRMS (only females; [EDSS 2-6.5; Age: 36.89 (4.93)] | Multifunction swing suspension training program vs Routine care | F: 3x/wk for 8 wks I:4 levels of difficulty with a swing suspension T: 1 hr/ session | T25FWT (sec) | S | No |
| Balance (n=10) | | | | | | | |
| Hebert J et al, 2016 [145] United States | RCT IG (n)=39 CG (n)=42 | PwMS [EDSS 0-6; Age: IG-46.5 (8.8); CG-43.0 (10.8)] | Balance and eye-movement exercises vs No intervention | F: phase 1: 2x/wk and daily balance exercises for 6wks phase 2: 1x/wk and daily home exercises for 8 wks | T25FWT (sec) | NS | No |

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| | | | | I: tailored to participant level<br>T: not specified | | | |
| Molhemi F et al, 2021 [72]<br>Iran | RCT<br>IG (n)=19<br>CG (n)=20 | PwMS [EDSS 0-6; Age: IG-36.8 (8.4); CG-41.6 (8.4)] | Balance training with VR<br>vs<br>Conventional balance training | F: 3x/wk for 6 wks<br>I: simple standing to weight shifts (tailored to participant's level)<br>T: 35 min/session | Self selected 10MWT (m/sec) | NS | 3 months (effects not retained) |
| Monjezi S et al, 2016 [146]<br>Iran | RCT<br>IG (n)=19<br>CG (n)=19 | PwMS [EDSS 2-5.5; Age: IG-50.0 (11.5); CG-49.4 (11.1)] | Dual-task walking<br>vs<br>Single task walking | F: 3x/wk for 4 wks<br>I: not specified<br>T: 45 min/session | Fast walking 10MWT (m/sec) | NS | 6 weeks (effects) not retained |
| Nilsagard Y et al, 2013 [147]<br>Australia | RCT (multicenter)<br>IG (n)=41<br>CG (n)=39 | PwMS [EDSS not reported; Age: IG-35.8 (6.91); CG-36.2 (9.16)] | Balance exercises using Wii games<br>vs<br>No intervention | F: 2x/wk for 6-7wks<br>I: tailored to suit each participant's ability and preference.<br>T: 30 min/session | T25FWT (sec) | NS | No |
| Robinson J et al, 2015 [77]<br>UK | RCT (three-arm trial)<br>IG (n)=21<br>CG (n)=15 | PwMS [EDSS 0-6; Age: 52.0 (5.8)] | IG-1: Exergaming with Wii Fit balance training<br>IG-2: traditional balance training (non-exergaming)<br>vs<br>No intervention Group | F: 2x/wk for 4wks<br>I: tailored to suit each participant's ability and preference.<br>T: 40-60 min/sessions | Self pace GAITRite walkway (cm/sec) | NS | No |
| Sosnoff J et al, 2017 [166]<br>United States | RCT<br>IG (n)=8<br>CG (n)=6 | PwMS [EDSS 0-6; Age: IG-48.3 (14.2); CG-56.8 (7.1)] | Dual-task walking<br>vs<br>Single task walking | F: 2x/wk for 12wks<br>I: perceived difficulty score of 7/10 scale<br>T: 1hr/session | Self pace GAITRite walkway (cm/sec) | NS | No |
| Veldkamp R et al, 2019 [167]<br>Belgium | RCT (multicenter)<br>IG (n)=20<br>CG (n)=20 | PwMS [EDSS 2-6; Age: IG-51.4 (9.3); CG-53.4 (9.2)] | Dual-task walking<br>vs<br>Single task walking | F: 2-3x/wk for 8wks<br>I: tailored to suit each participant's ability and preference.<br>T: 45 min/session | T25FWT (sec) | S | 1month (effects retained) |
| Najafi B et al, 2019 [148]<br>Iran | RCT<br>IG (n)=28<br>CG (n)=28 | RRMS (only females; [EDSS 1-5; Age: IG-38.39 (4.59) CG:36.36 (3.54)] | Stability exercises and exercises postural control exercises.<br>vs<br>No intervention | F: 3x/wk for 8 wks<br>I: 60% of HRmax<br>T: 60-80 min /session | T25FWT (sec) | S | No |
| Ozdogar A et al, 2020 [76]<br>Turkey | RCT (three arm trial)<br>IG (n)=20<br>CG (n)=17 | RRMS/SPMS [EDSS 0-6; Age: IG-40.1 (10.7)] | IG-1: Video-based exergaming<br>IG-2: conventional rehabilitation<br>vs<br>No intervention | F:1x/wk for 8 weeks<br>I: individual physical ability<br>T:45min/ minutes | T25FWT (sec) | NS | No |

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| Tramontano M et al, 2018 [149]<br>Italy | RCT<br>IG (n)=13<br>CG (n)=10 | PwMS [EDSS 5-7; Age: IG-50.64(11.73) CG:45.77 (10.91)] | Vestibular Rehabilitation vs Conventional therapy | F: 5x/wk for 4 weeks<br>I: individually tailored.<br>T:40 min/session | T25FWT (sec) | S | No |
| Aerobic and Resistance (n=6) | | | | | | | |
| Grazioli E et al, 2019 [151]<br>Italy | RCT (pilot study)<br>IG (n)=10<br>CG (n)=10 | PwMS [EDSS 2.5-5.5; Age: IG-45.91 (12.09) CG:39.40 (10.26)] | Strength and Aerobic Training vs Conventional Physical Therapy | F: 2x/wk for 12 wks<br>I: 65% of HRmax and 50% of 1RM<br>T: 1 hr/session | Fast walking 10MWT (sec) | S | No |
| Davies B et al, 2016 [150]<br>United States | RCT<br>IG (n)=14<br>CG (n)=13 | RRMS/SPMS (EDSS 3-6.5; Age: IG-54.0 (9.0) CG:52.6 (9.0)] | Therapeutic exercise Strength, flexibility, balance exercises, and aerobic training vs Motor adaptation | F: 5x/wk for 6 wks<br>I: Borg Scale 12-13<br>T: 1 hr/session | Self-selected walking GAITRite (m/sec) | NS | No |
| Novotna K et al, 2015 [152]<br>Czech Republic | RCT<br>IG (n)=24<br>CG (n)=26 | PwMS (EDSS 1.5-6; Age: 42.3 (10.8) | Aerobic-resistance circuit training vs Resistance circuit training | F: 2x/wk for 12 wks<br>I: Borg Scale 11-13<br>T: 1 hr/session | T25FWT (sec) | NS | 3 months (effects not retained) |
| Pau M et al, 2018 [153]<br>Italy | RCT<br>IG (n)=11<br>CG (n)=11 | PwMS (EDSS 1.5-5.5; Age: IG-47.4 (10.8) CG:44.5 (13.5)] | Aerobic and strength training Vs Unstructured physical activity program | F: 3x/wk for 24 wks<br>I: Aerobic:50% of the maximum workload (cardiopulmonary test) and 15% of 1RM<br>T: 1 hr/session | Self-pace 10MWT (m/sec) | NS | No |
| Romberg A et al, 2004 [154]<br>Finland | RCT (two center trial)<br>IG (n)=10<br>CG (n)=10 | PwMS (EDSS 1-5.5; Age: IG-43.8 (6.3) CG:43.9 (7.1)] | Strength and aerobic training vs No intervention | F: 3-4x/wk for 26wks<br>I: progression tailored to individual level.<br>T: 30 min/session | T25FWT (sec) | S | No |
| Aidar F et al, 2018 [56]<br>Brazil | RCT<br>IG (n)=13<br>CG (n)=13 | PwMS (EDSS 0-5.5; Age: IG-41.3 (7.3) CG:43.6 (7.6)] | Strength and aerobic training in a pool vs No intervention | F: 3x/wk for 12 weeks<br>I: Scale of perceived exertion (OMNI) 6-8<br>T: 45-60 min | T25FWT (sec) | S | No |

PwMS- people with multiple sclerosis; RRMS-relapsing -remitting MS; PPMS-primary progressive MS; SPMS-secondary progressive MS; PT-physiotherapy; FES-functional electrical stimulation; RCT- randomized controlled trial; IG-intervention group; CG-control group; 10MWT-10 meter walk test; 20MWT-20 meter walk test; T25FWT-timed 25 foot walk test; EDSS-Expanded disability status scale; PDDS-Patient Determined Disease Steps; WBV-whole body vibration; BWSTT-body weight support treadmill training; VR-virtual reality; F-frequency; I-intensity; T-Time; MI-Motor imagery; wk-week; min-minutes; hr-hour: MVC- maximal voluntary contraction; HRmax- age-predicted maximal heart rate; RPE-Rate of Perceived Exertion; TOCT-task oriented circuit training; tolerated maximum workload (TMW); RM-repetition maximum; Reps-repetitions in each set; TRX-total body resistance exercise; $VO_2$ peak-peak oxygen uptake; min-minutes; sec-seconds; m/sec-meters/second; cm/sec-centimeters/second; km/hr-kilometers/hour; ft/sec-feet/second.

### 2.3.3 Summary of the included studies

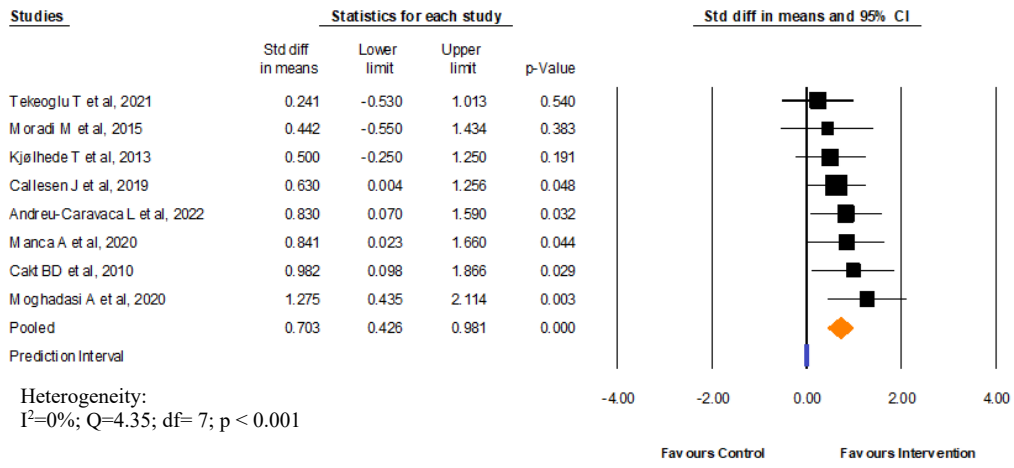
**Lower limb resistance (n=9)**

Nine studies, with 264 participants (age range between 16-59 years with EDSS ranging from 0-6.5), investigated the effectiveness of lower limb resistance training in improving gait speed. The meta-analysis (n=8) showed a large effect (d=0.70; [95%CI=0.42, 0.98]; $I^2$=0%; Q=4.35; df= 7; p < 0.001). Since Q is less than 7 and $I^2$ is 0%, we assumed that there was no dispersion of true effects, and therefore, the prediction interval was not reported (Figure 2.3a).

**Treadmill (n=13)**

Thirteen studies, with 476 participants (age range 20-84 years with EDSS ranging from 1.0-7.0), investigated the effectiveness of treadmill training on gait speed (Table 2.1). The meta-analysis (n=12) showed a moderate effect (d=0.52; 95%CI=0.23, 0.81) and limited heterogeneity between studies ($I^2$=49%; Q=21.41; df= 11; p =0.029) (Figure 2.3b).

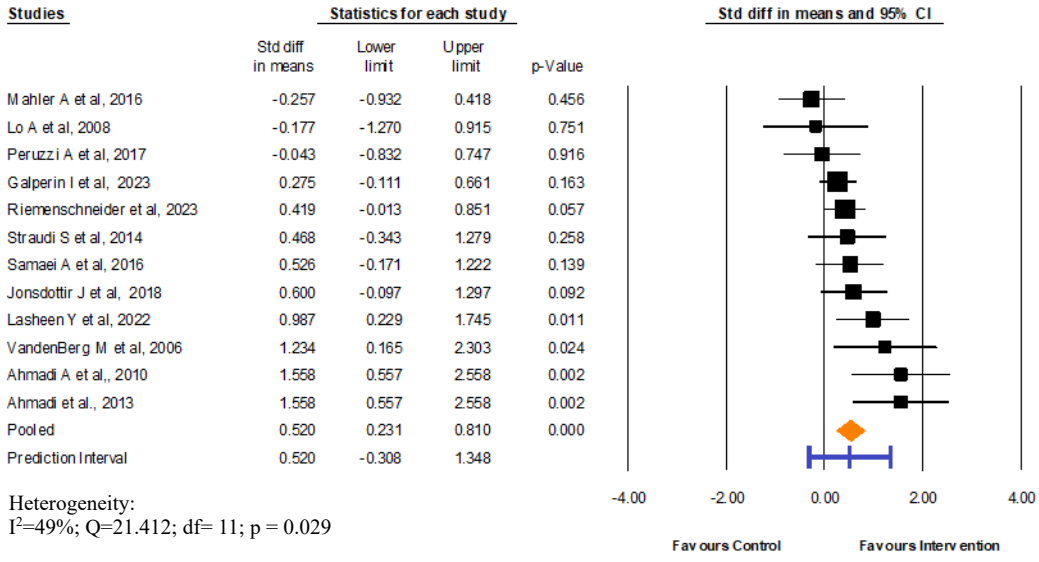
(a) Lower limb resistance




Heterogeneity:
$I^2$=0%; Q=4.35; df= 7; p < 0.001

*Note: There was no dispersion of true effects, so the prediction interval was not reported.*

(b) Treadmill




Heterogeneity:
$I^2$=49%; Q=21.412; df= 11; p = 0.029

**Figure 2.3 Meta-analysis of the effect of (a) Lower limb resistance (b) Treadmill**

**Whole body vibration (n=6)**

Six studies, with 192 participants (age range 16-74 years with EDSS ranging from 1.5-7.0), investigated the effect of whole body vibration on gait speed (Table 1). The meta-analysis (n=5) showed a moderate effect (d=0.41; 95%CI=-0.30, 1.13; p=0.25), but the effect was not statistically significant. We found significant heterogeneity between studies ($I^2$=79%; Q=18.95; df= 4; p= 0.001) (Figure 2.4a).

**Overground and Robotic gait (n=12)**

Twelve studies with 436 participants (age range between 18 and 72 years with EDSS ranging from 1.5 to 7.5) evaluated overground and robotic gait training on gait speed (Table 1). The meta-analysis (n=9) showed a small effect (d=0.23; 95%CI=-0.23, 0.70; p=0.33), but the effect was not statistically significant. We found significant heterogeneity between studies ($I^2$=72%; Q=28.16; df= 8; p<0.001) (Figure 2.4b).

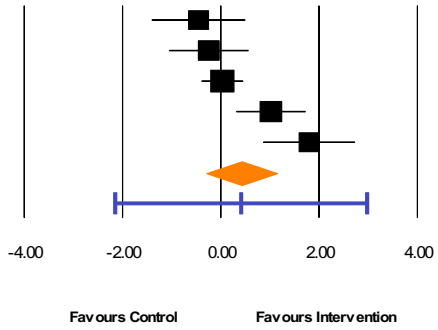
**Home exercise (n=10)**

Ten studies, with 353 participants (age range between 25-65 years with EDSS ranging from 2-8) evaluated the effects of home exercises on gait speed. The meta-analysis (n=8) showed a small effect (d=0.15; 95%CI=-0.15, 0.47; p=0.33), but the effect was not statistically significant. We found limited heterogeneity across studies ($I^2$=42%; Q=28.16; df=7; p=0.09) (Figure 2.4c).

**(a) Whole body vibration**

| Studies | Std diff in means | Lower limit | Upper limit | p-Value |
|---|---|---|---|---|
| Wolfsegger T et al., 2014 | -0.453 | -1.417 | 0.512 | 0.358 |
| Broekmans T et al, 2010 | -0.243 | -1.064 | 0.578 | 0.562 |
| Hilgers C et al, 2013 | 0.032 | -0.403 | 0.467 | 0.884 |
| Escudero-Uribe S et al, 2017 | 1.021 | 0.305 | 1.737 | 0.005 |
| Eftekhari E et al, 2012 | 1.798 | 0.850 | 2.746 | 0.000 |
| Pooled | 0.415 | -0.304 | 1.134 | 0.257 |
| Prediction Interval | 0.415 | -2.147 | 2.978 | |

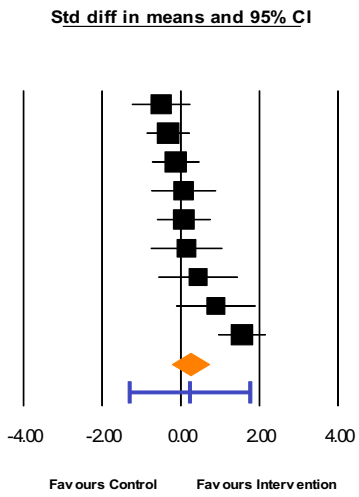
Heterogeneity:
$I^2$=79%; Q=18.95; df= 4; p =




**(b) Over ground & Robotic**

| Studies | Std diff in means | Lower limit | Upper limit | p-Value |
|---|---|---|---|---|
| Schwartz I et al, 2012 | -0.498 | -1.258 | 0.261 | 0.198 |
| Vaney C et al, 2012 | -0.321 | -0.885 | 0.244 | 0.266 |
| Martini D et al, 2018 | -0.128 | -0.749 | 0.492 | 0.685 |
| Gandolfi M et al, 2014 | 0.072 | -0.768 | 0.911 | 0.867 |
| Berriozabalgoitia R et al, 2021 | 0.078 | -0.620 | 0.777 | 0.826 |
| Sconza C et al, 2021 | 0.147 | -0.778 | 1.072 | 0.756 |
| Munari D et al, 2020 | 0.440 | -0.587 | 1.467 | 0.401 |
| Straudi S et al, 2013 | 0.894 | -0.134 | 1.921 | 0.088 |
| Straudi S et al, 2016 | 1.557 | 0.936 | 2.178 | 0.000 |
| Pooled | 0.234 | -0.238 | 0.706 | 0.332 |
| Prediction Interval | 0.234 | -1.299 | 1.767 | |

Heterogeneity:
$I^2$=72%; Q=28.16; df= 8; p<




**(c) Home exercises**

| Studies | Std diff in means | Lower limit | Upper limit | p-Value |
|---|---|---|---|---|
| Conroy S et al, 2018 | -0.713 | -1.585 | 0.160 | 0.109 |
| Miller L et al, 2009 | -0.251 | -0.970 | 0.467 | 0.493 |
| Heinrich I et al, 2021 | -0.170 | -0.804 | 0.464 | 0.599 |
| Hoang P et al, 2016 | 0.135 | -0.457 | 0.727 | 0.656 |
| Barrett CL et al, 2009 | 0.229 | -0.367 | 0.824 | 0.452 |
| Prosperini L et al, 2013 | 0.286 | -0.390 | 0.961 | 0.407 |
| Novotna K et al, 2019 | 0.672 | 0.016 | 1.327 | 0.045 |
| Mardaniyan Ghahfarrokhi M et al, 2022 | 0.864 | 0.115 | 1.612 | 0.024 |
| Pooled | 0.155 | -0.159 | 0.470 | 0.334 |
| Prediction Interval | 0.155 | -0.662 | 0.972 | |

Heterogeneity:
$I^2$=42%; Q=12.07; df= 7; p=0.098

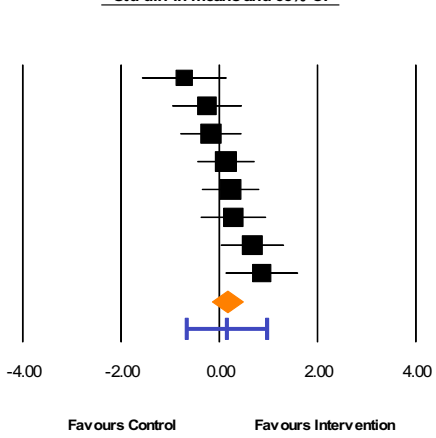



**Figure 2.4 Meta-analysis of the effect of (a) Whole body vibration (b) Over ground & Robotic gait (c) Home exercises**

**Individualized virtual PT (n=8)**

Eight studies with 335 participants (age range between 19-90 with an EDSS ranging from 0-6.5) evaluated the effectiveness of an individually tailored exercise program, which was virtually delivered and supervised. The meta-analysis (n=5) showed a small effect (d=0.15; 95%CI=-0.18, 0.48; p=0.37), but the effect was not statistically significant. We found limited heterogeneity between studies ($I^2$=23%; Q=5.19; df=4; p=0.26) (Figure 2.5a).

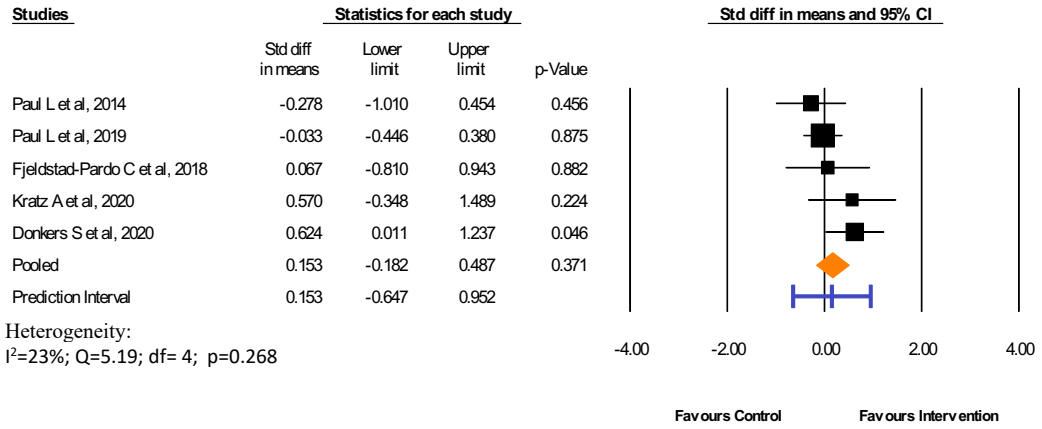
**Pilates and yoga (n=4)**

Four studies with 153 participants (age range between 25-94 with an EDSS ranging from 2-6.5) tested the effectiveness of Pilates (n=3) and yoga (n=1) in improving gait speed. The meta-analysis (n=4) showed a negligible effect (d=0.07; 95%CI=-0.27, 0.42; p=0.65), which was not statistically significant. We found limited heterogeneity between studies ($I^2$=14%; Q=3.47; df=3; p=0.32) (Figure 2.5b).

**Individualized in-person PT (n=12)**

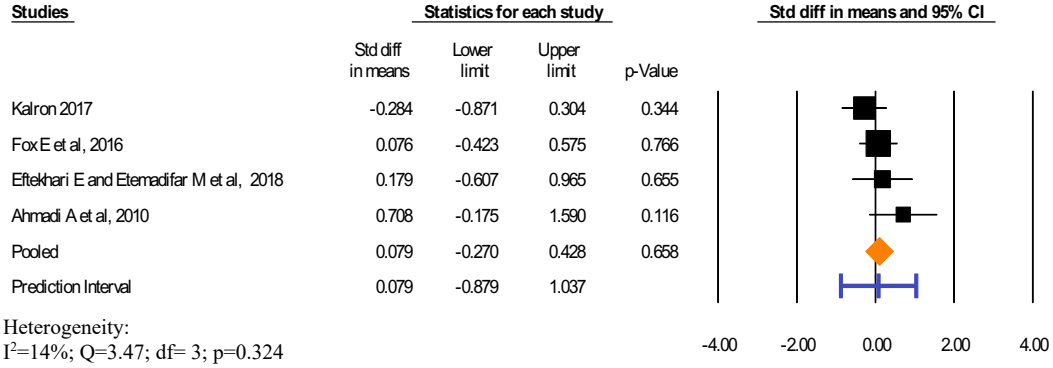
Twelve studies with 496 participants (age range between 27-65 years with an EDSS ranging from 0-8.5) tested individually tailored exercise programs, which were supervised by a physiotherapist at a hospital [137,141,143,162,164,165] or community [138-140,144] and delivered individually or in groups [142,163]. The meta-analysis (n=11) showed a negligible effect (d=0.03; 95%CI=-0.34, 0.40; p=0.86), and the effect was not statistically significant. We found significant heterogeneity between studies ($I^2$=70.3%; Q=33.72; df=10; p<0.001) (Figure 2.5c).

**(a) Individualized virtual PT**



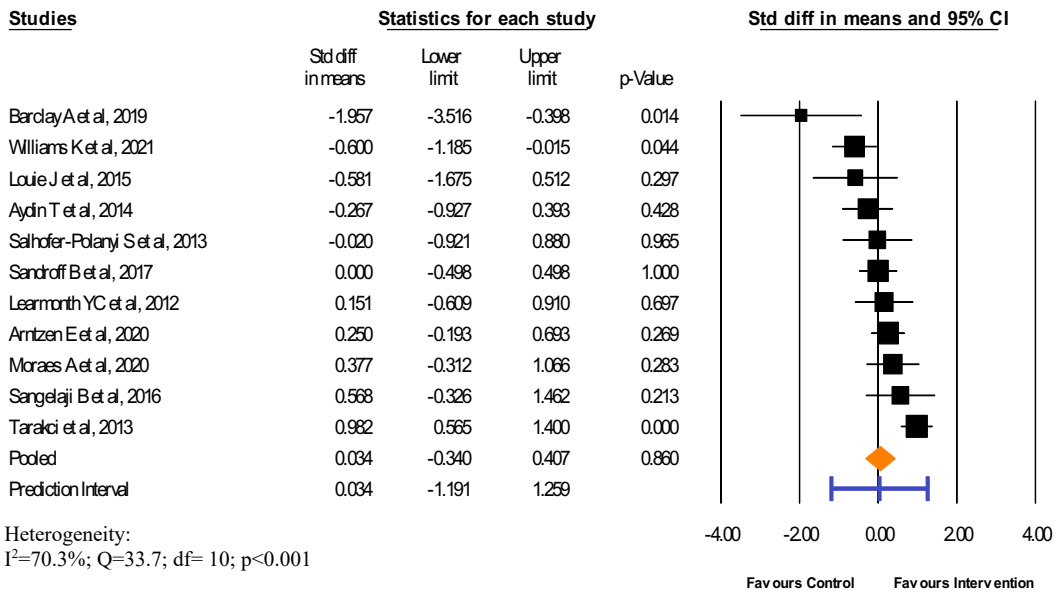

Heterogeneity:
$I^2$=23%; Q=5.19; df= 4; p=0.268

**(b) Pilates & yoga**




Heterogeneity:
$I^2$=14%; Q=3.47; df= 3; p=0.324

**(c) Individualized in-person PT**




Heterogeneity:
$I^2$=70.3%; Q=33.7; df= 10; p<0.001

**Figure 2.5 Meta-analysis of the effect of (a) Individualized virtual PT (b) Pilates & yoga (c) Individualized in-person PT**

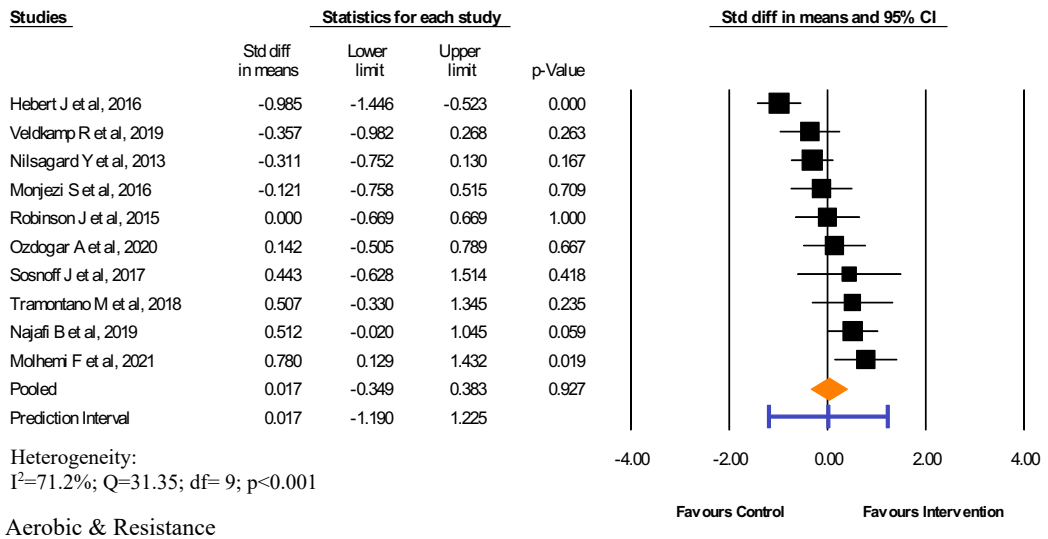
**Balance (n=10)**

Ten studies, with 406 participants (age range between 28-63 years with an EDSS ranging from 0-7.0) investigated balance training on gait speed. The meta-analysis (n=10) showed a negligible effect (d=0.01; 95%CI=-0.34, 0.38; p=0.92), and the effect was not statistically significant. We found significant heterogeneity across studies ($I^2$=71%; Q=31.35; df=9; p<0.001) (Figure 2.6a).

**Aerobic and Resistance (n=6)**

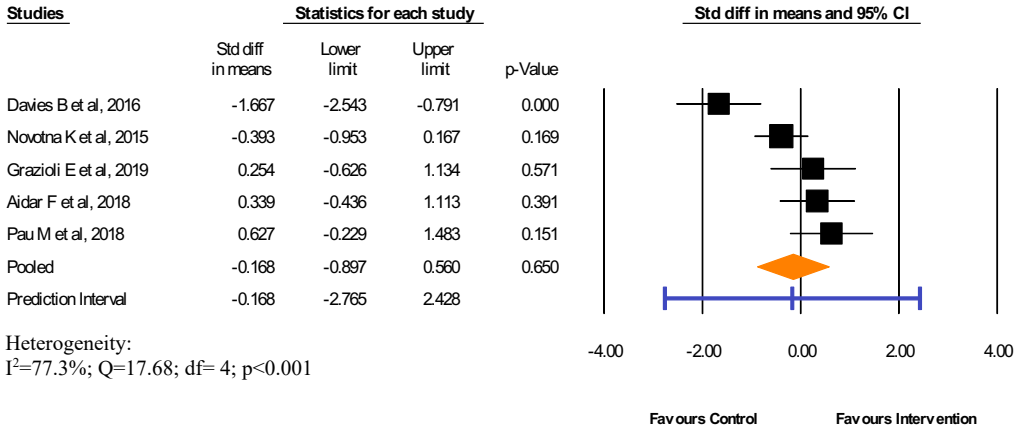
Six studies with 165 participants (age range between 32-63 years with an EDSS ranging from 0-6.6) investigated the effect of combined aerobic and resistance training [56,150-154]. The meta-analysis (n=5) showed a small effect favored the control group (d=-0.16; 95%CI=-0.89, 0.56; p=0.65), but the effect was not statistically significant. We found significant heterogeneity across studies ($I^2$=77%; Q=17.68; df=4; p<0.001) (Figure 2.6b) (refer to supplementary file 2.2).

(a) Balance




Heterogeneity:
$I^2$=71.2%; Q=31.35; df= 9; p<0.001

(b) Aerobic & Resistance




Heterogeneity:
$I^2$=77.3%; Q=17.68; df= 4; p<0.001

**Figure 2.6 Meta-analysis of the effect of (a) Balance (b) Aerobic and Resistance**

### 2.3.4 Methodological quality

The methodological quality of the included studies is summarized in Table 2.2. The mean score of PEDro was 6.4 (SD:1.5, range 3-10). Only a few trials reported blinding of subjects (n=14) and therapists (n=7), and more than half of the studies (n=53) mentioned intention-to-treat analysis. Most of the studies (n=65) had good methodological quality (PEDro=6-10), while other studies had fair (PEDro=4-5; n=23) to poor quality (PEDro=3; n=2).

**Table 2.2 Methodological quality of the trials included in this review**

| Author name; year | 1 | 2 | 3 | 4 | 5 | 6. | 7 | 8 | 9 | 10 | Study Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Lower limb Resistance (n=9) | | | | | | | | | | | |
| Moradi M et al, 2015 [99] | | | | | | | | | | | Poor |
| Caravaca L et al, 2022 [155] | | | | | | | | | | | Good |
| Cakt BD et al, 2010 [100] | | | | | | | | | | | Good |
| Callesen J et al, 2019 [50] | | | | | | | | | | | Good |
| Hayes H et al, 2011 [101] | | | | | | | | | | | Fair |
| Kjølhede T et al, 2013 [51] | | | | | | | | | | | Fair |
| Manca A et al, 2020 [102] | | | | | | | | | | | Good |
| Moghadasi A et al, 2020 [103] | | | | | | | | | | | Fair |
| Tekeoglu T et al, 2021 [104] | | | | | | | | | | | Good |
| Treadmill) (n=13) | | | | | | | | | | | |
| Ahmadi A et al,, 2010 [52] | | | | | | | | | | | Good |
| Jonsdottir J et al, 2018 [108] | | | | | | | | | | | Good |
| Lasheen Y et al, 2022 [156] | | | | | | | | | | | Good |
| Mahler A et al, 2016 [157] | | | | | | | | | | | Good |
| Samaei A et al, 2016 [106] | | | | | | | | | | | Good |
| VandenBerg M et al, 2006 [158] | | | | | | | | | | | Fair |
| Ahmadi et al., 2013 [57] | | | | | | | | | | | Fair |
| Straudi S et al, 2014 [105] | | | | | | | | | | | Good |
| Riemenschneider et al, 2023 [107] | | | | | | | | | | | Good |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Lo A et al, 2008 [68] | | | | | | | | | | | Good |
| Ruiz J et al, 2013 [159] | | | | | | | | | | | Good |
| Peruzzi A et al, 2017 [74] | | | | | | | | | | | Fair |
| Galperin I et al, 2023 [54] | | | | | | | | | | | Good |
| Whole Body Vibration (n=6) | | | | | | | | | | | |
| Broekmans T et al, 2010 [160] | | | | | | | | | | | Fair |
| Hilgers C et al, 2013 [109] | | | | | | | | | | | Good |
| Eftekhari E et al, 2012 [161] | | | | | | | | | | | Fair |
| Schyns F et al, 2009 [110] | | | | | | | | | | | Good |
| Wolfsegger T et al., 2014 [111] | | | | | | | | | | | Good |
| Escudero-Uribe S et al, 2017 [112] | | | | | | | | | | | Good |
| Overground and Robotic Gait (n=12) | | | | | | | | | | | |
| Sconza C et al, 2021 [115] | | | | | | | | | | | Good |
| Straudi S et al, 2020 [116] | | | | | | | | | | | Good |
| Gandolfi M et al, 2014 [67] | | | | | | | | | | | Fair |
| Vaney C et al, 2012 [70] | | | | | | | | | | | Good |
| Berriozabalgoitia R et al, 2021 [66] | | | | | | | | | | | Good |
| Martini D et al, 2018 [118] | | | | | | | | | | | Good |
| Munari D et al, 2020 [73] | | | | | | | | | | | Good |
| Straudi S et al, 2016 [114] | | | | | | | | | | | Good |
| Straudi S et al, 2013 [113] | | | | | | | | | | | Good |
| Schwartz I et al, 2012 [69] | | | | | | | | | | | Good |
| Beer S et al, 2008 [79] | | | | | | | | | | | Good |
| Shahraki M et al, 2017 [117] | | | | | | | | | | | Good |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Home Exercises (n=10) | | | | | | | | | | | |
| Taylor P et al, 2014 [120] | | | | | | | | | | | Fair |
| Barrett CL et al, 2009 [119] | | | | | | | | | | | Good |
| Conroy S et al, 2018 [121] | | | | | | | | | | | Fair |
| Hoang P et al, 2016 [122] | | | | | | | | | | | Good |
| Mardaniyan G M et al, 2022 [123] | | | | | | | | | | | Good |
| Miller L et al, 2009 [124] | | | | | | | | | | | Good |
| Prosperini L et al, 2013 [125] | | | | | | | | | | | Good |
| Heinrich I et al, 2021 [127] | | | | | | | | | | | Good |
| Seebacher B et al, 2018 [128] | | | | | | | | | | | Good |
| Novotna K et al, 2019 [168] | | | | | | | | | | | Fair |
| Individualized virtual PT (n=8) | | | | | | | | | | | |
| Eldemir K et al, 2023 [62] | | | | | | | | | | | Good |
| Kratz A et al, 2020 [129] | | | | | | | | | | | Good |
| Fjeldstad-Pardo C et al, 2018 [130] | | | | | | | | | | | Good |
| Kahraman T et al, 2020 [131] | | | | | | | | | | | Good |
| Donkers S et al, 2020 [132] | | | | | | | | | | | Fair |
| Flachenecker P et al, 2020 [133] | | | | | | | | | | | Fair |
| Paul L et al, 2014 [134] | | | | | | | | | | | Fair |
| Paul L et al, 2019 [135] | | | | | | | | | | | Good |
| Pilates and yoga (n=4) | | | | | | | | | | | |
| Eftekhari E and Etemadifar M, 2018 [61] | | | | | | | | | | | Fair |
| Fox E et al, 2016 [63] | | | | | | | | | | | Good |
| Kalron A et al., 2017 [64] | | | | | | | | | | | Good |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ahmadi A et al, 2010 [58] | | | | | | | | | | | Good |
| Individualized in-person PT (n=12) | | | | | | | | | | | |
| Aydin T et al, 2014 [162] | | | | | | | | | | | Fair |
| Salhofer-Polanyi S et al, 2013 [137] | | | | | | | | | | | Good |
| Williams K et al, 2021 [138] | | | | | | | | | | | Good |
| Tarakci Et al, 2013 [142] | | | | | | | | | | | Good |
| Arntzen E et al, 2020 [163] | | | | | | | | | | | Good |
| Learmonth YC et al, 2012 [139] | | | | | | | | | | | Good |
| Louie J et al, 2015 [140] | | | | | | | | | | | Good |
| Sandroff B et al, 2017 [141] | | | | | | | | | | | Good |
| Moraes A et al, 2020 [144] | | | | | | | | | | | Fair |
| Barclay A et al, 2019 [164] | | | | | | | | | | | Good |
| Sangelaji B et al, 2016 [143] | | | | | | | | | | | Good |
| Sepehri Far S et al, 2022 [165] | | | | | | | | | | | Poor |
| Balance (n=10) | | | | | | | | | | | |
| Hebert J et al, 2016 [145] | | | | | | | | | | | Good |
| Molhemi F et al, 2021 [72] | | | | | | | | | | | Good |
| Monjezi S et al, 2016 [146] | | | | | | | | | | | Good |
| Nilsagard Y et al, 2013 [147] | | | | | | | | | | | Good |
| Robinson J et al, 2015 [77] | | | | | | | | | | | Fair |
| Sosnoff J et al, 2017 [166] | | | | | | | | | | | Good |
| Veldkamp R et al, 2019 [167] | | | | | | | | | | | Good |
| Najafi B et al, 2019 [148] | | | | | | | | | | | Good |
| Ozdogar A et al, 2020 [76] | | | | | | | | | | | Good |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Tramontano M et al, 2018 [149] | | | | | | | | | | | Good |
| Aerobic and Resistance (n=6) | | | | | | | | | | | |
| Grazioli E et al, 2019 [151] | | | | | | | | | | | Fair |
| Davies B et al, 2016 [150] | | | | | | | | | | | Good |
| Novotna K et al, 2015 [152] | | | | | | | | | | | Good |
| Pau M et al, 2018 [153] | | | | | | | | | | | Fair |
| Romberg A et al, 2004 [154] | | | | | | | | | | | Fair |
| Aidar F et al, 2018 [56] | | | | | | | | | | | Fair |

| 1 | 0 |
|---|---|

1. Random allocation 2. Concealed allocation 3. Baseline comparability 4. Masked participants 5. Masked therapists 6. Masked assessors 7. Adequate follow-up 8. Intention to treat analysis 9. Between-group statistical comparison 10. Point estimates and variability. Study Quality based on PEDro score: 0-3 Poor; 4-5 Fair; 6-10 Good.

## 2.4 Discussion

The objective of the systematic review was to evaluate the existing evidence regarding the effectiveness of rehabilitation interventions to improve gait speed for people with MS. We report 3 key findings: 1) there is a large body of evidence (90 RCTs) testing rehabilitation interventions to improve gait speed in MS, 2) overall there was a positive, albeit small effect of the interventions on gait speed, and 3) considering subgroups of intervention, lower limb resistance and treadmill training were the most effective interventions to improve walking in MS.

### 2.4.1 A large body of evidence testing rehabilitation interventions to improve gait speed

We observed a growing body of evidence (90 RCTs) testing rehabilitation interventions; the first study appeared in 2006 [158], and about 30 RCTs were conducted in the last 5 years. Commonly tested interventions were progressive resistance, treadmill training with and without body weight support, robotic-assisted gait, and individually tailored in-person or virtual PT-supervised interventions. The duration of these interventions ranged from 3 weeks to 48 weeks, with varying intensities. Surprisingly, PT-supervised programs, task-specific overground and robotic gait or combined aerobic and resistance programs were not effective. This was likely due to significant variability in intervention dosage and the delivery of intervention. For instance, eight studies examined the effectiveness of individualized virtual PT. Of these, two studies which had 12-24 one-hour sessions with a clearly defined intensity regimen (20 repetitions with Thera bands[62] and maximum exertion using Borg scale [133]) reported improvement in gait speed. Conversely, the remaining six studies, which included 30-minute sessions without specified intensity, did not report improvements in gait speed. Furthermore, overground or robotic gait training is considered ‘context-specific task-oriented’ in which participants are trained on varied

surfaces and environments that are similar to day-to-day life. Notably, the gait speed varies during overground and robotic gait training [169]. Hence, scales that capture walking in different contexts (indoors, outdoors, obstacles, inclined surfaces) may be more appropriate to test the efficiency of such interventions [170]. Furthermore, whole-body vibration, Pilates and yoga, and aerobic and resistance groups all have 6 or fewer studies. In a heterogeneous condition like MS with variability in training programs, it is difficult to capture a trend.

### 2.4.2 Positive effect of rehabilitation in improving gait speed

Despite significant heterogeneity across trials, our review revealed a positive but small effect (d=0.233; p=0.01) of rehabilitation on gait speed in MS. Gait speed is considered an important clinical endpoint in both drug and exercise trials. The overall effect size reported here is comparable to the effectiveness of Fampridine (calcium channel blocker) on gait speed (effect size of 0.39) [171]. Similar effects of exercise on gait speed have been reported in other conditions such as Parkinson's disease (z=3.32; p=0.0009) [172] and acquired brain injury (z=2.01; p=0.04) [173]. Our findings also align with two other studies in MS: a systematic review of 22 studies (both RCTs and non-RCTs) investigating the effectiveness of exercise training on mobility, which reported a small effect size (d= 0.19) [89], and review of 13 RCTs evaluating various exercise interventions (aquatic, yoga, aerobic and resistance training) in ambulatory MS patients which also revealed a small overall effect of exercise on gait speed (10MWT, walk time mean difference of -1.76 seconds; 95% CI, −2.47 to −1.06; *P*<.001) [174]. In our review, participants' gait speeds at baseline were high in some of the studies [107,126,145,147,157,165-167], and that would have left no room for larger improvements (ceiling effect of the gait measures). Another possible explanation could be smaller sample sizes and shorter duration of rehabilitation interventions

compared to Fampridine drug trials [175]. Future trials should prioritize the integration of rehabilitation interventions with gait-improving drugs to potentially achieve an additive effect in enhancing gait speed.

### 2.4.3 Lower limb resistance and treadmill training were the most effective

Our findings confirmed a large effect of lower limb resistance (d= 0.70; 95% CI 0.42, 0.98; p<0.001) and a moderate effect of treadmill training (d= 0.52; 95%CI, 0.23, 0.81; p<0.001), on improvement in gait speed. In line with our findings, a recent systematic review reported the equal efficacy of resistance and aerobic training in improving gait speed on short walk tests such as 10MWT [49]. Notably, we reported nearly double the sizes compared to Taul-Madsen group (resistance training d=0.27; 95% CI, 0.07, -0.47 and aerobic training d=0.33; 95% CI, -1.49, 2.06). In contrast, our review included a more extensive dataset; eight studies investigating lower limb resistance and twelve studies on treadmill training and confidence intervals indicate a low degree of uncertainty. Notably, studies within the lower limb resistance group focused on exercises aimed at strengthening lower limb muscles, which are both functional and task-specific, that target the improvement of gait speed [51,100-104]. All the studies included almost similar intensity (50-80% of one repetition maximum or high-intensity progressive resistance), and no heterogeneity across the studies ($I^2$=0%). Treadmill training has been effective in other neurological disorders such as stroke [176], and Parkinson's disease [177]. Participants are forced to walk on treadmill at higher speeds than overground walking and involve repetitive gait cycles [177]. The steps taken are stable and synchronous with the treadmill speed, which likely improves gait speed [178]. The important issue of intervention dosage (intervention approach or the volume of training) is worthy of future research. To our knowledge, our systematic review is the first and

largest investigation into the effects of a comprehensive list of rehabilitation interventions on gait speed in MS. As research moves forward to combine rehabilitation with reparative drugs or plasticity-promoting central nervous system stimulation [81], it is important to employ superior interventions known to be effective on their own.

### 2.4.4 Limitations

Despite including a large dataset of RCTs there are some limitations to consider. Firstly, the heterogeneity across the tested interventions required us to categorize groups based on their similarity to one another rather than strict grouping criteria. Secondly, our review focused on only one moderator, the intervention type, while acknowledging the other potential modifiers, such as participant characteristics could have influenced the overall effect. Lastly, we included only short walk tests that measured gait speed, while several studies that included long walk tests, such as 6-minute walk tests, were excluded. We can, therefore, only discuss the effects of the interventions on gait speed, not walking endurance.

## 2.5 Conclusion

Our systematic review and meta-analysis of RCTs provide insights into the various interventions tested to improve gait speed in MS. There was significant heterogeneity across trials; caution is needed in interpreting the findings. Despite heterogeneity, exercise has an overall positive effect on walking in people with MS. Notably, lower limb resistance and treadmill training were observed to be the most effective interventions.

**Acknowledgements**

We thank MS Canada (endMS doctoral studentship) for supporting this study.

## Supplementary Material for Chapter 2

### 2.1 Supplementary file: Search Strategies

Searches[179] were run on August 2, 2021 and re-run on June 13, 2023.

### Ovid MEDLINE(R) ALL <1946 to June 12, 2023>

Search conducted June 13, 2023

| | |
|---|---|
| 1 | exp Multiple Sclerosis/ 69631 |
| 2 | multiple sclerosis.tw,kf. 90850 |
| 3 | pwms.tw,kf. 1772 |
| 4 | ms.ti. 44749 |
| 5 | or/1-4 139290 |
| 6 | exp Exercise/ 245512 |
| 7 | exp Exercise Therapy/ 63055 |
| 8 | exp Exercise Test/ 70905 |
| 9 | exp Exercise Movement Techniques/ 10247 |
| 10 | Early Ambulation/ 3251 |
| 11 | exercis*.tw,kf. 362848 |
| 12 | ((interval or resistance or endurance or circuit or balance or gait or step or stepper or muscle* or muscular* or isometric* or plyometric* or physical or fitness or athletic* or strength or aerobic) adj3 (activit* or train* or retrain* or re train* or therap* or intervention* or program* or conditioning)).tw,kf. 348107 |
| 13 | (aerobics or walk* or jog or jogging or running or recumbent stepping or swim* or bicycl* or cycling or pedal* or dance or dancing or yoga or pilates or exergam* or exer gam* or treadmill).tw,kf. 400265 |
| 14 | ((gait or walk* or physical) adj3 rehab*).tw,kf. 10218 |
| 15 | Virtual Reality/ 5473 |
| 16 | (virtual reality or vr).tw,kf. 22686 |
| 17 | Exoskeleton Device/ 1419 |
| 18 | (exoskeleton* or (exo adj skeleton*)).tw,kf. 4534 |
| 19 | Robotics/ 27235 |

20 (robot* or ragt).tw,kf. 70296

21 or/6-20 1082789

22 exp Gait/ 36912

23 gait*.tw,kf. 66531

24 ambulat*.tw,kf. 106607

25 exp Walking/ 67237

26 Walk Test/ 2538

27 walk*.tw,kf. 146863

28 (10mWT or T25FWT or 500mWT).tw,kf. 448

29 step test*.tw,kf. 2489

30 stepping.tw,kf. 10655

31 ((step* or stride*) adj (length or width or time)).tw,kf. 8765

32 ((double limb or single limb or "base of") adj support).tw,kf. 543

33 double support.tw,kf. 1222

34 cadence.tw,kf. 4330

35 velocity.tw,kf. 195948

36 ground reaction force*.tw,kf. 6904

37 or/22-36 497510

38 5 and 21 and 37 2809

39 randomized controlled trial.pt. 594416

40 controlled clinical trial.pt. 95334

41 randomi?ed.ab. 723934

42 placebo.ab. 238959

43 drug therapy.fs. 2598628

44 randomly.ab. 410192

45 trial.ab. 651611

46 groups.ab. 2528681

47 or/39-46 5699311

48 exp animals/ not humans.sh. 5129978

| | | |
|---|---|---|
| 49 | 47 not 48 | 4975466 |
| 50 | 38 and 49 | 1261 |
| 51 | (random* or crossover* or (cross adj over*) or placebo* or ((singl* or doubl* or tripl*) adj blind*) or assign* or allocat* or trial or rct).tw,kf. | 2181229 |
| 52 | 51 not medline.st. | 331866 |
| 53 | 38 and 52 | 159 |
| 54 | 50 or 53 | 1275 |
| 55 | limit 54 to english | 1247 |

Note: Lines 39-49 are based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format, with the addition of a wildcard in line 41.

## Embase (via Embase.com)[180,181]

Search conducted June 13, 2023

| No. | Embase.com Query | Results |
|---|---|---|
| #1 | 'multiple sclerosis'/de OR 'multiple sclerosis':ti,ab,kw OR pwms:ti,ab,kw OR ms:ti | 225758 |
| #2 | 'exercise'/exp OR 'kinesiotherapy'/exp OR 'exercise test'/exp OR 'mobilization'/de OR 'virtual reality'/de OR 'exoskeleton (rehabilitation)'/exp OR 'robotics'/exp | 672976 |
| #3 | exercis*:ti,ab,kw OR (((interval OR resistance OR endurance OR circuit OR balance OR gait OR step OR stepper OR muscle* OR muscular* OR isometric* OR plyometric* OR physical OR fitness OR athletic* OR strength OR aerobic) NEAR/3 (activit* OR train* OR retrain* OR 're train*' OR therap* OR intervention* OR program* OR conditioning)):ti,ab,kw) OR aerobics:ti,ab,kw OR walk*:ti,ab,kw OR jog:ti,ab,kw OR jogging:ti,ab,kw OR running:ti,ab,kw OR 'recumbent stepping':ti,ab,kw OR swim*:ti,ab,kw OR bicycl*:ti,ab,kw OR cycling:ti,ab,kw OR pedal*:ti,ab,kw OR dance:ti,ab,kw OR dancing:ti,ab,kw OR yoga:ti,ab,kw OR pilates:ti,ab,kw OR exergam*:ti,ab,kw OR 'exer gam*':ti,ab,kw OR treadmill:ti,ab,kw OR (((gait OR walk* OR physical) NEAR/3 rehab*):ti,ab,kw) OR 'virtual reality':ti,ab,kw OR vr:ti,ab,kw OR exoskeleton*:ti,ab,kw OR ((exo NEAR/1 skeleton*):ti,ab,kw) OR robot*:ti,ab,kw OR ragt:ti,ab,kw | 1349609 |
| #4 | #2 OR #3 | 1539353 |
| #5 | 'walking'/exp OR 'walk test'/exp OR 'walking parameters'/exp OR 'ground reaction force'/de | 175766 |
| #6 | gait*:ti,ab,kw OR ambulat*:ti,ab,kw OR walk*:ti,ab,kw OR 10mwt:ti,ab,kw OR t25fwt:ti,ab,kw OR 500mwt:ti,ab,kw OR 'step test*':ti,ab,kw OR stepping:ti,ab,kw OR (((step* OR stride*) NEXT/1 (length OR width OR time)):ti,ab,kw) OR ((('double limb' OR 'single limb' OR 'base of') NEXT/1 support):ti,ab,kw) OR 'double support':ti,ab,kw OR cadence:ti,ab,kw OR velocity:ti,ab,kw OR 'ground reaction force*':ti,ab,kw | 667910 |
| #7 | #5 OR #6 | 696509 |
| #8 | #1 AND #4 AND #7 | 6165 |
| #9 | 'randomized controlled trial'/de | 769230 |

| | | |
|---|---|---|
| #10 | 'controlled clinical trial'/de | 440085 |
| #11 | random*:ti,ab,tt | 1934147 |
| #12 | 'randomization'/de | 97302 |
| #13 | 'intermethod comparison'/de | 298883 |
| #14 | placebo:ti,ab,tt | 361037 |
| #15 | compare:ti,tt OR compared:ti,tt OR comparison:ti,tt | 619720 |
| #16 | (evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab) | 2716880 |
| #17 | (open NEXT/1 label):ti,ab,tt | 106359 |
| #18 | ((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt | 272155 |
| #19 | 'double blind procedure'/de | 207854 |
| #20 | (parallel NEXT/1 group*):ti,ab,tt | 31560 |
| #21 | crossover:ti,ab,tt OR 'cross over':ti,ab,tt | 123039 |
| #22 | ((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt | 449558 |
| #23 | assigned:ti,ab,tt OR allocated:ti,ab,tt | 481092 |
| #24 | (controlled NEAR/8 (study OR design OR trial)):ti,ab,tt | 450382 |
| #25 | volunteer:ti,ab,tt OR volunteers:ti,ab,tt | 281167 |
| #26 | 'human experiment'/de | 630820 |
| #27 | trial:ti,tt | 398780 |
| #28 | #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 | 6254963 |

| | | |
|---|---|---|
| #29 | ((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database OR databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'randomly assigned':ti,ab,tt) | 3083 |
| #30 | 'cross-sectional study' NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'control group':ti,ab,tt OR 'control groups':ti,ab,tt) | 372478 |
| #31 | 'case control*':ti,ab,tt AND random*:ti,ab,tt NOT ('randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt) | 21117 |
| #32 | 'systematic review':ti,tt NOT (trial:ti,tt OR study:ti,tt) | 248633 |
| #33 | nonrandom*:ti,ab,tt NOT random*:ti,ab,tt | 18695 |
| #34 | 'random field*':ti,ab,tt | 2877 |
| #35 | ('random cluster' NEAR/4 sampl*):ti,ab,tt | 1555 |
| #36 | review:ab AND review:it NOT trial:ti,tt | 1090553 |
| #37 | 'we searched':ab AND (review:ti,tt OR review:it) | 47714 |
| #38 | 'update review':ab | 136 |
| #39 | (databases NEAR/5 searched):ab | 64245 |
| #40 | (rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de | 1210156 |
| #41 | 'animal experiment'/de NOT ('human experiment'/de OR 'human'/de) | 2541507 |
| #42 | #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 | 4281456 |
| #43 | #28 NOT #42 | 5526355 |
| #44 | #8 AND #43 | 2553 |
| #45 | #44 AND [english]/lim | 2514 |

Note: In the original search run August 2, 2021, there was a syntax error in line #3. The OR was missing between exoskeleton*:ti,ab,kw **OR** (exo NEAR/1 skeleton*):ti,ab,kw. This error was corrected when the search was re-run on June 13, 2023.

Lines #9-#43 are a version of the Cochrane Embase RCT filter for Embase.com. Available at https://drive.google.com/file/d/10JU-2vicvIc83_PghgelfqY5aQnYd-hB/view.

## Web of Science Core Collection

Search conducted: June 13, 2023

Editions searched:

Arts & Humanities Citation Index (A&HCI)--1975-present

Conference Proceedings Citation Index – Science (CPCI-S)--1990-present

Conference Proceedings Citation Index – Social Science & Humanities (CPCI-SSH)--1990-present

Emerging Sources Citation Index (ESCI)--2015-present

Science Citation Index Expanded (SCI-EXPANDED)--1900-present

Social Sciences Citation Index (SSCI)--1956-present

| # | Web of Science Core Collection Query | Results |
|---|---|---|
| #1 | TS=("multiple sclerosis" OR pwms) OR TI=(ms) | 229,356 |
| #2 | TS=(exercis* OR ((interval OR resistance OR endurance OR circuit OR balance OR gait OR step OR stepper OR muscle* OR muscular* OR isometric* OR plyometric* OR physical OR fitness OR athletic* OR strength OR aerobic) NEAR/3 (activit* OR train* OR retrain* OR (re NEAR/0 train*) OR therap* OR intervention* OR program* OR conditioning)) OR aerobics OR walk* OR jog OR jogging OR running OR "recumbent stepping" OR swim* OR bicycl* OR cycling OR pedal* OR dance OR dancing OR yoga OR pilates OR exergam* OR (exer NEAR/0 gam*) OR treadmill OR ((gait OR walk* OR physical) NEAR/3 (rehab*)) OR "virtual reality" OR VR OR exoskeleton* OR (exo NEAR/0 skeleton*) OR robot* OR ragt) | 4,122,021 |
| #3 | TS=(gait* OR ambulat* OR walk* OR 10mWT OR T25FWT OR 500mWT OR stepping OR (step NEAR/0 test*) OR ((step* OR stride*) NEAR/0 (length OR width OR time)) OR (("double limb" OR "single limb" OR "base of") NEAR/0 support) OR "double support" OR cadence OR velocity OR ("ground reaction" NEAR/0 force*)) | 3,046,544 |
| #4 | #1 AND #2 AND #3 | 4,632 |
| #5 | TS=(random* OR crossover* OR (cross NEAR/0 over*) OR placebo* OR ((singl* OR doubl* OR tripl*) NEAR/0 blind*) OR assign* OR allocat* OR trial OR rct) | 4,452,623 |
| #6 | #4 AND #5 | 1,469 |
| #7 | #6 AND LA=English | 1,440 |

## SPORTDiscus with Full Text (via EBSCO)

Search conducted: June 13, 2023

| # | SPORTDiscus Query | Results |
|---|---|---|
| S1 | DE "MULTIPLE sclerosis" OR TI ("multiple sclerosis" OR pwms OR ms) OR AB ("multiple sclerosis" OR pwms) OR KW ("multiple sclerosis" OR pwms) | 3,659 |
| S2 | DE "EXERCISE" OR DE "AEROBIC exercises" OR DE "ANAEROBIC exercises" OR DE "AQUATIC exercises" OR DE "BACK exercises" OR DE "BUTTOCKS exercises" OR DE "CALISTHENICS" OR DE "CHAIR exercises" OR DE "CHEST exercises" OR DE "CIRCUIT training" OR DE "COMPOUND exercises" OR DE "EXERCISE adherence" OR DE "EXERCISE therapy" OR DE "EXERCISE video games" OR DE "FOOT exercises" OR DE "GYMNASTICS" OR DE "HATHA yoga" OR DE "HIP exercises" OR DE "ISOKINETIC exercise" OR DE "ISOLATION exercises" OR DE "ISOMETRIC exercise" OR DE "ISOTONIC exercise" OR DE "KNEE exercises" OR DE "LEG exercises" OR DE "PILATES method" OR DE "PLYOMETRICS" OR DE "QI gong" OR DE "REDUCING exercises" OR DE "RUNNING" OR DE "STRENGTH training" OR DE "TAI chi" OR DE "TREADMILL exercise" OR DE "YOGA" OR DE "EXERCISE tests" OR DE "TREADMILL exercise tests" OR DE "PHYSICAL activity" OR DE "PHYSICAL fitness" OR DE "PHYSICAL training & conditioning" OR DE "ANAEROBIC training" OR DE "BASE training (Exercise)" OR DE "BODYBUILDING" OR DE "COMPOUND exercises" OR DE "CONTINUOUS training (Exercise)" OR DE "CROSS-training (Sports)" OR DE "CYCLING training" OR DE "DANCE training & conditioning" OR DE "ENDURANCE sports training" OR DE "FUNCTIONAL training" OR DE "RESISTANCE training" OR DE "RUNNING training" OR DE "WEIGHT training" OR DE "YOGA training & conditioning" OR DE "VIRTUAL reality" OR DE "ROBOTIC exoskeletons" OR SU exercis* | 297,588 |
| S3 | TI (exercis* OR ((interval OR resistance OR endurance OR circuit OR balance OR gait OR step OR stepper OR muscle* OR muscular* OR isometric* OR plyometric* OR physical OR fitness OR athletic* OR strength OR aerobic) N3 (activit* OR train* OR retrain* OR (re N0 train*) OR therap* OR intervention* OR program* OR conditioning)) OR aerobics OR walk* OR jog OR jogging OR running OR "recumbent stepping" OR swim* OR bicycl* OR cycling OR pedal* OR dance OR dancing OR yoga OR pilates OR exergam* OR (exer N0 gam*) OR treadmill OR ((gait OR walk* OR physical) N3 rehab*) OR | 459,426 |

| | | |
|---|---|---|
| | "virtual reality" OR exoskeleton* OR robot* OR ragt)) OR AB (exercis* OR ((interval OR resistance OR endurance OR circuit OR balance OR gait OR step OR stepper OR muscle* OR muscular* OR isometric* OR plyometric* OR physical OR fitness OR athletic* OR strength OR aerobic) N3 (activit* OR train* OR retrain* OR (re N0 train*) OR therap* OR intervention* OR program* OR conditioning)) OR aerobics OR walk* OR jog OR jogging OR running OR "recumbent stepping" OR swim* OR bicycl* OR cycling OR pedal* OR dance OR dancing OR yoga OR pilates OR exergam* OR (exer N0 gam*) OR treadmill OR ((gait OR walk* OR physical) N3 rehab*) OR "virtual reality" OR exoskeleton* OR robot* OR ragt)) OR KW (exercis* OR ((interval OR resistance OR endurance OR circuit OR balance OR gait OR step OR stepper OR muscle* OR muscular* OR isometric* OR plyometric* OR physical OR fitness OR athletic* OR strength OR aerobic) N3 (activit* OR train* OR retrain* OR (re N0 train*) OR therap* OR intervention* OR program* OR conditioning)) OR aerobics OR walk* OR jog OR jogging OR running OR "recumbent stepping" OR swim* OR bicycl* OR cycling OR pedal* OR dance OR dancing OR yoga OR pilates OR exergam* OR (exer N0 gam*) OR treadmill OR ((gait OR walk* OR physical) N3 rehab*) OR "virtual reality" OR VR OR exoskeleton* OR (exo N0 skeleton*) OR robot* OR ragt)) | |
| S4 | S2 OR S3 | 563,565 |
| S5 | DE "GAIT in humans" OR DE "WALKING" OR DE "FITNESS walking" OR DE "WALKING speed" OR DE "PHYSIOLOGICAL aspects of walking" OR DE "STEP tests" OR DE "GROUND reaction forces (Biomechanics)" | 20,630 |
| S6 | TI (gait OR gaits OR gaitrite OR ambulat* OR walk* OR 10mWT OR T25FWT OR 500mWT OR stepping OR (step N0 test*) OR ((step* OR stride*) NEAR/0 (length OR width OR time)) OR (("double limb" OR "single limb" OR "base of") N0 support) OR "double support" OR cadence OR velocity OR ("ground reaction" N0 force*)) OR AB (gait OR gaits OR gaitrite OR ambulat* OR walk* OR 10mWT OR T25FWT OR 500mWT OR stepping OR (step N0 test*) OR ((step* OR stride*) NEAR/0 (length OR width OR time)) OR (("double limb" OR "single limb" OR "base of") N0 support) OR "double support" OR cadence OR velocity OR ("ground reaction" N0 force*)) OR KW (gait OR gaits OR gaitrite OR ambulat* OR walk* OR 10mWT OR T25FWT OR 500mWT OR stepping OR (step N0 test*) OR ((step* OR stride*) NEAR/0 (length OR width OR time)) OR (("double limb" OR "single limb" OR "base of") N0 support) OR "double support" OR cadence OR velocity OR ("ground reaction" N0 force*)) | 77,452 |
| S7 | S5 OR S6 | 80,107 |

| | | |
|---|---|---|
| S8 | S1 AND S4 AND S7 | 617 |
| S9 | DE "RANDOMIZED controlled trials" OR DE "CLINICAL trials" OR DE "CROSSOVER trials" OR DE "BLIND experiment" | 27,205 |
| S10 | random* OR crossover* OR (cross N0 over*) OR placebo* OR ((singl* OR doubl* OR tripl*) N0 blind*) OR assign* OR allocat* OR trial OR rct | 128,233 |
| S11 | S9 OR S10 | 128,396 |
| S12 | S8 AND S11 | 197 |
| S13 | S8 AND S11 Narrow by Language: - english | 196 |

## PEDro: Physiotherapy Evidence Database

Search conducted: June 13, 2023

Abstract & Title: "multiple sclerosis" gait

Method: Clinical Trial

Match all search terms (AND)

97 results

## Cochrane Central Register of Controlled Trials

Issue 6 of 12, June 2023

Search conducted: June 13, 2023

| ID | Search | Hits |
|---|---|---|
| #1 | [mh "Multiple Sclerosis"] | 5876 |
| #2 | ("multiple sclerosis" OR pwms):ti,ab,kw OR ms:ti | 12779 |
| #3 | #1 OR #2 | 12779 |
| #4 | [mh Exercise] OR [mh "Exercise Therapy"] OR [mh "Exercise Test"] OR [mh "Exercise Movement Techniques"] OR [mh ^"Early Ambulation"] OR [mh ^"Virtual Reality"] OR [mh ^"Exoskeleton Device"] OR [mh Robotics] | 57927 |
| #5 | (exercis* OR ((interval OR resistance OR endurance OR circuit OR balance OR gait OR step OR stepper OR muscle* OR muscular* OR isometric* OR plyometric* OR physical OR fitness OR athletic* OR strength OR aerobic) NEAR/3 (activit* OR train* OR retrain* OR (re NEXT train*) OR therap* OR intervention* OR program* OR conditioning)) OR aerobics OR walk* OR jog OR jogging OR running OR "recumbent stepping" OR swim* OR bicycl* OR cycling OR pedal* OR dance OR dancing OR yoga OR pilates OR exergam* OR (exer NEXT gam*) OR treadmill OR ((gait OR walk* OR physical) NEAR/3 (rehab*)) OR "virtual reality" OR vr OR exoskeleton* OR (exo NEXT skeleton*) OR robot* OR ragt):ti,ab,kw | 223696 |
| #6 | #4 OR #5 | 224177 |

| | | |
|---|---|---|
| #7 | [mh Gait] OR [mh Walking] OR [mh ^"Walk Test"] | 8926 |
| #8 | (gait* OR ambulat* OR walk* OR 10mWT OR T25FWT OR 500mWT OR stepping OR (step NEXT test*) OR ((step* OR stride*) NEXT (length OR width OR time)) OR (("double limb" OR "single limb" OR "base of") NEXT support) OR "double support" OR cadence OR velocity OR ("ground reaction" NEXT force*)):ti,ab,kw | 91665 |
| #9 | #7 OR #8 | 91682 |
| #10 | #3 AND #6 AND #9 in Trials | 1567 |

## International Clinical Trials Registry Platform (ICTRP)

Search conducted: June 13, 2023

### Search 1: Basic Search

"multiple sclerosis" AND gait

129 results

### Search 2: Advanced Search

Condition: multiple sclerosis

Intervention: exercise OR training OR physical OR treadmill OR exoskeleton OR robot OR robotic OR virtual reality OR VR

Recruitment status: All

507 results

## ClinicalTrials.gov

Search conducted: June 13, 2023

Advanced Search:

Condition or disease: "multiple sclerosis"

Other terms: gait OR walk OR walking

Intervention/treatment: exercise OR training OR physical OR treadmill OR exoskeleton OR robot OR robotic OR "virtual reality" OR VR

Outcome measures: gait OR step OR stride OR velocity OR cadence

Applied Filters:

Interventional

Adult (18–64)

Older Adult (65+)

195 results

## 2.2 Supplementary file: Summary of the included studies

### Lower limb resistance (n=9)

Four studies included upper and lower-extremity progressive resistance training [51,99,100,103], while 5 studies included only lower limb resistance training [50,101,102,104,155], Walking tests used to measure speed were T25FWT [50,104,182], and 10MWT [99-103,155]. The exercise duration ranged between 6 weeks to 24 weeks. Of these nine studies, two did not report significant improvement in walking speed [99,101]. Only one study had a follow-up of 6 months, while the effects were not retained [51] (Table 1).

### Treadmill (n=13)

Of the 13 studies, 9 used treadmill training [26-28,32,97-101], 2 tested body weight-supported treadmill [29,102], and 2 tested treadmill combined with virtual reality [54,55]. The exercise duration ranged between 3 weeks and 48 weeks. Five studies showed significant improvements in walking speed [57,58,106,108,156]. Only 5 studies had a follow-up, ranging from 1 to 6 months [54,105-107,183], while effects were retained only in 2 studies [54,106].

### Whole body vibration (n=6)

The duration of exercise ranged between 3 weeks to 20 weeks, and the walking speed was assessed as 25FWT [160] and 20MWT [111], 10MWT [109,110,161] and GAITRite [112]. Two studies reported improvements in walking speed [112,161]. Of these 6 studies, only 1 had a follow-up of 2 weeks, and the effects were not retained [111].

**Overground and Robotic gait (n=12)**

Of the 12 studies, 10 tested robotic-assisted gait training [37-46,48], while two tested overground walking [118] and walking with auditory stimulation [117]. The exercise duration ranged between 3 weeks and 3 months. Studies measured gait speed using T25FWT [115,116,118], 10MWT, [66,69,70,73,114,117] 20MWT [79] and GAITRite walkway [67,113]. Of these twelve studies, six reported significant improvement in walking speed [73,113,115,117], while in 2 of these 6 studies, improvement in gait speed favored the control group [69,70]. Nine studies had follow-ups ranging from 1 to 9 months, while the effects were retained in only one study [113].

**Home exercise (n=10)**

The home-based interventions include conventional physiotherapy [119-121,123,124], balance exercises [125,126], step training [99,122] and motor imagery [128]. They used T25FWT [121-123,125], and 10MWT. [119,122,124] The duration of exercise ranged between 8-24 weeks. Five out of 10 studies showed significant improvement in gait speed [119,120,122,125,128]. Only one study had a follow-up of 8 weeks, while the effects were not retained.

**Individualized virtual PT (n=8)**

The interventions include Pilates training via videoconference [62], exercise therapy delivered via telephone [129,130] or telerehabilitation-based motor imagery [131] and web-based exercises using videos, text, and audio descriptions [132-135]. The duration of exercise ranged between 6 to 26 weeks. T25FWT [129-132,134,135] and 10MWT [62,133] were used to measure gait speed. Two studies reported significant improvement in gait speed [62,133]. Only one study had a follow-up of 3 months, and the effects were not retained [135].

**Pilates and yoga (n=4)**

The duration of exercise ranged between 8 to 12 weeks. Studies assessed gait speed using 10MWT [58,61,63] and walking on a treadmill [64]. Only one study had a follow-up of 4 weeks, and the effects were retained [63].

**Individualized in-person PT (n=12)**

Twelve studies tested individually tailored exercise programs supervised by a physiotherapist at a hospital [137,141,143,162,164,165] or community [138-140,144] and delivered individually or in groups [142,163]. The duration of exercise ranged between 3 weeks to 24 weeks. Studies used 25FWT, 10MWT[138,142,143,162,163], and 6MWT.[140] Of these 12 studies, 6 reported significant improvement in gait speed after training [140,142-144,163,165]. Only 3 studies had a follow-up of 8 weeks to 12 weeks, and the effects were retained in 2 studies [140,163].

**Balance (n=10)**

Ten studies investigated balance training on walking speed. Interventions tested were virtual reality or exergaming [72,76,77,147], dual-task training [146,166,167] and balance and stability exercises [145,148,149]. The exercise duration ranged between 4 weeks and 12 weeks. They measured gait speed using 25FWT [76,145,147-149,167] and GAITRite,[77,166] and 10MWT [72,146]. Of these 10, three studies reported significant improvement in walking speed after training [148,149,167]. Three studies had follow-ups ranging from 1 to 3 months [72,146,167], and the effects were retained in one study [184].

**Aerobic and Resistance (n=6)**

Six investigated the effect of combined aerobic and resistance training [56,150-154]. The exercise duration ranged between 6 weeks to 26 weeks. They used 25FWT [56,152,154], 10MWT [151,153] and GAITRite [150] to measure gait speed. Of these 6 studies, 3 studies reported significant improvement in walking speed after the training [56,151,154]. Only one study had a follow-up of 3 months, and the effects were not retained [152].

# Chapter 3 Cardiorespiratory fitness protects against covert worsening of gait variability over two years in people with multiple sclerosis


## Abstract

**Background:** Gait is typically symmetrical and consistent and subtle increases in gait variability can suggest loss of neural control. In multiple sclerosis (MS), covert walking changes precede clinical signs, often not detectable on observation, and measurement of gait variability could be a potential biomarker of covert neurodegeneration. Both cognition and fitness could influence changes in gait variability. This study aimed to examine gait variability over two years in clinically stable people with MS and determine whether fitness or cognition could predict change in gait variability.

**Research question:** Does gait variability serve as a longitudinal biomarker in people with MS, and is fitness or cognition protective against changes in gait variability?

**Methods:** 49 people with stable MS (65.3% females) were recruited from MS clinics. At the initial assessment (T1), cognition was assessed using the Montreal Cognitive Assessment, and fitness was measured as maximal oxygen update ($VO_{2max}$) during a graded exercise test using a whole-body recumbent stepper. People with MS performed self-selected walking on an instrumented walkway at initial assessment (T1) and after two years (T2), and stride time variability (STV) was measured as the coefficient of variation of stride time.

**Results:** The average age of the participants was 45.86 ±12.18 years, and the average time between assessments was 17.7± 5.0 months. The average STV was 7.33% at T1 and increased to 8.13% at T2 ($p=0.042$). After controlling for age, sex, time between assessments, cognition and

STV at T1, $VO_{2max}$ at T1 was a significant predictor of STV at T2 ($\beta = -0.395$, $p = .014$), accounting for 11.4% of the variance. Cognition at T1 did not predict changes in STV.

**Significance:** Lower cardiorespiratory fitness, but not cognition, predicted worsening gait variability over two years. Gait variability may be a sensitive biomarker of covert gait changes not apparent to an observer.

**Key Words**: Gait variability, pathological gait, neurological impairment, multiple sclerosis, cardiorespiratory fitness, cognition

## 3.1 Introduction

Gait requires the coordination of multiple body systems, but steps are almost always consistent and symmetrical. Gait variability (i.e., stride-to-stride fluctuations) reflects the loss of neural control for rhythmic stepping [185,186], and is a sensitive biomarker of executive function in healthy populations [187,188]. Recent evidence showed that gait variability tends to increase in older adults and people with neurological disorders [189] [190,191] and is associated with altered brain structure and function in areas important for sensorimotor integration and coordination [192-194]. The increase in gait variability, indicative of subtle disruptions in gait symmetry, may precede clinically measurable impairments and potentially serve as an early biomarker for neurodegeneration in diseases such as multiple sclerosis.

Multiple sclerosis (MS) is a chronic autoimmune disorder in which the immune system attacks the myelin sheath, causing disruptions in nerve signals that affect muscle coordination and walking [195]. People with MS having mild disability (Expanded Disability Status Scale (EDSS) <4) often report changes in walking even without evident clinical signs detectable on observation [196,197]. Although disease-modifying drugs effectively suppress acute relapses, the disease progresses over time. Recent evidence highlights that covert disability progression occurs independent of relapses, referred to as 'progression independent of relapse activity' [198].

Monitoring subtle gait changes, especially in the early phase of the disease, could help identify disease progression and guide treatment decisions to improve mobility for persons with MS [81]. Automated methods using electronic walkways that permit extraction of spatiotemporal gait parameters reveal novel and potentially important gait variables to detect impairment in MS [199]. In cross-sectional studies, increased gait variability is associated with higher disability [200,201], cognitive decline [202,203], increased energy cost of walking [204] and higher risk of falls [205,206]. For

instance, stride time variability was associated with decreased executive function in patients with dementia [207]. Moreover, two studies in MS showed that increased gait variability was significantly associated with lower cognitive scores [208,209]. Our previous work suggests that having better cognitive function may protect against deterioration of dual-task walking in people with MS [210]. Based on these findings, gait variability has the potential to become an early biomarker in not only detecting covert progression but also determining the neuroprotective effects of disease modifying drugs or lifestyle modifications such as exercise [211,212].

Cardiorespiratory fitness refers to the ability of the heart and lungs to provide oxygen during movement [213]. Recent studies suggest that higher levels of cardiorespiratory fitness could reduce blood-brain barrier permeability and modulate neurotrophins like brain-derived neurotrophic factor and cytokines, fostering neuroplasticity [214], which further helps to enhance brain health and functional connectivity in MS [215,216]. Moreover, MS patients with higher fitness levels have reduced corticospinal inhibition [212] and enhanced capacity for adaptive changes in the brain, suggesting neuronal and synaptic plasticity [217,218]. Such evidence supports that fitness could protect against an increase in gait variability.

Whether gait variability serves as longitudinal biomarker in a neurodegenerative disease such as MS and whether fitness is protective against changes in gait variability is not known. The aim of this study was to 1) examine the change in stride time variability over two years in clinically stable people with MS and 2) determine whether cardiorespiratory fitness and cognition (measured at Time 1 [T1]) could predict the change in gait variability over two years (T2).

## 3.2 Methods

### 3.2.1 Participants

Following approval from the Health Research Ethics Board (HREB#2016.1208) and completion of informed written consent according to Declaration of Helsinki, we recruited participants from MS clinics in St. John's who agreed to attend annual assessments. Participants who were ≥18 years old and had a definite diagnosis of MS as per revised McDonald criteria by a neurologist [219] were included and EDSS scores were obtained from their medical records. Annual visits at the Recovery and Performance lab included clinical tests, cardiorespiratory fitness, walking, cognition, and patient-reported outcomes. We included participants for whom a) there were two testing sessions: baseline (T1) and a second assessment (T2), within 24 months from T1, b) had complete gait data at both time points (T1&T2), and c) fitness ($V0_{2max}$) and cognition using Montreal Cognitive Assessment (MoCA) collected at their first visit (T1). Participants were excluded if a) the duration between the two visits was > 2 years, b) the EDSS score was >4 (indicating moderate to severe disability), c) they experienced a relapse in the previous 90 days, d) they had any musculoskeletal impairments or e) were pregnant. Since clinical disability can change over time, we confirmed from the participants' self-reports and the health records that there was neither a relapse nor a change in the EDSS score between the two assessment time points. We aimed to obtain at least 40 participants with complete data in order to control for at least four confounding variables in the regression modeling.

### 3.2.3 Cognition

Since cognitive-motor interference is common in MS [191,220], we controlled for cognition at baseline in the regression model. Comprehensive neuropsychological testing is impractical for our participants due to logistical and time constraints. We administered the MoCA, a valid and reliable rapid screening tool for assessing cognition in people with MS at T1 (Figure 3.1). The MoCA includes eight cognitive domains: attention, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation, making it particularly suitable for capturing the heterogeneous cognitive impairments often seen in MS patients. Administering the MoCA takes around 10 minutes; the maximum achievable score is 30 points [221]. An extra point was given to individuals with ≤ 12 years of formal education. A score ≥ 26 is considered normal cognitive function [222].

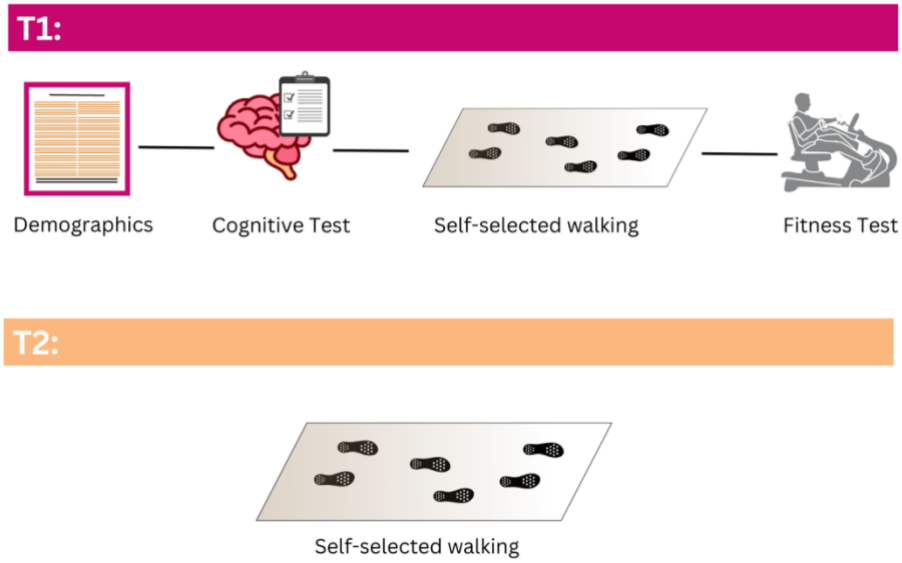
### 3.2.4 Stride Time Variability (STV)

We used an instrumented walkway (1.2 × 4.3 m, Protokinetics, Havertown, USA) to measure walking speed and STV (Figure 3.1). The walkway contains sensors that measure temporal and spatial parameters for each stride, and we asked participants to walk at their self-selected pace to determine walking speed [223] and STV [187]. Walking speed was normalized by the participant's height (cm/s/height$_{cm}$). STV was measured as the coefficient of variation (CV) extracted from the PKMAS software raw data [PKMAS software, Protokinetics, Havertown, USA] and was measured in percentage (%); CV= (standard deviation (SD)/mean) x100 for 1 stride. Data from both left and right footfalls were pooled to calculate CV, and we included an average of 4-5 strides per trial.

### 3.2.4 Cardiorespiratory Fitness

Cardiorespiratory fitness was determined ($VO_{2max}$) during exercise on a whole-body recumbent stepper (NuStep, Ann Arbor, Michigan, USA). As previously described [211,212,215], participants engaged in a graded exercise at a rate of 80 strides per minute, with the workload progressively increasing every 2 minutes. Inhaled oxygen and exhaled carbon dioxide were measured using an indirect calorimetry system (Moxus, AEI Technologies, Pittsburgh, Pennsylvania, USA). Participants were instructed to continue the exercise until the point of exhaustion was reached.

To establish $VO_{2max}$, participants had to meet at least two of the three following criteria: (a) a plateau in $VO_2$ (<80 mL · min−1) despite an escalation in workload; (b) a respiratory exchange ratio ($VCO_2/VO_2$) equal to or exceeding 1.1; (c) heart rate within ± 10 beats per minute of the predicted maximum heart rate, calculated using the equation 206.9 − (0.67 × age), or 164 − (0.7 × age) if the participant was on β-blockers. The relative value of $VO_{2max}$ (mL · min/Kg) was computed by dividing the peak oxygen uptake by the participant's body weight. Heart rate and blood pressure measurements were taken before and during the test using an electronic monitoring device.




At baseline (T1): After collecting demographic information, participants' cognition was assessed using the Montreal Cognitive Assessment (MoCA), and they were asked to complete walking at their self-selected pace on an instrumented walkway to measure their stride time variability. Lastly, participants completed a fitness test ($VO_{2max}$) on a whole-body recumbent stepper. Participants' stride time variability was repeated at T2 on the same instrumented walkway. The change (%) in the variability was measured as T2-T1.

*Figure was created using the free version of www.canva.com. Images used from freeicons used under the respective content licenses.*

**Figure 3.1Assessment procedure at Baseline (T1) and over two years (T2)**

### 3.2.5 Statistical analysis

Following data inspection for normality using the Shapiro-Wilk test, demographic variables such as age, gender, assessment duration and EDSS were analyzed using descriptive statistics. Continuous variables were reported as mean and standard deviations (SD), and ordinal and nominal data were reported as median, range and proportions (%). To analyze the difference in STV, walking speed and EDSS between two time points, a Paired t-test and Wilcoxon Signed Rank test were performed, respectively. As age and sex could affect $VO_{2max}$ and gait variability, we controlled for these confounders. We performed two multiple linear regression models to determine whether fitness predicted STV at T2 while controlling for age, gender, time between visits, cognition, and baseline STV (T1) and the second to determine whether cognition predicted STV at T2 while controlling for age, gender, time between visits, fitness, and baseline STV (T1). We constructed the models in two blocks. In Block 1, we controlled for our confounding variables, and then in Block 2 we added the predictor (either $VO_{2max}$ or cognition). We used a variance inflation factor of ≤5 and a tolerance value of ≤ 1 to consider multicollinearity among predictor variables. We reported confidence intervals (CI), and the statistical significance was set at $p<0.05$. Analyses were performed using SPSS Version 27 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism 9 software version 9.2 for Windows (California, USA).

## 3.3 Results

### 3.3.1 Demographic and clinical characteristics of the participants

Out of 56 participants, 7 were excluded as the follow-up assessment was beyond 2 years. The final sample was n=49; 32 (65.3%) were females. All the participants were diagnosed with RRMS, with a median EDSS of 2.0. The average age was 45.86 (± 12.18) years, and the average

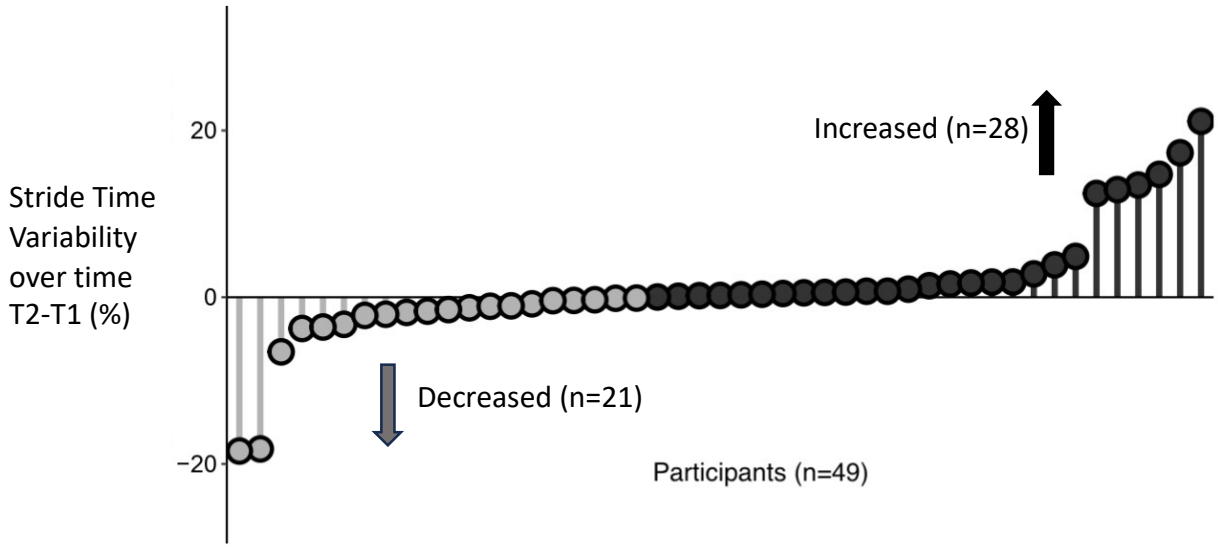
time between assessments was 17.7 ± 5.0 months. The average fitness and cognition at T1 were 27.4 ± 7.7 mL/kg/min and 26.4 ± 2.4, respectively. The average STV was 7.33% at T1 and increased to 8.13% at T2 (p=0.042). There was no significant difference in EDSS scores (p= .135) or walking speed (p=.745) over 2 years. Participants' characteristics are summarized in Table 3.1.

**Table 3.1 Participants' characteristics (n=49)**

| Variables | M±SD or n (%) |
|---|---|
| Age (years) | 45.86 ± 12.18 |
| Sex (Male; Female) | 17 (34.7%); 32 (65.3%) |
| EDSS (median) | 2.0 (0-4.0) |
| Disease duration (years) | 13.2 ± 8.7 |
| Disease-modifying drug therapy (yes; no) | n=41 (83.7%); n=8 (16.3%) |
| Time between T1 & T2 (months) | 17.7 ± 5.0 |
| $VO_{2max}$ ($mL.kg^{-1}.min^{-1}$) at T1 | 27.4 ± 7.7 |
| Cognition scores at T1 (MoCA) | 26.4 ± 2.4 |
| Stride Time Variability (CV%) at T1 | 7.33 ± 7.0 |
| Stride Time Variability (CV%) at T2 | 8.13 ± 7.3 |
| Walking speed ($cm/s/height_{cm}$) at T1 | 0.62 ± 0.12 |
| Walking speed ($cm/s/height_{cm}$) at T2 | 0.62 ± 0.11 |

### 3.3.2 Stride time variability over two years

The change in STV during walking at self-selected pace (T2-T1) ranged from -18.45% (improved) to 21.1% (worsened). About 57.1% of the participants (n=28) experienced increased gait variability, indicating a deterioration in their gait over time. (Figure 3.2)




Changes in stride time variability between T1 and T2 ranged from -18.45% (decreased: grey spikes) to 21.1% (increased: black spikes). More than half (57.1%) of participants showed increased change, indicating maintenance or worsening. T1 = time point 1; T2 = time point 2.

**Figure 3.2 Change in stride time variability over two years**

### 3.3.3 Baseline fitness, but not cognition, predicted Stride time Variability at T2 after controlling for other covariates

After controlling for age, sex, assessment duration, cognition and STV at T1, $VO_{2max}$ at T1 was a significant predictor of gait variability at T2 ($\beta = -0.395$, $p = .014$). It accounted for an additional 11.4% of the variance compared to Model 1 ($R^2 = .169$; F change = 1.751, $f^2 = 0.20$). Specifically, for every 1mL.kg-1.min-1 increase of $VO_{2max}$, the STV decreased by 0.68% at T2 (Table 3.2a). In the second model, baseline cognition did not significantly predict variability at T2 ($\beta = 0.138$, $p = .365$) and accounted for only 1.4% of the variance compared to Model 1 (F change = 3.152, $f^2 = 0.394$) (Table 3.2b).

**Table 3.2a Regression analysis: Fitness at T1 as a predictor and STV at T2**

| Model 1 | Predictors | B | SE | β | 95% CI for B | p | $R^2$ |
|---|---|---|---|---|---|---|---|
| **Block 1** | Age (years) at T1 | -.096 | .160 | -.087 | -.419, .228 | .554 | .169 |
| | Gender | 1.807 | 4.308 | .065 | -6.880, 10.495 | .677 | |
| | Time between assessments | -.553 | .405 | -.205 | -1.370, .263 | .179 | |
| | STV at T1 | .668 | .247 | .392 | .171, 1.165 | **.010** | |
| | Cognition at T1 | .346 | .862 | .063 | -1.393, 2.084 | .690 | |
| **Block 2** | Age (years) at T1 | -.216 | .158 | -.196 | -.535, .103 | .178 | .283 |
| | Gender | 6.610 | 4.459 | .237 | -2.388, 15.609 | .146 | |
| | Time between assessments | -.707 | .385 | -.262 | -1.485, .071 | .074 | |
| | STV at T1 | .553 | .236 | .325 | .076, 1.029 | **.024** | |
| | Cognition at T1 | .757 | .826 | .138 | -.910, 2.425 | .365 | |
| | $VO_{2max}$ at T1 | -.680 | .264 | -.395 | -1.212, -.147 | **.014** | |

**Table 3.2b Regression analysis: Cognition at T1 as a predictor and STV at T2**

| Model 2 | Predictors | B | SE | β | 95% CI for B | p | $R^2$ |
|---|---|---|---|---|---|---|---|
| **Block 1** | Age (years) at T1 | -.242 | .155 | -.220 | -.555, .071 | .126 | .268 |
| | Gender | 5.06 | 4.121 | .182 | -3.244, 13.376 | .226 | |
| | Time between assessments | -.620 | .373 | -.230 | -1.372, .132 | .104 | |
| | STV at T1 | .514 | .232 | .302 | .046, .981 | **.032** | |
| | $VO_{2max}$ at T1 | -.633 | .258 | -.368 | -1.154, -.112 | **.018** | |
| **Block 2** | Age (years) at T1 | -.216 | .158 | -.196 | -.535, .103 | .178 | .283 |
| | Gender | 6.610 | 4.459 | .237 | -2.388, 15.609 | .146 | |
| | Time between assessments | -.707 | .385 | -.262 | -1.485, .071 | .074 | |
| | STV at T1 | .553 | .236 | .325 | .076, .1.029 | **.024** | |
| | $VO_{2max}$ at T1 | -.680 | .264 | -.395 | -1.212, -.147 | **.014** | |
| | Cognition at T1 | .757 | .826 | .138 | -.910, 2.425 | .365 | |

## 3.4 Discussion

We aimed to evaluate the longitudinal changes in STV among clinically stable individuals with MS and determine whether baseline levels of fitness or cognition could predict covert STV changes. Our findings showed there was an overall increase in STV over two years which was variable within individuals. About 57% of the sample showed varying degrees of worsening of STV over time (Figure 3.2). Although others have suggested that cognition is a key predictor of STV in healthy persons and those experiencing neurodegenerative conditions [185,207,220], we show for the first time that baseline fitness levels significantly predicted the variability at the second time point (T2; Table 3.2a)). In a field that is focusing on early detection of sensorimotor symptoms in the absence of relapses, [224] measurement of STV shows promise as a sensitive longitudinal biomarker [225,226].

### 3.4.1 Stride Time variability as a sensitive gait biomarker

Stride time, often referred to as the 'gait clock,' provides valuable information about internal rhythmicity and coordination during walking [227]. Any disturbance of the multi-level control system of walking affects coordination and STV [228]. Stride to stride fluctuations are associated with falls [229] and increased energy expenditure during walking [204], and STV fluctuations occur among healthy older adults without any evident underlying disease [230]. Several lines of evidence support that gait dynamics and stride variability may be influenced by factors beyond muscle mechanics [230] such as cardiovascular health [231], and higher- level cognition (especially executive function) [210]. In cross-sectional studies of gait variability, people with MS with mild disability (n=43) demonstrated greater variability in temporal measures (step time CV- 2.6% and single -support time CV -3.2 %) [232] than healthy controls. In a small sample (n=9),

people with mild MS-related disability (median EDSS-2.0) also showed greater step length variability (CV-1.3%) [233]. Notably, gait variability can be reported as a function of spatial or temporal parameters which makes comparison difficult. An estimate of 0.01 seconds was considered a clinically meaningful change in stance and swing time variability (measured as standard deviation) in older adults [234]. Establishing clinically meaningful change in STV from both the clinicians' and patients' perspectives is an important area for future research.

### 3.4.2 Gait variability changed over time without clinically documented relapse or progression

More than half of the participants had increased gait variability, while walking at self-selected speed, without documented relapse or change in health status. (Figure 3.2). One possible explanation is that participants may have experienced subtle changes in the brain that were not evident on clinical observation or even recorded using magnetic resonance imaging. Others have shown that STV was higher in community dwelling elderly fallers than the elderly non-fallers compared to young adults ($p<0.0001$), despite the fact that there were was no differences in gait speed between fallers and non-faller groups [235]. Rosano and colleagues reported that gait variability was associated with the presence of white matter hyperintensities and subclinical brain infarcts in highly functioning older adults [236]. While it is evident that individuals with MS exhibit greater levels of gait variability in both short [201] and longer walking distances [237], the precise mechanisms driving gait variability remains unclear. Considering that gait control involves a complex interplay of various neural processes and the coordination of trunk and limb movements [238], it is likely that gait variability results from a combination of deficits rather than a single isolated mechanism [239]. Here we show that STV was a sensitive biomarker of longitudinal

change in gait in the absence of clinically observable metrics. Our results suggest that subtle improvement and worsening of gait can be calculated using the temporal gait variability parameter, STV, during self-selected walking on an electronic walkway. To what extent these changes relate to underlying deterioration or improvement in the central nervous system is an important area for future study.

### 3.4.3 Higher fitness level predicted preservation of gait variability over time

MS is a chronic demyelinating disease with a pathology involving both white matter and gray matter areas of the brain [195], and a growing body of evidence supports that aerobic fitness helps to preserve the integrity of brain tissue [217], decreases proinflammatory cytokines, modulates neurotrophins [215], increases cortical excitability [211,212] and functional neuronal plasticity in people with MS [217]. Since, increased gait variability is associated with cortical and sub cortical infarcts and white matter lesions in the brain [236], we hypothesized that fitness could be protective against increased gait variability in MS. However, there is limited evidence regarding how lifestyle factors affect longitudinal gait changes in MS [201,240]. A longitudinal study among 410 healthy older adults (mean age 72 years) showed that participants with cardiovascular disease at baseline had greater changes in step length variability over 5 years [241]. In a large epidemiological study involving 10,615 participants aged 20–87 years, lower levels of fitness at baseline indicated a higher rate of falls while walking (AOR 1.8; 95% CI 1.1,2.8), especially among men [242]. In a cross-sectional study of healthy older women, greater engagement in moderate to vigorous physical activity was related to lower gait variability [243]. Our results support that, after controlling for other covariates, fitness accounts for about 11.4% of the variance in change of STV. It is likely that those participants with higher fitness (and likely

higher engagement in moderate to physical activity) have greater capacity of neuroplasticity and repair. Lozinski and Yong argue that exercise influences structural and functional brain changes, including neurogenesis and remyelination [244]. Unfortunately, many people with MS have very low levels of fitness, which in our previous work, is related to greater levels of corticospinal inhibition, a condition which blunts capacity for neuroplasticity [212]. Exercise induces increased brain excitability even among patients with progressive forms of MS, which provides hope for the neuroprotective effects of exercise in MS [245].

### 3.4.4 Baseline cognition failed to predict gait variability over two years

Cognitive ability, related to executive function and attention, influences gait control [246] and deterioration of these cognitive functions affects stride variability [247]. Impaired cognition prolongs foot contact time on the ground which increases stride to stride fluctuations [248] and higher cognitive scores predict preserved dual task walking in MS [210]. Based on these findings, we hypothesized that cognitive scores at baseline could predict STV at year 2. However, our results showed that cognition was not a significant predictor of change in variability. One possible explanation could be that the average MoCA score of our participants was $26.4 \pm 2.4$ which indicates normal cognitive function [222]. Moreover, we analyzed stride time CV while participants walked at their self-selected speed. A recent longitudinal prospective study in healthy older adults showed that stride time CV while performing a verbal fluency task was associated with cognitive decline but not during typical walking [249]. Another longitudinal retrospective study in ageing population also showed that stride time variability was a significant predictor of cognitive decline over 25 years [250]. Since we examined participants over 2-years, the duration of follow-up may have been too short to observe cognitive changes.

There is substantial heterogeneity among reports of how gait variability is calculated (spatial or temporal variability). We chose stride time variability because it is the most consistent variability metric currently reported in older adults and in people with other neurological diseases. A comparison of methodology to calculate gait variability would help to ascertain a gold standard in the field. This comparison may evaluate various approaches, considering factors such as sensitivity, accuracy, reproducibility, and applicability to different populations or conditions. We report that fitness accounts for about 11.4% of the variance in change of STV, suggesting that other factors, outside of those that we controlled for, that could affect variability are at play, such as fatigue or sleep.

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# Chapter 4 Incongruence between cardiorespiratory fitness and subjective reports of physical activity in multiple sclerosis: A focus on sex differences


## Abstract

**Purpose:** The link between moderate- to vigorous-intensity physical activity (MVPA) and cardiorespiratory fitness in individuals with Multiple Sclerosis (MS) remains unclear. This study examined the relationship between self-reported MVPA and objectively assessed cardiorespiratory fitness, emphasizing sex differences.

**Methods:** 107 adults with MS (77 females), aged (mean ± standard deviation) 47.2 ± 10.2 years, were recruited from a local MS clinic. Fitness was measured as maximal oxygen uptake ($\dot{V}O_{2max}$) during a graded maximal exercise test using a recumbent stepper. MVPA (24-hour recall) was estimated as the duration of activities ≥ 3 MET (Metabolic Equivalent of Task). MET-minutes were calculated by multiplying MET by duration. We explored sex differences in self-reported MVPA, cardiorespiratory fitness, and disability; examined sex differences in associations between these variables; and investigated whether MET-minutes of MVPA predicted $\dot{V}O_{2max}$ in females and males.

**Results:** Mean $\dot{V}O_{2max}$ was 24.79 $mL \bullet kg^{-1} \bullet min^{-1}$, indicating poor cardiorespiratory fitness levels, despite high levels of self-reported MVPA (mean = 412.5 MET-minutes). Fifty-three percent of males and 40% of females had $\dot{V}O_{2max}$ levels below the $20^{th}$ age- and sex-standardized population percentile, indicating poor cardiorespiratory fitness. There were statistically significant associations between MVPA and $\dot{V}O_{2max}$ (Rho = 0.27, $p$ = .01), as well as disability and $\dot{V}O_{2max}$ (Rho = -0.35, $p$ = .02), in females but not males. A regression model using sex, age, body mass, disability, and MVPA to estimate $\dot{V}O_{2max}$ was valid in predicting $\dot{V}O_{2max}$ values that

were statistically equivalent to those measured in the laboratory in females but not males. However, the inclusion of MVPA did not add to the predictive value of this equation.

**Conclusions:** Despite reporting high levels of MVPA, people with MS had poor cardiorespiratory fitness. MVPA, fitness, and disability were associated in females only, indicating sex differences should be considered in fitness appraisal. Self-reported MVPA did not predict fitness, suggesting 24-hour recall may not be representative of true activity or fitness levels in persons with MS. Future work should examine sex differences in associations between MVPA and fitness using objective measures such as accelerometry.

Keywords: Aerobic; Cardiorespiratory fitness; Exercise; Multiple sclerosis; Physical activity; Sex

## 4.1 Introduction

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system, characterized by chronic disability accumulation and episodes of new neurologic impairment with incomplete recovery [251]. Among people with MS, having vascular comorbidities are associated with accelerated neurodegeneration, early disability, and loss of independence [252,253]. Lifestyle factors are crucial for the mitigation of disability accumulation [251,254]. Exercise and physical activity are critical treatments for the promotion of metabolic and brain health and should be a routine part of the MS care [215,255-258]. Guidelines recommend that people with MS engage in at least 150 minutes of moderate-to-vigorous physical activity (MVPA) per week [259,260]. Unfortunately, individuals with MS are less active and more sedentary than healthy controls and even persons with other neurologic disorders like stroke and spinal cord injury [261]. Individuals with MS report disease-related impairments, fatigue, and logistical challenges as barriers to engaging in physical activity [262]. Health professionals cite concerns about patient fatigue and safety as barriers to prescribing physical activity, despite evidence of its safety in MS [263-265].

One of the first steps in prescribing exercise is determining the individual's level of fitness. The gold standard cardiorespiratory fitness assessment involves graded maximal exercise testing with indirect calorimetry to measure maximal oxygen uptake ($\dot{V}O_{2max}$) [266]. $\dot{V}O_{2max}$ testing in MS is a valid and reliable measure of aerobic capacity [267], and shows good relationships with disease-specific and general health-related outcomes of the International Classification of Functioning, Disability and Health model [268]. However, maximal exercise testing and indirect calorimetry require specialized equipment, trained evaluators, and a highly controlled environment. These requirements often preclude maximal exercise testing in real world clinical

or community settings outside the laboratory setting [269]. When a formal fitness test is impractical, healthcare providers may rely on subjective reports from their patients. Self-report questionnaires are considered reliable, easy to administer, and more affordable and accessible than fitness testing [270]. In healthy controls, there is good concordance between self-reported physical activity levels, self-appraised fitness, and $\dot{V}O_{2max}$ [271]. However, in MS and other clinical populations, greater susceptibility to recall bias, perceived social desirability and expectations of others could contribute to the misrepresentation of self-reported physical activity levels [272,273].

MS is a disease with known sex differences, including incidence and onset, disease progression, and the nature and severity of physical and psychosocial impairments [251,274,275]. In general, when it comes to reporting fitness and PA data among individuals with MS, sex differences are typically overlooked [268,276]. One study of 92 persons with MS (58 females) found no significant associations between self-reported physical activity and cardiorespiratory fitness ($\dot{V}O_{2peak}$) [277]. However, the authors did not discriminate between different intensities of physical activity, nor examine sex differences in physical activity or its association with peak $\dot{V}O_2$ [277]. The study sample was recruited from a waiting list of individuals referred for admission to inpatient rehabilitation, so it is likely not representative of people with MS with stable disease who are capable of exercising independently [277]. In another larger study of 380 individuals with MS (249 females), females were less likely to reach $\dot{V}O_{2max}$ before volitional exhaustion compared to males [278]. Also, this study did not compare cardiorespiratory fitness and physical activity levels between the sexes. It is important to note that the study participants were hospital inpatients and may not be representative of independent, community-dwelling individuals. Taken together, these findings allude to the lack of evidence on sex differences in self-reported physical

activity levels and cardiorespiratory fitness in MS, highlighting the need for further research to fill existing knowledge gaps.

To address these gaps, the present study aimed to: (1) explore sex differences in self-reported MVPA and $\dot{V}O_{2max}$; (2) examine relationships between self-reported MVPA, $\dot{V}O_{2max}$, and disability status, with an emphasis on sex differences; and (3) determine whether self-reported MVPA could predict $\dot{V}O_{2max}$ in females and males with MS.

## 4.2 Materials and Method

### 4.2.1 Participants

We conducted this cross-sectional study in a neurorehabilitation research laboratory located within a tertiary rehabilitation hospital. Following institutional Health Research Ethics Board approval (HREB#: 2015.103), participants provided informed written consent as per the Declaration of Helsinki. The study sample was recruited from a local MS neurology clinic, and participants were independently ambulatory with stable disease.

We recruited consecutive adults diagnosed with MS—using the 2010 or 2017 iterations of the McDonald criteria [279,280] from a MS neurology clinic at Health Sciences Centre, St. John's. We included participants who were aged 18-65 years, had no relapses or new disease activity for ≥ 3 months, could walk independently with or without gait aids (Expanded Disability Status Scale [EDSS] 0-6) [281], and had no contraindications to exercise [282]. We excluded individuals who scored ≤ 22 on the Montréal Cognitive Assessment, indicating cognitive impairment [283]. We extracted EDSS scores, and sex assigned at birth from health records.

We planned sample size estimation based on our intention to derive a prediction equation for $\dot{V}O_{2max}$ using participant characteristics and self-reported MVPA. We estimated the target

sample size using G*Power v3.1.9.7 (Aichach, Germany) [284], using data from a recent meta-analysis that suggested sex differences account for up to 36% of the variance in $\dot{V}O_{2max}$ [268]. Based on the coefficient of variation ($R^2$ =0.36) and effect size ($f^2$ = 0.56) gleaned from the study [268], using $\alpha$ = .05 and power( 1-$\beta$) = 0.80) for a multiple linear regression with up to five predictors, we estimated 54 total participants (27 females, 27 males) would be required to derive a prediction equation for $\dot{V}O_{2max}$. To validate the prediction equation, we estimated an additional 54 participants (27 females, 27 males) would be required, resulting in a total target sample size of 108. This approach was taken to ensure the validity of the predictive model [285].

### 4.2.2 Self-reported MVPA

We asked participants to recall all activities during the previous 24 hours, describing the details of the activity, duration, and intensity [286]. The 24-hour previous-day recall is a valid tool to estimate active and sedentary behaviors in adults of varying fitness levels [287-291]. Previous-day recall methods agree with objective measurements of physical activity, direct observations, and energy expenditure [287-289,291]; and they minimize reporting errors compared to longer-term questionnaires by reducing recall bias due to forgetting [287,289]. Reported activities included sleeping, sitting, walking, activities of daily living, home exercises, and sports, such as running and bicycling. Because of evidence that persons with MS have problems with accurate recall of duration [292], we cleaned self-reported activity data by omitting all values under 10 minutes per day and truncating values over 240 minutes per day [293]. We converted self-reported activities to metabolic equivalents of task (MET) using the 2011 Compendium of Physical Activities [294]. Based on the World Health Organization threshold values, we classified activities with MET ratings > 3.0 METs as MVPA [295]. We calculated MET-minutes of MVPA by multiplying the MET

value of each activity by the duration in minutes [295], and reported values for the previous 24 hours.

### 4.2.3 Cardiorespiratory fitness

We measured cardiorespiratory fitness using a graded maximal exercise test on a total body recumbent stepper (NuStep T4r, Ann Arbor, MI, USA) [296,297]. We instructed participants to avoid alcohol and recreational drugs for ≥ 24 hours, to avoid caffeine and nicotine for ≥ 6 hours, and to sleep for ≥ 6 hours. We measured height (cm), body mass (kg), and body mass index (BMI; $kg \bullet m^{-2}$) with a calibrated device (Health-O-Meter®, McCook IL, USA), familiarized participants with the experimental setup, and adjusted the arm and leg attachments of the ergometer based on participant limb length. Participants wore a mask connected to a two-way non-rebreathing valve (Hans Rudolph, Inc., Shawnee, KS, USA). An automated open-circuit indirect calorimetry system with calibrated gas analyzers (Model S-3A and Anarad AR-400; Ametek, Pittsburgh, PA) and tachometer (Model S-430; Vacumetrics/Vacumed Ltd., Ventura, CA) measured expired gas and breathing volumes for breath-by-breath analysis (AEI Technologies, Inc., Pittsburgh, PA, USA). A chest-worn heart rate (HR) monitor transmitted HR data wirelessly (H10, Polar Electro, Oy, Finland).

Resting blood pressure, $\dot{V}O_2$, and HR were measured 5 minutes before exercise. During the test, participants maintained a stepping rate of 80 per minute. The exercise began at a load level of 3 (20 Watts) on a standard scale of 1-10 and increased by 20 Watts every 2 minutes. If participants did not stop by load level 10, we increased the stepping rate by 10 per minute every 2 minutes. Criteria for test termination were: (1) volitional exhaustion, (2) inability to maintain workload, or (3) signs of excessive fatigue [296]. We recorded relative $\dot{V}O_2$ (normalized to body

mass; mL•min$^{-1}$•kg$^{-1}$), HR (bpm), and rating of perceived exertion (RPE; 10-points) [298] at rest before exercise, every 2 minutes during exercise, and after exercise. Participants achieved true $\dot{V}O_{2max}$ if they met two or more of the following criteria: (1) no increase in absolute $\dot{V}O_2 \geq 150$ mL•min$^{-1}$, despite increasing workload; (2) respiratory exchange ratio > 1.10; (3) HR > 90% of the age-predicted maximum; and/or (4) RPE > 8/10 [299]. Besides reporting relative $\dot{V}O_{2max}$, we also reported age- and sex-adjusted percentile ranks of cardiorespiratory fitness as per the American College of Sports Medicine (ACSM) [266]. Individuals with a $\dot{V}O_{2max}$ below the 20$^{th}$ percentile for their age and sex have an elevated risk of all-cause mortality [300].

### 4.2.4 Statistical analysis

We performed all statistical analyses using SPSS Version 27 (IBM Corporation, Armonk, NY, USA). We tested data distributions for normality using the Shapiro-Wilk test and visual inspection of histograms and Q-Q plots. We conducted parametric and non-parametric tests for normal and non-normal data, respectively. All tests were two-tailed, with the statistical significance threshold at $p < .05$.

Descriptive statistics were reported as proportions (%), mean (standard deviation [SD]), or median (range) for categorical, normal, or non-normal continuous data respectively. Sex differences and variable relationships were assessed using parametric (unpaired *t*-test) or non-parametric tests (Mann-Whitney *U*-test or Pearson Chi-square test), and correlations were conducted using Pearson (r) or Spearman Rho (ρ) correlation tests. We estimated effect sizes for *t*-tests using Cohen's *d* with 95% confidence intervals (CI) and interpreted them as trivial (< 0.2 ), small (0.2), medium (0.5), and large (≥ 0.8) [301]. For *U*-tests, we used effect sizes *r* categorized

as trivial (<0.1), small (0.1-0.3), medium (0.3-0.5), or large (>0.5) [301]. Chi-square effect sizes were calculated using Cohen's h with 95% CI, and interpreted as above for Cohen's d [301].

We conducted Spearman correlations between self-reported MVPA, cardiorespiratory fitness, and EDSS scores, with correlation coefficients interpreted as trivial (< 0.1), weak (0.1), moderate (0.3), and strong (≥ 0.5) [301]. Correlations were performed for the total sample and separately by sex. Sex differences were compared using Fisher *z*-transformations and Cohen's *q*-effect sizes with 95% CI, interpreted as above for Cohen's *d* and *h* effect sizes [301].

To determine whether self-reported MVPA predicted $\dot{V}O_{2max}$, we performed a standard multiple linear regression using sex, age, body mass, EDSS, and MET-minutes of MVPA as predictors. These variables were chosen based on their documented contribution to $\dot{V}O_{2max}$ [267,277] and sex differences in cardiorespiratory fitness [302,303]. We compared combinations of predictor variables using stepwise linear regression and chose the final model as the combination with the lowest Akaike Information Criterion (AIC) value. The final model was entered as a standard multiple regression and included each of the above variables–sex, age, body mass, EDSS, and MET-minutes of MVPA. Using a random number generator, we assigned participants to either a regression derivation group (n = 50 [34 females, 16 males]) or a validation group (n = 57 [43 females, 14 males]) The regression equation was derived from the derivation group and validation group. Groups did not differ significantly in demographics, self-reported physical activity, or $\dot{V}O2max$ ($p > .05$), except for higher EDSS in the validation group (median [range]: test group 1.5 [0-6], validation group 2.0 [0-6], $p = .024$).

We verified the assumption of independence of observations using a Durbin-Watson (DW) statistic of ~2 (DW = 2.056); linearity and homoscedasticity between independent and dependent variables by inspecting plots of unstandardized predicted values versus studentized residuals ($R^2$

= $1.31 \times 10^{-5}$); lack of multicollinearity by ensuring Pearson correlations between independent variables were ≥ 0.7 (Pearson r ≤ |0.467|) and variance inflation factors (VIF) were < 10 (VIF ≤ 1.382) [304]. There were no outliers (> ± 3 SD from the mean). We confirmed normally distribution ofresiduals by inspecting histogram and P-P plots for an approximate bell curve and diagonal line, respectively [304]. The model's overall coefficients of variance accounted for ($R^2$ and adjusted $R^2$) and unstandardized coefficients (B) with standard errors were reported for the derivation group to generate the $\dot{V}O_{2max}$ prediction equation for later validation.

We validated the model using cross-validation [285], and computed predicted $\dot{V}O_{2max}$ values in the validation group using the regression equation from the derivation group [305]. The validity of these estimates was assessed using equivalece testing and Bland-Altman plots [306]. We employed the two one-sided tests (TOST) approach to equivalence testing, with paired-samples t-tests [307]. We set the equivalence threshold (standardized effect size of interest [Cohen's d]) at 10% above or below the measured $\dot{V}O_{2max}$ in the derivation group because this is an acceptable margin of error between predicted versus measured $\dot{V}O_{2max}$ in other work that devised $\dot{V}O_{2max}$ prediction equations (Cohen's d value of |0.42|) [305]. Non-equivalence was determined if the effect sizes (Cohen's d) of measured versus predicted $\dot{V}$O2max values in the validation group exceeded ± 0.42 [307]. Both whole group validation and sex differences in the performance of the regression equation were explored using the TOST approach. We also constructed Bland-Altman plots [306] to assess the degree of error between predicted versus measured $\dot{V}O_{2max}$ and determine the error pattern in females and males [305]. Using this approach, predicted $\dot{V}O_{2max}$ values were considered valid if: (1) the difference between, and average of, predicted and measured $\dot{V}O_{2max}$ values were correlated; and (2) predicted $\dot{V}$O2max values fell within 2 SD of measured $\dot{V}O_{2max}$ values [306].

## 4.3 Results

### 4.3.1 Participants

Out of 120 participants screened, 13 were excluded due to exercise contraindications [282], leaving 107 individuals in the final sample. The average age (mean ± SD) was 47.2 ± 10.2 years, with a majority being females (n = 77), and 88.8% having relapsing-remitting MS. The median (range) EDSS was 2.0 (0-6.0). Males were significantly taller and heavier ($p < .001$), but other demographic and disease characteristics were not significantly different between sexes (Table 4.1).

**Table 4.1 Participant characteristics for the total sample**

| Variable | Total (n = 107) | Female (n = 77) | Male (n = 30) | Test Statistic | *p*-value | Effect Size (95% CI) |
|---|---|---|---|---|---|---|
| Age (years) (mean [SD]) | 47.2 (10.2) | 47.3 (9.9) | 47.2 (11.2) | $t = 0.027$ | .978 | $d = 0.01$ (-0.42 to +0.43), trivial |
| Body Mass (kg) (median [range]) | 79.2 (48.0-122.2) | 73.9 (48.0-118.3) | 86.5 (61.2-122.2) | $U =$ 1657.5 | < .001* | $r = 0.34$ (0.14-0.53), medium |
| Height (m) (mean [SD]) | 1.70 (0.08) | 1.67 (0.06) | 1.78 (0.07) | $t = -7.915$ | < .001* | $d = -1.70$ (-2.18 to -1.22), large |
| BMI ($kg•m^{-2}$) (median [range]) | 27.6 (17.9-44.5) | 26.8 (17.9-44.5) | 27.9 (19.6-40.6) | $U =$ 1251.0 | .506 | $r =0.06$ (-0.13 to +0.26), trivial |
| MS Type (n [%]) | RRMS 95 (88.8) PMS 12 (11.2) | RRMS 68 (88.3) PMS 9 (11.7) | RRMS 27 (90.0) PMS 3 (10.0) | $\chi^2 =$ 0.062 | .804 | $h = -0.06$ (-0.29 to +0.22), trivial |
| EDSS (median [range]) | 2.0 (0.0-6.0) | 2.0 (0.0-6.0) | 2.0 (0.0-6.0) | $U =$ 1207.5 | .710 | $r =0.04$ (-0.16 to +0.23), trivial |

*$p < .05$, *$p < .001$. 95% CI, 95% confidence interval; BMI, body mass index; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; RRMS, relapsing-remitting MS; PMS, progressive MS (including primary and secondary progressive MS).

### 4.3.2 Self-reported MVPA and cardiorespiratory fitness

On average, participants reported engaging in approximately 90 minutes of MVPA (> 3.0 METs) in 24 hours, accumulating 412.5 MET-minutes. These 24-hour values were close to the recommended weekly 450 MET-minutes of MVPA [308,309]. Only 10 participants (9.3%) reported no physical activity. The average $\dot{V}O_{2max}$ for participants was 24.8 ± 7.7 ml/kg/min, placing the median participant in the 10$^{th}$ fitness percentile (poor) [266] (Table 4.2). Based on the criteria outlined above, 84 participants (78.5%) reached their true $\dot{V}O_{2max}$. For the remaining 23 participants (21.5%), peak $\dot{V}O_2$ values are reported as $\dot{V}O_{2max}$.

**Table 4.2 Self-reported physical activity and cardiorespiratory fitness**

| Variable | Total (n = 107) | Female (n = 77) | Male (n = 30) | Test Statistic | *p*-value | Effect Size (95% CI) |
|---|---|---|---|---|---|---|
| MVPA (minutes) (median [range]) | 90.0 (0.0-330.1) | 90.0 (0.0-330.1) | 90.0 (0.0-180.0) | *U* = 989.5 | .251 | *r* = -0.11 (-0.30 to + 0.08), small |
| MVPA (MET-minutes) (median [range]) | 412.5 (0.0-1433.6) | 360.0 (0.0-1433.6) | 507.6 (0.0-1051.5) | *U* = 1322.5 | .245 | *r* = 0.11 (-0.08 to +0.30), small |
| $\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) (mean [SD])[¶] | 24.80 (7.70) | 23.03 (7.04) | 29.34 (7.59) | *t* = -4.080 | < .001** | *d* = -0.88 (-1.31 to -0.44), large |
| $\dot{V}O_{2max}$ (percentile) (median [range]) | 10 (4-95) | 5 (4-90) | 17.5 (4-95) | *U* = 1467.0 | .026* | *r* = 0.22 (0.02-0.41), small |

*$p < .05$, **$p < .001$., [¶]84 participants (78.5%) reached their true $\dot{V}O_{2max}$. The proportions of females (n = 61 [79.2%]) and males (n = 23 [76.7%]) who reached true $\dot{V}O_{2max}$ were not significantly different ($\chi^2_{(1)} = 0.083$, $p = .773$). 95% CI, 95% confidence interval; MET, metabolic equivalent of task; MVPA, moderate- to vigorous-intensity physical activity; $VO_{2max}$, peak oxygen uptake.

There was no significant difference between males and females regarding self-reported MVPA ($p > .05$) (Table 4.2, Figure 4.1). The proportions of females (n = 61 [79.2%]) and males (n = 23 [76.7%]) who reached true $\dot{V}O_{2max}$ were not significantly different ($\chi^2_{(1)} = 0.083$, $p = .773$). Males demonstrated a 27% higher relative $\dot{V}O_{2max}$, with a large effect size, compared to females ($p < .001$). When cardiorespiratory fitness was expressed in terms of age- and sex-normalized values, males ranked significantly higher, with a median (range) percentile score of 10 (4-95) versus 5 (4-90) for females and small effect size ($p = .026$) (Table 4.2, Figure 4.1). Approximately half of both females' and males' cardiorespiratory fitness ranks fell below the 20$^{th}$ percentile.

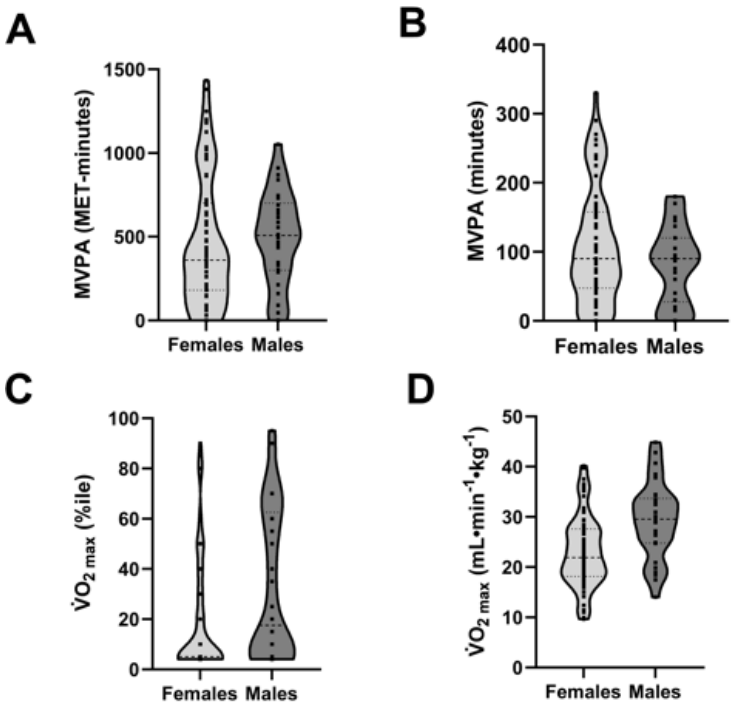


**Figure 4.1. Violin plots illustrating female (light grey) and male (dark grey) moderate- to vigorous-intensity physical activity (MVPA) and cardiorespiratory fitness (maximum oxygen uptake [$\dot{V}O_{2max}$]).**

Squares are individual data points. Shaded regions represent the distribution of the data. Dashed and dotted lines represent the median and interquartile range (IQR), respectively.

A) Metabolic equivalent of task (MET-minutes of MVPA, B) minutes of MVPA, C) age- and sex-normalized $\dot{V}O_{2max}$ percentiles (%ile). and D) $\dot{V}O_{2max}$ ($mL \bullet kg^{-1} \bullet min^{-1}$).

### 4.3.3 Associations between MVPA, $\dot{V}O_{2max}$, and disability

Considering the total sample, we observed statistically significant positive associations between higher $\dot{V}O_{2max}$ and higher MET-minutes of MVPA (Rho = 0.20, $p < .05$). Higher $\dot{V}O_{2max}$ was also associated with lower disability (EDSS) (Rho = -0.26, $p < .01$). There was no statistically significant relationship between self-reported MVPA and disability (Rho = -0.10, $p > .05$) (Table 4.3).

**Table 4.3 Correlations between cardiorespiratory fitness, disability status, and self-reported physical activity**

| Variable | Total (n = 107) | Female (n = 77) | Male (n = 30) | Test Statistic | p-value | Effect Size (95% CI) |
|---|---|---|---|---|---|---|
| MVPA (MET-min) (Rho, ρ [95% CI]) | | | | | | |
| $\dot{V}O_{2max}$ (mL•kg$^{-1}$•min$^{-1}$) | 0.20 (0.00-0.38)* weak | 0.27 (-0.07 to +0.38),* weak | 0.12 (-0.18 to +0.53), weak | z = 0.237 | .813 | q = 0.05 (-0.19 to +0.30), trivial |
| $\dot{V}O_{2max}$ (percentile) | 0.24 (0.04-0.41)* weak | 0.22 (-0.01 to +0.43), weak | 0.19 (-0.20 to +0.52), weak | z = 0.139 | .889 | q = 0.03 (-0.22 to +0.28), trivial |
| EDSS (Rho, ρ [95% CI]) | | | | | | |
| MVPA (MET-min) | -0.09 (-0.28 to + 0.11) trivial | -0.07 (-0.30 to +0.16), trivial | -0.11 (-0.46 to +0.27), weak | z = 0.179 | .858 | q = 0.04 (-0.21 to +0.29), trivial |
| $\dot{V}O_{2max}$ (mL•kg$^{-1}$•min$^{-1}$) | -0.26 (-0.44 to -0.07)* weak | -0.35 (-0.54 to -0.13),* moderate | -0.20 (-0.53 to +0.18), weak | z = 0.724 | .469 | q = -0.16 (-0.41 to +0.09), small |
| $\dot{V}O_{2max}$ (percentile) | -0.17 (-0.35 to +0.03) weak | -0.27 (-0.47 to -0.04),* weak | -0.02 (-0.39 to +0.35), weak | z = 1.142 | .253 | q = -0.26 (-0.51 to -0.01), small |

*$p$ < .05, 95% CI, 95% confidence interval; EDSS, Expanded Disability Status Scale; MET, metabolic equivalent of task; MVPA, moderate- to vigorous-intensity physical activity; $\dot{V}O_2max$, maximum oxygen uptake.

When we analyzed sexes separately, we found a statistically significant yet weak relationship between higher $\dot{V}O_{2max}$ and greater MVPA among females (Rho = 0.27, $p$ = .01) but not males ($p$ > .05). As well, lower disability (EDSS) was significantly associated with higher $\dot{V}O_{2max}$ in females (Rho = -0.35, $p$ =.002), but not males (Rho = -0.20, $p$ > .05) (Table 4.3).

To ascertain whether the lack of statistically significant correlations in males was due to sample size insufficiency, we calculated post hoc sample size requirements based on current sample size (n = 30 males), statistical power, correlation coefficients, and $p$-values using G*Power v3.1.9.7 (Aichach, Germany) [284]. To achieve a statistically significant association between MET-minutes of MVPA and relative $\dot{V}O_{2max}$ (power = 0.37, Rho = 0.12, $p$ = .280), a target sample size of 185 males would be required. For a statistically significant association between EDSS and relative $\dot{V}O_{2max}$ (power = 0.53, Rho = -0.20, $p$ = .290), 102 males would be required. To achieve a statistically significant association between EDSS and percentile ranked $\dot{V}O_{2max}$ (power = 0.64, Rho = -0.11, $p$ = .580), 445 males would be required. Given that $\dot{V}O_{2max}$ was significantly associated with both MET-minutes of MVPA EDSS in our sample of 77 females, we interpret this to represent a sex difference, rather than a function of a low sample size of males.

### 4.3.4 Predicting $\dot{V}O_{2max}$ from self-reported MVPA

Thirty-four females and 16 males (n = 50) were used to derive the regression equation and 43 females and 14 males (n = 57) to validate the equation. Except for a small yet statistically significant difference in EDSS, these groups were not significantly different in terms of demographic or disease characteristics, self-reported MVPA, or objectively measured cardiorespiratory fitness (Table 4.4).

**Table 4.4 Comparison of participant characteristics, self-reported physical activity, and cardiorespiratory fitness for regression equation derivation and validation groups**

| Variable | Derivation Group (n = 50) | Validation Group (n = 57) | Test Statistic | p-value | Effect Size (95% CI) |
|---|---|---|---|---|---|
| Participant characteristics | | | | | |
| Age (years) (mean [SD]) | 45.8 (10.4) | 48.8 (9.8) | t = -1.691 | .094 | d = -0.33 (-0.71 to +0.56), small |
| Sex (n [%[) | Female 34 (68.0) Male 16 (32.0) | Female 43 (75.4) Male 14 (24.6) | $\chi^2$ = 0.730 | .393 | h = -0.11 (-0.53 to +0.32), trivial |
| Body Mass (kg) (median [range]) | 80.3 (48.0-122.2) | 76.7 (52.2-118.3) | U = 1342.0 | .604 | r = 0.05 (-0.14 to +0.24), trivial |
| Height (m) (mean [SD]) | 1.70 (0.09) | 1.69 (0.08) | t = 0.650 | .517 | d = 0.13 (-0.25 to +0.51), trivial |
| BMI ($kg•m^{-2}$) (median [range]) | 27.7 (17.9-40.6) | 26.9 (19.7-44.5) | U = 1347.0 | .626 | r = 0.05 (-0.14 to +0.24), trivial |
| MS Type (n [%]) | RRMS 44 (88.0) PMS 6 (12.0) | RRMS 51 (89.5) PMS 6 (10.5) | $\chi^2$ = 0.058 | .810 | h = -0.03 (-0.18 to +0.15), trivial |
| EDSS (median [range]) | 1.5 (0.0-6.0) | 2.0 (0.0-6.0) | U = 1780.0 | .024* | r = 0.22 (0.03-0.41), small |
| Self-reported physical activity | | | | | |
| MVPA (minutes) (median [range]) | 88.5 (0.0-270.0) | 90.0 (0.0-330.1) | U = 1442.5 | .913 | r = 0.01 (-0.18 to +0.20), trivial |
| MVPA (MET-minutes) (median [range]) | 420.0 (0.0-1380.0) | 412.5 (0.0-1433.6) | U = 1361.5 | .692 | r = 0.04 (-0.15 to +0.23), trivial |

| | | | | | |
|---|---|---|---|---|---|
| Cardiorespiratory fitness | | | | | |
| $\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) (mean [SD])[‡] | 25.30 (7.10) | 24.35 (8.23) | t = 0.635 | .526 | d = 0.12 (-0.26 to +-.50), trivial |
| $\dot{V}O_{2max}$ (percentile) (median [range]) | 10 (4-95) | 10 (4-90) | U = 1488.0 | .685 | r = 0.04 (-0.15 to +0.23), trivial |

*$p$ < .05, *$p$ < .001, [‡]The proportions of participants in the regression derivation (n = 42 [84.0%]) and validation groups (n = 42 [73.7%]) who reached true $\dot{V}O_{2max}$ were not significantly different ($\chi^2_{(1)}$ =1.680, $p$ = .195). 95% CI, 95% confidence interval; BMI, body mass index; EDSS, Expanded Disability Status Scale; MET, metabolic equivalent of task; MS, multiple sclerosis; MVPA, moderate- to vigorous-intensity physical activity; RRMS, relapsing-remitting MS; PMS, progressive MS (including primary and secondary progressive MS); $\dot{V}O_{2max}$, maximum oxygen uptake.

In the regression derivation group, the overall model was statistically significant ($F_{(5, 49)}$ = 6.327, $p < .001$). The combination of sex, age, body mass, EDSS, and MVPA accounted for 35%-42% of variance in $\dot{V}O_{2max}$ ($R^2 = 0.418$, adjusted $R^2 = 0.352$) (Table 4.5). MVPA was the only variable that did not significantly contribute to the predictive ability of the model ($p > .05$). The model met all assumptions. Using the multiple regression, we derived the following equation to analyze sex differences in the prediction of $\dot{V}O_{2max}$:

$\dot{V}O_{2max}$ ($mL \bullet min^{-1} \bullet kg^{-1}$) = (8.211 × Sex [1 = F, 2 = M]) – (0.228 × Age) – (0.247 × Body Mass [kg]) – (0.996 × EDSS) + (0.004 × MET-minutes of MVPA in last 24 hours) + 44.737.

**Table 4.5 Multiple regression results for objectively measured fitness ($\dot{V}O_{2max}$), based on derivation group**

| $\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) | B (95% CI) | SE B | β | $R^2$ | Adjusted $R^2$ |
|---|---|---|---|---|---|
| Model** | | | | 0.418 | 0.352 |
| Constant | 44.737 (31.680-57.794)** | 6.479 | | | |
| Sex (F, M) | 8.211 (4.239-12.184)** | 1.971 | 0.545** | | |
| Age (years) | -0.228 (-0.394 to -0.062)* | 0.083 | -0.334* | | |
| Body Mass (kg) | -0.247 (-0.379 to -0.115)** | 0.065 | -0.510** | | |
| EDSS | -0.996 (-1.914 to -0.078)* | 0.455 | -0.264* | | |
| MVPA (MET-minutes) | 0.004 (-0.002 to +0.009) | 0.003 | 0.168 | | |

*$p < .05$, **$p < .001$; 95% CI, 95% confidence interval; B, unstandardized regression coefficient; β, standardized regression coefficient; EDSS, Expanded Disability Status Scale; MET, metabolic equivalent of task; MVPA, moderate- to vigorous-intensity physical activity; $R^2$, coefficient of variation; SE B, standard error of estimate; $\dot{V}O_2max$, maximum oxygen uptake.

When we ran the regression in the validation group, the overall model remained statistically significant ($F_{(5, 56)} = 12.989$, $p < .001$, $R^2 = 0.560$, adjusted $R^2 = 0.517$). Again, MET-minutes of MVPA in the last 24 hours did not reach statistical significance as a predictor variable ($p > .05$). In the validation group, measured and predicted $\dot{V}O_{2max}$ values were both equivalent ($d$ [95% CI] = ± 0.10 [± -0.16 to +0.36]) and not significantly different ($p > .05$; Table 4.6).

**Table 4.6 Performance of $\dot{V}O_{2max}$ prediction equation in the validation group**

| Measured $\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) (mean [SD]) | Predicted $\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) (mean [SD]) | Effect Size (95% CI) | Test Statistic | *p*-value |
|---|---|---|---|---|
| *Validation Group (n = 57)* | | | | |
| 24.35 (8.23) | 23.81 (5.34) | *d* = 0.01 (-0.164 to +0.356)‖ trivial | *t* = 0.038 | .970 |
| *Females (n = 43)* | | | | |
| 22.32 (7.56) | 22.32 (4.64) | *d* = 0.001 (-0.30 to +0.30)‖ trivial | *t* = -0.790 | .434 |
| *Males (n = 14)* | | | | |
| 30.61 (7.16) | 28.39 (4.83) | *d* = 0.41 (-0.15 to +0.92) small | *t* = 1.368 | .195 |

*$p < .05$, **$p < .001$, ‖measured and predicted $\dot{V}O_2max$ are equivalent; 95% CI, 95% confidence interval; EDSS, Expanded Disability Status Scale; MET, metabolic equivalent of task; MVPA: moderate- to vigorous-intensity physical activity; $\dot{V}O_{2max}$, maximum oxygen uptake.

When considering sex differences, we found that measured and predicted $\dot{V}O_{2max}$ values were both equivalent (*d* [95% CI] = ± 0.001 [± -0.30 to +0.30]) and not significantly different ($p > .05$), in females (Table 4.6). However, in males, although not significantly different ($p > .05$), the measured and predicted $\dot{V}O_{2max}$ values were also nonequivalent (*d* [95% CI] = ± 0.41 [± -0.15 to +0.95]; Table 4. 6).

Figure 4.2 illustrates Bland-Altman plots of measured and predicted $\dot{V}O_{2max}$ values in females (Figure 4.2A) and males (Figure 4.2B) in the validation group. For both females and males, the difference between, and average of, predicted and measured $\dot{V}O_{2max}$ values were significantly correlated (females: $r = 0.501$, $p = .001$; males: $r = 0.497$, $p = .042$).

The plots show that predicted $\dot{V}O_{2max}$ values for all participants fell within 2 SD of measured $\dot{V}O_{2max}$ within both sexes.

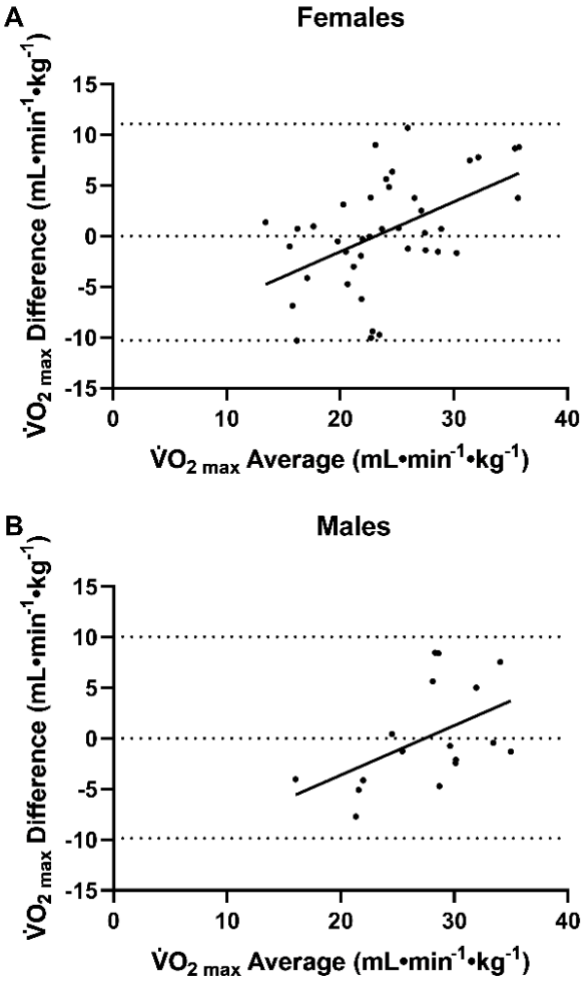


**Figure 4.2 Bland-Altman plots of measured and predicted cardiorespiratory fitness ($\dot{V}O_{2max}$; mL•kg-1•min-1) in the validation group of participants (n = 57; 43 females, 14 males).**

Based on the regression equation: $\dot{V}O_{2max}$ (mL•min$^{-1}$•kg$^{-1}$) = (8.211 × Sex [1 = F, 2 = M]) – (0.228 × Age) – (0.247 × Body Mass) – (0.996 × EDSS) + (0.004 × MET-minutes of MVPA) + 44.737, obtained from the derivation group of participants (n = 50; 34 females, 16 males). The x-axis represents the average of measured and predicted $\dot{V}O_{2max}$ values, and the y-axis represents the difference between measured and predicted values. Dashed lines represent the mean and ± 2 standard deviations (SD) from the mean. Panels A and B demonstrate the prediction equation in females and males, respectively.

## 4.4 Discussion

This study aimed to (1) explore sex differences in self-reported MVPA and $\dot{V}O_{2max}$; (2) examine relationships between self-reported MVPA, $\dot{V}O_{2max}$, and disability status, with an emphasis on sex differences; and (3) determine whether self-reported MVPA could predict $\dot{V}O_{2max}$ in females and males with MS.

MS participants had low levels of cardiorespiratory fitness despite high self-reported levels of MVPA in the last 24 hours, suggesting incongruence between objective fitness levels and self-reported estimates of physical activity. Compared to females, males tended to have greater overall cardiorespiratory fitness, despite similar levels of disability. Next, associations between cardiorespiratory fitness, MVPA, and disability were statistically significant in females only. Lastly, the regression equation including age, sex, body mass, and EDSS, and self-reported MET-minutes of MVPA predicted 35%-42% of variance in objectively measured $\dot{V}O_{2max}$; however, self-reported MVPA was the only predictor variable that did not significantly contribute to the equation. The model was valid in females only. We believe these findings suggest that: (1) persons with MS tended to overestimate their physical activity levels; and (2) 24-hour physical activity recall was not a valid method for estimating cardiorespiratory fitness in persons with MS.

### 4.4.1 Low cardiorespiratory fitness in males and females with MS

In the present study, the mean ± SD $\dot{V}O_{2max}$, based on 107 fitness tests conducted on an outpatient MS clinic sample, was 24.80 ± 7.70 $mL \bullet min^{-1} \bullet kg^{-1}$, representing fitness in the poor to fair range [266]. Approximately half of all participants had $\dot{V}O_{2max}$ fitness ranks below their age- and sex-normalized 20$^{th}$ percentile [266]. Such low levels of fitness are concerning because of the

links between low fitness, metabolic comorbidities, MS disability accumulation, and mortality [252,253,300]. A systematic review by Langeskov-Christensen et al. (2015) reported similar $\dot{V}O_{2max}$ values in people with MS to those found here, but without considering sex differences [268].

In our sample, despite exceeding recommended physical activity levels, both females (23.03 ± 7.04 mL•min$^{-1}$•kg$^{-1}$) and males (29.34 ± 7.59 mL•min$^{-1}$•kg$^{-1}$) failed to reach the range of 'good' $\dot{V}O_{2max}$ values. There is limited research investigating sex-based differences in physical fitness in MS. A cross-sectional study by Romberg et al., (2004) involving 92 individuals with MS (58 females), with a mean age of 44 years, reported fitness values similar to those reported here (21 mL•min$^{-1}$•kg$^{-1}$ for females and 27 mL•min$^{-1}$•kg$^{-1}$ for males) [277]. Interestingly, they reported significant associations between level of disability (EDSS), and fitness, which was stronger in males than females [277]. This finding conflicts with our result that lower disability was associated with higher $\dot{V}O_{2max}$ in females (Rho = -0.35, $p$ = .002) but not males (Rho = -0.20, $p$ > .05). These differences could be explained by the fact that in the Romberg et al. (2004) study, males had higher mean disability scores (EDSS 3.0) than females (EDSS 2.2) while our median EDSS was 2.0 and the same for both sexes. It is important to note that their sample was recruited from a waitlist for inpatient rehabilitation, where participants presumably had rehabilitation needs for walking and balance. Conversely, our sample represents people attending regular outpatient neurology clinic visits, who were not referred to rehabilitation, had independent mobility, and whose disease was stable. Given that males tend to have a more severe MS disease course [251], it is possible that their sample was representative of males with severe disease [277]. The method of fitness testing also influences $\dot{V}O_{2max}$ values. Previous studies (Bjarnadottir et al., 2007; Romberg et al., 2004) measured fitness using a cycle leg ergometer. The challenge with using a leg ergometer is that the workload is restricted to the lower limbs, such that individuals

with greater leg weakness may not be able to reach their maximal values. Previous research by Ponichtera-Mulcare et al. (1995) confirmed that MS patients could achieve their predicted maximal fitness values when using both upper and lower body testing but not when using only the arms or legs. In our study, we used a recumbent stepper, a device that has become widely available in the past 15 years and which permits workload distribution between the upper and lower body. Remarkably, even when using a more modern adapted device (recumbent stepper), our group of independent and clinically stable participants had fitness values in the poor to fair range.

### 4.4.2 Incongruence between objective fitness and self-reported physical activity in males

Participants reported 90 minutes of MVPA in the last 24 hours (412.5 MET-minutes). For comparison, we were unable to find other studies in MS using 24-hour physical activity recall. In representative MS studies using other self-report instruments, average weekly physical activity levels were variable and included 150 minutes per week of MVPA (≥ 4 MET) [310], 2710 MET-minutes per week of leisure-time activity of any type and intensity [292], and 1901 MET-minutes per week of at least low-intensity physical activity exceeding (≥ 3.3 MET) [311]. These observations suggest that participants in the current study tended to over-estimate their levels of MVPA using 24-hour recall. Indeed, participants' 24-hour MVPA estimates approached the weekly recommended 450 MET-minutes of MVPA from population physical activity guidelines [308,309].

Although males tended to report higher levels of MVPA in the previous 24 hours than females (507 MET-minutes vs 360 MET-minutes), this difference was not statistically significant ($p > .05$). Unlike females, males' self-reported MVPA was not associated with cardiorespiratory

fitness. In contrast to our findings, Anens et al. (2014) reported lower physical activity levels in males with MS using the Physical Activity Disability Survey (PADS-R), suggesting that more severe disease in males may limit their physical activity levels to a greater extent than females [312]. Notably, males and females in our sample had similar levels of disability on the neurologist scored EDSS. Other studies using objective assessments such as uniaxial accelerometry [313 314] or daily step counts measured by a motion sensor [315] or Fitbit Flex2 device [316] found no sex-related differences among individuals with MS. In a systematic review involving 58 studies, Streber et al. (2016) reported that sex was inconsistently associated with physical activity in individuals with MS [317].

Subjective and objective measures of MVPA often show disparities in MS, possibly due to the misinterpretation of activity intensity, which can have significant implications when clinicians evaluate physical activity patterns in individuals with MS [276]. One such source of over-representative physical activity self-reporting may be the use of a 24-hour recall instrument. Although these tools have been validated in healthy populations [287-291], previous-day estimates have been shown to misrepresent MVPA due to lack of standardized definitions of activity types and intensity [288,290,291], for uncommon or unfamiliar activities [287], and for persons with lower fitness [291]. Indeed, potential misclassification of self-reported physical activity in persons with MS can be attributed to a poor understanding or misinterpretation of activity intensity and duration [292]. Kinnett-Hopkins et al. (2019) highlighted ambiguities in how individuals with MS perceive and interpret physical activity, contributing to the challenges in accurately reporting their activity levels [318]. Such challenges are not exclusive to the MS population and have been observed in other chronic conditions such as diabetes [319], rheumatoid arthritis [320], and chronic low back pain [321]. These limitations can be circumvented by using standardized self-report tools

that have been validated in the patient population, as well as operationalization of activity descriptions and intensities [322]. Alternatively, objective tools such as accelerometers may provide more valid characterization of physical activity levels [276,292,323,324].

### 4.5 Limitations

One of the limitations of the current study was the self-reported questionnaire used to estimate participants' activities in the last 24 hours. We chose the 24-hour recall because of its accuracy and lower vulnerability to recall bias [272,273]; however, previous day estimates of activities may not represent a participant's typical day, especially in persons with MS who may be more vulnerable to inaccurate recall than apparently healthy people [325]. In addition to the timeframe of recall, the process of undertaking an open recall exercise is more nuanced than administering a structured questionnaire. This difference could impact inter-rater and test-retest reliability of MVPA estimates, thereby reducing the applicability of the present findings to wider clinical practice [292]. Objective measures of physical activity such as accelerometry yield more accurate MVPA results and may better identify sex differences when predicting $VO_{2max}$ in future work [276]. Also, we did not explore factors such as fatigue, pain, heat sensitivity, comorbidities, lifestyle factors, or medical treatments, nor how they relate to fitness. Since our regression model accounted for 35-42% of the variance in $\dot{V}O_{2max}$, other unmeasured variables may be at play. Future work is needed to re-examine our findings by using other self-report tools or objective measures of MVPA.

## 4.6 Conclusions

Despite reporting high levels of MVPA, people with MS had low levels of cardiorespiratory fitness. MVPA, fitness, and disability were associated in females only, indicating sex differences should be considered in fitness appraisal. Self-reported MVPA did not predict fitness, suggesting 24-hour recall may not be representative of true activity or fitness levels in persons with MS. Low overall levels of fitness point to a need for exercise prescription to promote metabolic and brain health; however, sex should be considered during both fitness appraisal and exercise prescription. Future work should examine sex differences in associations between MVPA and fitness using objective measures such as accelerometry.

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# Chapter 5 Discussion

## 5.1 Thesis Overview

In the first stage of my doctoral work, I conducted a systematic review and a meta-analysis (Chapter 2), in which the aim was to determine optimal rehabilitation interventions to improve gait speed in people with MS. In the second stage (Chapter 3), the aim was to monitor covert worsening of gait, especially in the early phase of the disease, and help identify disease progression. In order to assess covert walking changes, I examined the change in gait speed and stride time variability over two years in clinically stable people with MS. I determined whether cardiorespiratory fitness (measured at Time 1 [T1]) could predict the change in gait variability over two years (T2). The reason for investigating was to identify covert gait changes not apparent on observation. In the third stage (Chapter 4), the aim was to determine fitness levels in people with MS and examine relationships between self-reported MVPA, $\dot{V}O_{2max}$, and disability status with an emphasis on potential sex differences, and determine whether self-reported MVPA could predict $\dot{V}O_{2max}$ in females and males with MS. The reason for investigating these relationships was to identify whether self-reported MVPA could serve as a valid and reliable indicator for estimating cardiorespiratory fitness in females and males and whether sex should be considered during both fitness appraisal and exercise prescription in future trials.

## 5.2 Summary of findings

The main findings from the studies (Chapters 2, 3, and 4) included in the thesis are summarized in the following sections.

### 5.2.1 Findings from Chapter 2

The aim of the systematic review (Chapter 2) was to conduct a comprehensive review of tested rehabilitation interventions to improve gait speed in people with MS. The secondary aim was to determine the optimal approaches to improve gait speed.

This systematic review included 90 RCTs that met our inclusion criteria, of which 77 trials were included for meta-analysis, and the key findings were:

1) There was a significant amount of research focused on testing rehabilitation interventions aimed at improving gait speed. In fact, the review included 90 RCTs, indicating a substantial interest in this area within the scientific community. About 30 RCTs conducted in the last 5 years indicate a recent surge in research activity in this field.

2) There was significant heterogeneity across trials. The interventions differed significantly in their effects on gait speed in people with MS.

3) Despite significant heterogeneity across trials, a positive but small effect of interventions on improving gait speed in people with MS was observed.

4) Lower limb resistance and treadmill training were the most effective interventions to improve gait speed in MS.

In this study, I learnt that

1) There is a need to delve deeper into understanding the factors contributing to heterogeneity across trials.

2) There is a need to focus on optimizing intervention parameters such as intensity, duration, and mode of delivery to maximize the efficacy of rehabilitation approaches.

3) It is important to understand the underlying mechanisms of effective interventions and explore potential synergies between rehabilitation interventions and pharmacological treatments.

4) There is a need for implementation research to investigate strategies for integrating these effective rehabilitation interventions into clinical practice to ensure widespread accessibility and adoption.

### 5.2.2 Findings from Chapter 3

The primary aim of the second study (Chapter 3) was to examine gait variability over two years in clinically stable people with MS. This would help in understanding covert neurodegeneration and contributing factors in people with mild to no disability (EDSS<4). The secondary aim was to determine whether fitness or cognition could predict changes in gait variability over two years.

In this study, the key findings were

1) Overall, there was an increase in stride time variability over two years, which was variable within individuals.

2) Gait variability changed over time without clinically documented relapse or change in disability status. About 57.1% of the participants (n=28) experienced increased gait variability, indicating a deterioration in their gait over time.

3) Higher cardiorespiratory fitness levels predicted preservation of gait over two years.

4) Baseline cognition failed to predict gait variability over time.

In this study, I learnt that

1) Stride time variability is a sensitive biomarker of longitudinal change in gait in the absence of clinically observable metrics.

2) The findings suggest the potential protective role of cardiorespiratory fitness on gait variability.

3) The limited predictive power of baseline cognition on gait variability over time suggests that other factors, outside of those we controlled for, affect variability , such as fatigue or sleep.

### 5.2.3 Findings from Chapter 4

The primary aim of the third study (Chapter 4) was to explore sex differences in self-reported MVPA and $\dot{V}O_{2max}$. To address this aim, MVPA and $\dot{V}O_{2max}$ were measured in females (n=77) and males (n=30) with MS. The secondary aim was to examine relationships between self-reported MVPA, $\dot{V}O_{2max}$, and disability status, with an emphasis on sex differences, and determine whether self-reported MVPA could predict $\dot{V}O_{2max}$ in females and males with MS. In this study, the key findings were

1) Incongruence between objective fitness levels and self-reported estimates of physical activity

2) Approximately half of females' and males' cardiorespiratory fitness ranks fell below the $20^{th}$ percentile; indicating poor fitness levels compared to the general population matched for age and sex.

3) Associations between cardiorespiratory fitness, MVPA, and disability were statistically significant in females but not in males.

4) Regression equation including age, sex, body mass, EDSS, and self-reported MET-minutes of MVPA predicted 35%-42% of variance in objectively measured $\dot{V}O_{2max}$ and was valid only in females.

In this study, I learned that

1) There is a need to investigate the factors contributing to the incongruence between self-reported MVPA and objectively measured fitness, such as social desirability bias, inaccuracies in self-reporting methods, or differences in perception of physical activity intensity.

2) People with MS (both males and females) had cardiorespiratory fitness ranks falling below the 20th percentile, indicating a considerable portion of the population with low fitness levels.

3) It is important to explore biological, sociocultural, and environmental factors that may influence the relationships between fitness, physical activity, and disability differently in males and females with MS

### 5.3 Overall discussion of thesis findings

This body of work contributed to the field of MS rehabilitation by gaining a deeper understanding of the factors influencing gait in individuals with MS. In the following section, I have linked the findings from the studies (Chapters 2, 3, and 4) and interpreted them considering existing scientific literature and current evidence-based clinical practice.

### 5.3.1 Optimal rehabilitation interventions

Over the past 30 years, there has been a significant advancement in the management of MS. These advancements have not only improved pharmacological treatments in reducing relapse rates [326] but have also expanded our understanding of non-pharmacological interventions such as exercise in reducing disability progression in MS [262]. Historically, individuals with MS were advised to avoid physical activity due to concerns about exacerbating symptoms or causing fatigue. However, research over the past two decades has challenged this notion, demonstrating that exercise is not only safe but also beneficial for individuals with MS [327,328]. Initial evidence considered exercise as tertiary prevention while recent basic science and clinical research showed that exercise is also effective in primary [329]and secondary prevention [330]of MS. Exercise has been shown to downregulate pro-inflammatory cytokines while preserving brain structure and function [331]. Furthermore, exercise helps to improve symptoms such as fatigue [332], pain [333], mobility [334], cognition [335], balance [336], depression [337] and enhance health-related quality of life [338]. While there is a large growing body of evidence in favor of exercise as an effective treatment for people with MS, it creates challenges for rehabilitation providers in determining the optimal approach. In the first study (Chapter 2) a systematic review of literature related to rehabilitation interventions was conducted to determine the optimal rehabilitation approaches to improve gait in MS. In this study, it was surprising to see that 90 RCTs were included and around 30 RCTs were conducted in the past 5 years (Figure 2.2). Additionally, various interventions were being tested, and it was quite challenging to categorize them into intervention groups. Despite heterogeneity across trials, rehabilitation has a positive effect in improving gait in people with MS. Lower limb rehabilitation (Figure 2.3a) and treadmill (Figure 2.3b) were the most effective interventions to improve gait speed in people with MS. It is likely that the mode of delivery and

the intensity training contribute to the superior efficacy of these interventions. These approaches are functional and task-specific, tailored to the specific needs and abilities of individuals, thereby optimizing their effectiveness in improving gait. As effective rehabilitation interventions help to improve gait [331,336,338], future research should combine rehabilitation interventions with pharmacological treatments to achieve potential additive effects.

### 5.3.2 Covert neurodegeneration and protective role of cardiorespiratory fitness in MS

Disability in MS results from acute focal inflammation and axonal injury commonly associated with relapse activity. However, some of the RRMS patients experience 'silent progression', wherein disability progresses independent of relapse activity. It is challenging to understand the pathological and molecular mechanisms of silent progression and early identification of the transition from RRMS to SPMS. A recent longitudinal study reported that silent progression goes unnoticed and occurs even before it is evident on clinical examination [26]. Silent progression is a result of focal 'smoldering' lesions and diffuse axonal loss in normally appearing white and grey matter [339]. Hence, it is important to understand and identify the transition as it has important implications for therapeutic decision-making. In the longitudinal study among people with RRMS, gait variability changed in people with no evidence of relapse (Chapter 3). People with higher fitness levels had less deterioration in gait over time, suggesting a potential opportunity for minimizing silent progression. Therefore, beyond mere identification of silent progression, it is equally important to understand factors that could curb this progression.

### 5.3.4 Clinical Implications

In the first study of this thesis (Chapter 2), a systematic review of the literature was performed to identify rehabilitation interventions to improve gait speed in people with MS. The summary of results from trials included in this review was sufficiently conclusive to agree that rehabilitation has a positive effect in improving gait speed in people with MS. Furthermore, lower limb resistance and treadmill training were most effective in improving gait speed in MS. However, future RCTs are required to integrate the most effective rehabilitation interventions with gait-enhancing drugs to potentially achieve an additive effect in improving gait speed in people with MS.

In the second study of this thesis (Chapter 3), the longitudinal changes in the gait were assessed in clinically stable people with MS. The findings from this study indicated that silent progression or covert neurodegeneration over time is seen in the absence of relapse. Notably, people with higher cardiorespiratory fitness demonstrated an advantage in the preservation of gait over time. The results are promising and support future longitudinal studies to assess changes in gait over an extended period of time and identify other relevant factors that could reduce gait deterioration in people with MS. Further studies to understand how sex influences fitness and its impact on the disease progression are needed, which could help to develop tailored interventions and personalized treatment approaches for people with MS.

### 5.3.5 Recommendations for future research

Although exercise has an overall positive effect on improving gait speed in MS (Chapter 2), the additive effect that exercise provides when combined with gait-improving medications in

improving gait is still unclear. Therefore, future research should focus on RCTs that integrate rehabilitation with pharmacological therapies to improve gait in MS. Researchers should focus on understanding the mechanisms related to additive effect-induced neuroprotective benefits for people with MS.

The second study of this thesis (chapter 3) indicated that gait changes occur even in clinically stable people with MS and the protective role of cardiorespiratory fitness in preserving gait in people with MS. I learned two opportunities for future research on the link between fitness and gait. First of all, a significant change in stride time variability was observed, but not gait speed, raising a possibility that stride time variability might serve as a longitudinal biomarker in people with MS. Secondly, cardiorespiratory fitness accounted for only 11.4 % of the variance in gait variability after controlling for age, gender, the time between assessments, baseline stride time variability and cognition. Hence, there is a need to determine the factors outside of those that we controlled for, that contribute to gait variability in MS.

In the third study (Chapter 4), both males and females with MS had poor cardiorespiratory fitness levels, raising a possibility of deconditioning and disability progression. Secondly, there were sex differences in the association between self-reported MVPA, fitness and clinical disability; future research should focus on exploring how sex influences fitness and its impact on disease progression, which could lead to tailored interventions and personalized treatment approaches.

### 5.4 Concluding remarks

Overall, the findings from the thesis contribute to the basis for silent progression in the absence of relapse while considering the protective role of fitness in predicting gait changes in

people with MS. One of the takeaways from the thesis is that silent progression and neurodegeneration are evident in clinically stable (no change in EDSS) people with MS. Early detection of these changes can be identified using functional assessments such as gait. More importantly, the gait variability identified as a sensitive biomarker of neurodegeneration in this thesis can be considered in identifying silent progression, which is not apparent to an observer. Furthermore, the thesis unveils the protective role of fitness in predicting the silent progression of MS. The thesis highlights the sex differences, emphasizing the need to consider sex-specific factors in developing personalized interventions for people with MS. Lastly, I conducted the largest review of rehabilitation interventions to improve gait speed and found that two approaches stood out. Delineating these two helps guide therapists in choosing the best treatments for their patients.

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# Chapter 7 Appendices

# Appendix 7.1 Registration on PROSPERO for the study titled 'Optimal rehabilitation interventions to improve gait speed in multiple sclerosis: A systematic review and meta-analysis

**From:** **CRD-REGISTER** irss505@york.ac.uk
**Subject:** PROSPERO Registration message [261776]
**Date:** July 20, 2021 at 2:30 AM
**To:** sburagadda@mun.ca

Dear Mrs Buragadda,

We apologise for the delay in dealing with your registration, an ever-increasing number of applications has led to a backlog and substantial delays for some users.

PROSPERO is currently prioritising submissions related to COVID-19. To enable us to focus on these submissions, and to avoid additional delay, during the pandemic we will automatically publish submissions that have been waiting more than 30 days for registration.

This applies to your systematic review "Optimal dosage parameters of exercise on gait in people with MS: A systematic review" which was published on our website on Jul 18, 2021.

The records will be published exactly as submitted, without review by the PROSPERO team, so the public record will indicate:

"To enable PROSPERO to focus on COVID-19 registrations during the 2020 pandemic, this registration record was automatically published exactly as submitted. The PROSPERO team has not checked eligibility"

Review owners have always been responsible for the quality and content of PROSPERO records, and high-quality well-written records will continue to speak for themselves.

Your registration number is: CRD42021261776

You are free to update the record at any time, all submitted changes will be displayed as the latest version with previous versions available to public view. Please also give brief details of the key changes in the Revision notes facility and remember to update your record when your review is published. You can log in to PROSPERO and access your records at https://www.crd.york.ac.uk/PROSPERO

Best wishes for the successful completion of your review.

Yours sincerely,

PROSPERO Administrator
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PROSPERO is funded by the National Institute for Health Research and produced by CRD, which is an academic department of the University of York.

Email disclaimer: https://www.york.ac.uk/docs/disclaimer/email.htm

Other non-commercial resources that may be of interest
SRDR-Plus is a systematic review data management and archival tool that is available free of charge http://srdrplus.ahrq.gov.

**Appendix 7.2 Ethics approval for the two studies titled 'Cardiorespiratory fitness protects against covert worsening of gait variability over two years in people with multiple sclerosis' and 'Incongruence between cardiorespiratory fitness and subjective reports of physical activity in multiple sclerosis: A focus on sex differences'**

**HREB - Approval of Ethics Renewal 20161208**
administrator@hrea.ca
**Sent:** Friday, March 22, 2024 10:43 PM
**To:** Anthony Sarah(Key Contact) [sarah.anthony@easternhealth.ca]
**Cc:** Ploughman Michelle(Co-Principal Investigator) [mploughm@mun.ca]; Moore, Craig; Stefanelli Mark(Principal Investigator) [cstefanelli@nl.rogers.com]; Hreaadministrator

Researcher Portal File #: 20161208

Dear Dr. Mark Stefanelli:

This e-mail serves as notification that your ethics renewal for study HREB # 2015.103 – Health Research Innovation Team in Multiple Sclerosis (HIT MS) Provincial Portfolio – has been **approved**. Please log in to the Researcher Portal to view the approved event.

Ethics approval for this project has been granted for a period of twelve months effective from 30 Apr 2024 to 30 Apr 2025.

Please note, it is the responsibility of the Principal Investigator (PI) to ensure that the Ethics Renewal form is submitted prior to the renewal date each year. Though the Research Ethics Office makes every effort to remind the PI of this responsibility, the PI may not receive a reminder. The Ethics Renewal form can be found on the Researcher Portal as an "Event".

The ethics renewal will be reported to the Health Research Ethics Board at their meeting dated 04 Apr 2024

Thank you,

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