# EXERCISE IN NONAMBULATORY PEOPLE WITH MULTIPLE SCLEROSIS

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A Dissertation Submitted to the School of Human Kinetics in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy (PhD) – Human Kinetics

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## ABSTRACT

Multiple sclerosis (MS) is an immune-mediated disorder characterized by neuroinflammation, demyelination, and neurodegeneration that results in the degradation of neurological structures within the central nervous system (CNS). This degradation of neurological structures often has a substantial impact on the ambulatory abilities of people living with MS, with an estimated 30% of the MS population requiring a wheelchair for mobility (i.e., nonambulatory). Unfortunately, current pharmacological interventions have limited efficacy for those with progressed disability and alternative strategies for disease management must be considered, such as exercise training. To date, most of the MS exercise training literature has not focused on nonambulatory people with MS, limiting evidence-based exercise recommendations for this population. As such, the central purpose of this dissertation was to inform exercise prescription and delivery for nonambulatory people with MS. In order to achieve this goal, three studies were conducted.

The first study in this dissertation (presented across two manuscripts) evaluated the safety and physiological response of nonambulatory people with MS to three adapted exercise modalities (arm cycle ergometer, recumbent stepper, functional electrical stimulation cycle). This study determined that acute adapted exercise was well-tolerated by nonambulatory people with MS, with few adverse events reported across all exercise sessions. Notably, participants favoured recumbent stepper and functional electrical stimulation cycling exercise over arm cycle ergometer exercise. Further, participants were capable of exercising at an intensity that satisfied the American College of Sport Medicine's criteria for moderate-to-vigorous physical activity on all adapted modalities. This suggests all tested modalities are capable of promoting improvements in health-related fitness outcomes.

The second study, a systematic review and meta-analysis, explored outcome measures that capture 'participation' in MS exercise trials, and the influence of exercise training on 'participation'. Described within the International Classification of Functioning, Disability and Health (ICF) as the "involvement in life situations", 'participation' outcomes provide insight into the impact of MS on everyday life. Findings from this study demonstrated variability in how 'participation' has been captured, with an emphasis on items describing 'mobility'. Further, the meta-analysis revealed that exercise training had a moderate, positive effect on outcomes that capture participation, a novel finding regarding the benefits of exercise training in MS.

The final study of this dissertation, an online-based survey, identified perceived exercise benefits, barriers, and needs among nonambulatory people with MS. This study demonstrated that nonambulatory people with MS perceive health improvements and personal accomplishments as the greatest benefits associated with exercise engagement. The sample also cited environmental challenges and MS symptoms as prominent barriers to exercise engagement. The current sample identified that exercise facilities, specifically exercise equipment, were failing to accommodate their exercise needs.

Collectively, the findings from this dissertation will help address prominent gaps in the exercise training literature involving nonambulatory people with MS. Addressing such gaps will contribute to advancing evidence-informed exercise interventions, promoting measurable health improvements, and ultimately increasing engagement in exercise for nonambulatory people with MS.

## ACKNOWLEDGMENTS

First and foremost, I would like to thank my supervisor, **Dr. Lara Pilutti** for her continuous support, guidance, and mentorship throughout my graduate studies. As my supervisor, you have provided me numerous opportunities to succeed and grow as a researcher and academic. Thank you for always challenging me and demonstrating the importance of hard work.

To my dissertation committee (**Dr. Michael De Lisio, Dr. Jennifer Reed, and Dr. Lisa Walker**) thank you for the critical feedback you provided throughout my doctoral studies. Your insight was essential in the development and completion of my doctoral research.

To all members of the Clinical Exercise Physiology Lab, past and present, it has been a pleasure to work with you all! A special thank you to **Dr. Afolasade Fakolade** and **Dr. John Farrell III** for your guidance, leadership, and willingness to always discuss ideas with me throughout my studies.

To my friends, thank you for always keeping me grounded and in high spirits. I am very lucky to have so many great people who have supported me throughout this academic journey. A special shoutout to my friend **Dr. Lizzie Hubbard** for not only being a great friend, but also a great mentor.

To the Halili Family (**Elvira, Gezim, Rina**), thank you for your hospitality, support, and kindness throughout my studies. You have welcomed me into your home with open arms and treated me like family. I cannot thank you enough!

To my parents, (**Peter and Sandi**) thank you for everything. Without you, I would not be where I am today. No matter how often I failed, your insight, encouragement, and love allowed me to push forward with determination and confidence. I am lucky I can always depend on you both.

To ***Lyra Halili***, thank you for your unrelenting encouragement and love. The importance of your support cannot be measured. You showed me first-hand the value of determination and you never let me give up on myself. As I embark on the next chapter in my life, I am fortunate and thankful to be doing it with you by my side. You are my best-friend and I love you.

Lastly, I want to acknowledge and thank all the amazing research participants I have been fortunate enough to work with during my PhD. Without your generosity and willingness to volunteer your time, my research would, quite literally, not be possible. Thank you!

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## MANUSCRIPT CONTRIBUTIONS

The manuscripts of this dissertation (Chapters 2 – 5) are the work of Thomas Edwards in collaboration with co-authors. For all manuscripts, Mr. Edwards was responsible for developing the research questions, conceptualizing the study designs, collecting, and analyzing data, and writing all manuscripts. The co-authors of the manuscripts include: Dr. Lara Pilutti (Chapter 2 – 5), Dr. Afolasade Fakolade (Chapters 2 & 4), Dr. Lisa Walker (Chapter 2 & 3), Ms. Katie Lindale (Chapter 5), Dr. Ulrik Dalgas (Chapter 4), and Ms. Anne-Sophie Michelsen (Chapter 4).

### Chapter 2: The Safety of Exercise for Nonambulatory People with Multiple Sclerosis

Dr. Pilutti assisted in the development of the research question, study design conceptualization, development of study materials, recruitment of participants, data analysis and interpretation of results. Dr. Walker assisted in the development of the research question and recruitment of participants. All co-authors provided editorial feedback on the manuscript.

### Chapter 3: Characterizing the Physiological Response to Exercise in Nonambulatory People with Multiple Sclerosis

Dr. Pilutti assisted in the development of the research question, study design conceptualization, development of study materials, recruitment of participants, data analysis and interpretation of results. Dr. Walker assisted in the development of the research question and recruitment of participants. All co-authors provided editorial feedback on the manuscript.

### Chapter 4: Exercise Training Improves Participation in Persons with Multiple Sclerosis: A Systematic Review and Meta-Analysis

This manuscript is under review in *Journal of Sport and Health Science.* Dr. Pilutti assisted in the development of the research question, literature search strategy development, data analysis, data coding, article quality assessment, and interpretation of results. Dr. Dalgas assisted in the development of the research question, literature search strategy development, and interpretation of results. Ms. Michelsen assisted with data extraction and methodological quality assessment. Dr. Fakolade assisted with data extraction, data coding, and methodological quality assessment. All co-authors provided editorial feedback on the manuscript.

### Chapter 5: Understanding Exercise Benefits, Barriers, and Needs in Nonambulatory People with Multiple Sclerosis

Dr. Pilutti assisted in the development of the research question, study design conceptualization, survey document development, data analysis and interpretation of results. Dr. Fakolade assisted in the study design conceptualization, survey document development, data analysis, data coding, and interpretation of results. Ms. Lindale assisted in the development of the survey document, data analysis, data coding, and interpretation of results. All co-authors provided editorial feedback on the manuscript.

# CHAPTER 1 – Introduction and Literature Review

## 1.1 – General Introduction

Multiple sclerosis (MS) is an immune-mediated disorder of the central nervous system (CNS) characterized by neuroinflammation, demyelination, and neurodegeneration that results in the degradation of the optic nerve, cerebrum, cerebellum, brainstem, and spinal cord.[1] Due to the pathology of MS, affected individuals often experience progressive, compounding neurological impairment that worsens over time.[2] These neurological impairments often manifest as physical and/or cognitive disabilities that ultimately hinder an individual's ability to perform routine activities of daily life.[3] One of the most debilitating and life-altering consequences associated with MS is the loss of mobility.[4]

As disability accumulates, many individuals with MS require an assistive device for mobility, with many people requiring the use of wheelchair. It is estimated that roughly 30% of the MS population is nonambulatory and requires the use of a wheelchair for mobility, with speculations that this number will increase as the MS population ages.[5,6] Unfortunately, the efficacy of pharmacological treatments for preventing disability accumulation is limited, especially for those with higher disability, and alternative strategies for disease management must be explored.[2,7] One such strategy that continuously shows promise is exercise training.[8] Despite numerous systematic reviews and meta-analyses reporting the benefits of exercise training for people with MS, many studies have not included nonambulatory individuals.[9,10] As such, there remains an evidence gap in the current MS exercise literature pertaining to nonambulatory people with MS. Importantly, this lack of evidence has, in part, contributed to low rates of exercise engagement in this population.[11] To begin to address this evidence gap, this dissertation will examine the role of exercise training for nonambulatory people with MS. Specifically, this dissertation will evaluate the safety (adverse events frequency and symptomatic response) and

cardiorespiratory response associated with adapted exercise in nonambulatory people with MS. Further, this dissertation will explore the use of participation outcomes among exercise training studies involving those with MS and provide insight into how exercise may influence such outcomes. This investigation of participation outcomes will enable the identification of outcome measures that are potentially relevant and feasible for use in exercise trials involving nonambulatory people with MS. Lastly, this dissertation will investigate factors affecting community exercise engagement (i.e., benefits, barriers, and needs) in nonambulatory people with MS that can be used to promote long-term exercise engagement. Collectively, the overarching purpose of this dissertation is to "*inform evidence-based exercise prescription and delivery for nonambulatory people with MS".*

### 1.2 – Epidemiology of Multiple Sclerosis

It is estimated that over 100,000 Canadians and 2.8 million individuals worldwide are currently living with MS.[12,13] Presently, Canada has the highest prevalence of MS in the world, resulting in considerable personal, social, and economic costs for Canadians.[13,14] Typically, initial diagnosis of MS occurs between the ages of 20 and 40 with initial symptoms rarely presenting before the age 10 or after the age 60.[15] As MS diagnosis often occurs in early adulthood, the most productive years of a person's life are significantly disrupted. As a result, MS is the most prevalent non-traumatic causes of neurological disability in adults.[16]

Interestingly, the prevalence of MS varies considerably by geographical location, as the highest prevalence of MS is observed in countries located in the northern hemisphere. Indeed, the highest prevalence of MS is found in North America and Europe (>100/100,000 inhabitants), while in Eastern Asia and Africa the prevalence is substantially lower (2/100,000 inhabitants).[17] This trend is further supported by the fact that the countries with the highest prevalence of MS (Canada,

San Marino, Denmark) are all northern countries.[18] These patterns in geographic distribution suggest that environmental factors may influence the development of MS. One proposed hypothesis for explaining geographic differences in MS prevalence is related to differences in vitamin D exposure across latitudinal gradients. Higher levels of vitamin D have been associated with reduced risk for developing MS and individuals living in northern countries receive less sunlight-derived vitamin D.[19,20] However, it is important to note that the prevalence of MS in southern hemisphere regions is lower than in locations in the northern hemisphere, despite comparable distances from the equator and sunlight exposures.[20] Other environmental and lifestyle factors, such as Epstein-Barr virus infection, poor air quality, tobacco usage, adolescent obesity, and high saturated fat diets have all been implicated as possible risk factors for MS.[17,21,22]

In addition to environmental risk factors, there are several biological risk factors that are thought to influence MS susceptibility. Biological sex is an important risk factor implicated in the development of MS. While the exact numbers fluctuate, an estimated three women are diagnosed with MS for every male diagnoses.[23] Ethnicity is another biological risk factor that seemingly influences the development of MS, as a higher prevalence of MS has been observed in non-Hispanic whites compared to other ethnic groups.[17] However, this assertion has been disputed by other studies, suggesting a higher prevalence in African Americans.[24] Furthermore, various genes have been identified and characterized as "MS susceptibility genes", that are thought to predispose certain individuals to developing MS.[25]

### 1.3 – Pathophysiology of Multiple Sclerosis

The ability of the immune systems to produce immune cells capable of distinguishing between foreign pathogens (i.e., disease-causing substances) and self-tissue is fundamental to proper immunological function.[26] Unfortunately, for reasons often not fully understood, the immune

system may erroneously produce immune cells that attack otherwise healthy tissues and/or cells within the body.[27] While there are biological mechanisms in place to eliminate these harmful immune cells, failure of such mechanisms may result in immune-mediated damaged to healthy tissues, resulting in autoimmune disease.[27] Such is the case with multiple sclerosis (MS).[1] The complex pathology of MS involves an abnormal, immune-mediated response which causes immune cells to attack otherwise healthy structures within the CNS, particularly the myelin sheath.[28] While there has been no consensus on the exact cause of this autoimmune attack, the mechanisms by which these immune cells contribute to the neuroinflammatory and neurodegenerative pathology have been extensively characterized.[28–34]

In the context of MS pathology, neuroinflammation is the result of an errant infiltration of the CNS by self-reactive immune cells.[32] In healthy individuals, a specialised population of immune cells unique to the CNS (microglial cells) act as the primary form of immune defense within the CNS, with the blood-brain barrier (BBB) preventing unwarranted immune cells from entering from the periphery.[33] In the case of MS, however, an intricate and multi-step interaction involving the BBB and harmful immune cells results in erroneous penetration of the BBB by self-reactive immune-cells.[33] This initial penetration is thought to increase the permeability of the BBB and result in a significant influx of damaging immune cells to the CNS.[33] Following degradation of the BBB, immune cells invade the CNS and begin to secrete cytokines, cell-signaling proteins vital to immune function.[34] These cytokines have either pro-inflammatory or anti-inflammatory functions and are ultimately culpable for the neuroinflammatory pathology of MS.[35] Indeed, a disparity between pro-inflammatory and anti-inflammatory cytokines has been implicated as the primary mechanism for neuroinflammation, as individuals with MS demonstrate elevated levels of pro-inflammatory cytokines compared healthy individuals in the serum and cerebral spinal fluid (CSF).[35–38]

In addition to increased neuroinflammation, the increased presence of harmful immune cells within the CNS also has negative implications for CNS structures by contributing to neurodegeneration. Neurodegeneration is characterized by progressive destruction of neurons within the CNS and is an unfortunate cornerstone of MS pathology.[34] Similar to neuroinflammation, the neurodegenerative aspect of MS pathology is the result of CNS infiltration by harmful, self-reactive immune cells.[34] After crossing the BBB, these immune cells promote a coordinated autoimmune attack on the structures of the CNS, particularly the myelin sheath. In heathy individuals, the myelin sheath surrounds the axonal body of neurons within the CNS, accelerating electrical impulses, and optimizing neurotransmission.[39] In MS, the myelin sheath is often the primary target of immune-mediated attacks, resulting in axonal demyelination.[28] During these attacks, macrophages mistakenly identify proteins derived from the myelin sheath as a potential threat. These macrophages then target and destroy large portions of the myelin sheath, causing considerable structural damage.[32] Habitual autoimmune attacks result in substantial and irreversible damage to the myelin sheath and other CNS structures. Over time, this damage accumulates and ultimately results in brain volume loss, contributing to the neurodegenerative pathology of MS.[40]

### 1.4 – Classification of Multiple Sclerosis

While MS is an unpredictable disease, trends have emerged in clinical presentations that have resulted in the classification of clinical disease courses. Prior to a definite diagnosis of MS, most individuals experience an initial clinical episode characterized by the emergence of new symptoms suggestive of an inflammatory, demyelinating CNS disease.[41] This initial clinical episode is known as clinically isolated syndrome (CIS). Although individuals often recover from this episode, CIS is often recognized as the initial manifestation of MS as upwards of 85% of CIS cases result in a

diagnosis of MS.[41] The clinical presentation of the disease is typically classified as three types: relapsing-remitting MS (RRMS), secondary-progressive MS (SPMS), and primary-progressive MS (PPMS).[42] The most prevalent presentation of MS is RRMS and accounts for approximately 85% of diagnoses at onset. RRMS is characterized by episodic inflammatory attacks (i.e., relapses) and periods between relapses (i.e., remissions).[43] During a relapse, individuals often experience an exacerbation of ongoing symptoms as well as novel neurologic symptoms which persists for over 24 hours.[1,43] Unfortunately, a relapse can cause permanent damage to the neurological structures, resulting in increased neurological disability. As a result, MS relapses often cause substantial physical, emotional, and economic burden for people living with MS, and for those who support them.[44]

As MS pathology advances, the disease course may change and individuals with a RRMS onset typically transition to a SPMS course within 10 to 15 years of diagnosis.[45,46] Individuals with SPMS rarely experience relapses, and clinical disability accumulates over time, resulting in long-term neurodegeneration. This neurodegeneration often causes increased functional impairments, more severe disability, and worsening symptology.[42,47] Lastly, PPMS involves a similar clinical course as SPMS, except individuals who have PPMS experience continuous disease progression and symptom accumulation from disease-onset.[42] Damage and lesions are also more common within the spinal cord in PPMS compared to RRMS.[42]

Pharmacological management of MS primarily involves the use of immunomodulatory and anti-inflammatory disease-modifying therapies. These therapies have been effective for reducing the frequency and severity of relapses, but have limited efficacy in halting the disease and preventing disability accumulation long-term.[2] Unfortunately, there are considerably fewer treatment options for those with progressive disease courses, compared to those with relapsing

MS, given the underlying differences in disease pathology and therapeutic targets (i.e., inflammatory vs. neurodegenerative).[48,49]

### 1.5– Impact of Multiple Sclerosis

The International Classification of Functioning, Disability and Health (ICF) model provides a framework and language which can be used to describe health and disability in a standardized manner.[50] In the context of the ICF, the impact of disability can be described within 'body structures' (i.e., anatomical parts of the body and components), 'body functions' (i.e., physiological functions of body systems), 'activities' (i.e., execution of tasks or actions) or 'participation' (i.e., involvement in life situations) categories. The ICF has been applied to describe function and disability in people with MS and comprehensive and core set of ICF items relevant to persons with MS have been identified.[51–54]

As inflammatory attacks persist within the CNS, damage to 'body structures' begins to accumulate, and over time, becomes seemingly irreversible.[55] Magnetic resonance imaging (MRI) has determined extensive lesion presentation in the brains of people with MS, with both white and grey matter regions affected.[56] Extensive brain atrophy has also been reported in people with MS, with estimates of brain volume loss of approximately 1.4% per year, a rate far greater than that associated with normal aging.[40,57] Damage to CNS structures is not limited to the brain, as extensive spinal cord damage has also been reported.[58] Axonal density within the spinal cord has been reported to be reduced by approximately 65% in people with MS compared to age-matched controls, with annual reductions in spinal cord area of approximately 1.5% per year.[59,60] Lastly, evidence suggests that the pathology of MS contributes to diminished retinal nerve integrity, as longitudinal data involving people with MS have demonstrated significant retinal structural loss compared to healthy controls.[61]

Damage to these 'body structures' often manifests as unpredictable physical and neuropsychological symptoms experienced by people with MS, reflected as impairments in 'body functions' within the ICF.[51,62] Impaired vision, reduced cardiorespiratory and muscular fitness, spasticity, balance dysfunction, and sexual dysfunction are all common impairments experienced by people with MS.[42,63–65] Further, increased fatigue, pain, numbness, symptoms of depression and anxiety, and cognitive impairment are often experienced by people with MS and are thought to negatively impact quality of life (QoL).[66]

From a patient perspective, some of the most life-altering consequence of MS are reported at the 'activities' level.[67] It is estimated that approximately 75% of people living with MS experience clinically significant walking impairment, with many individuals (74%) reporting disrupted activities of daily living due to walking impairment.[67,68] Additionally, people with MS who experience walking impairment report reduced rates of employment, diminished capacity for self-care, reduced social interaction, increased isolation, limited access to healthcare, and increased financial burden.[67–69] As a result, many individuals with MS identify walking impairment as the most challenging aspect of living with MS.[67]

Lastly, people with MS have reported substantial limitations in 'participation' following diagnosis.[53] One study involving 105 people with MS reported that approximately 77% of the sample had significantly restricted societal participation compared to age- and sex-matched controls.[70] People with MS have also reported substantially reduced QoL (both physical and mental), further highlighting participation limitations in this population.[71,72]

### 1.6 – Disability Status in Multiple Sclerosis

Given the heterogeneity in impairments and limitations experience by people with MS, a 10-point, MS-specific scale (Expanded Disability Status Scale [EDSS])[73] is used to quantify the overall level

of neurological impairment experienced by an individual. This tool is commonly used for characterizing disability status in clinical and research settings. The EDSS quantifies disability in seven functional systems as well as ambulation and produces an aggregate rating to describe overall disability level. The seven functional systems include: visual (1), brainstem (2), pyramidal (3), cerebellar (4), sensory (5), bowel/bladder (6), cerebral (7), and ambulation function. The overall EDSS score is rated on a ordinal scale ranging between 0 (*normal neurological function*) and 10.0 (*death due to MS*).[73] Individuals with MS with an EDSS score between 1.0 and 3.5 are considered fully ambulatory, with minimal disease burden. Those with an EDSS score between 4.0 and 6.5 often experience ambulatory impairments and moderate-severe symptoms. Lastly, individuals with an EDSS rating of 7.0 and higher are essentially restricted to a wheelchair (i.e., nonambulatory).[73]

### 1.7 – Nonambulatory Individuals with Multiple Sclerosis

Due to the neurodegenerative pathology of MS, disability accumulates over the course of the disease, resulting in varying degrees of symptomatic burden and mobility loss.[74] Within ~8.5 years of initial diagnosis, individuals with MS typically reach a disability benchmark associated with substantial symptomatic burden (EDSS = 4.0) such as fatigue, visual loss, numbness and/or tingling, bladder/bowel dysfunction, and/or cognitive impairment, and restricted ambulation.[1,2] Within 20 years of diagnosis, people with MS experience greater symptomatic burden and loss of mobility often requiring the use of assistive devices (EDSS = 6.0).[1] It also during this 20 year period that many individuals with relapsing RRMS transition to a SPMS course.[1,2] Within 30 years of diagnosis, many individuals with MS require the use of a wheelchair or scooter for mobility (EDSS $\geq$ 7.0).[1,2] While these trajectories for disease progression are informative, it is important acknowledge these data are dated (2003) and may have changed with the development of newer

diagnostics techniques and therapies.[75] A more recent longitudinal investigation of 155 people with MS reported more pronounced disability accumulation in individuals with moderate/severe MS (EDSS = 4.0-9.5) compared to those with mild MS (EDSS = 0-3.5) across a 10-year time period, suggesting that disability accumulation accelerates over the disease course.[7]

It is estimated that approximately 30% of all people living with MS are nonambulatory.[6] Relative to those with less disability, nonambulatory people with MS experience substantial physical impairments which contribute to significant mobility loss, a high frequency of falls, and subsequent fall-related injuries.[7,76,77] Furthermore, a relationship between disability and comorbid health conditions has been reported, as comorbidity prevalence is thought to influences\ disability at diagnosis and causes a more rapid disability trajectory.[78,79] This substantial increase in disease burden often results in diminished functional independence and increased reliance on support-partners to carry-out activities of daily living which can result in negative health and socioeconomic impacts for both the individual with MS and support-partners.[71] These factors severely limit societal participation for nonambulatory people with MS and negatively impact QoL.[80,81] Given the substantial disease burden and the limited efficacy and options of disease-modifying therapies for this population,[7] nonambulatory people with MS arguably have the greatest need for alternative strategies for disease management, such as exercise training.[82]

### 1.8 – Physical Activity, Exercise, and Fitness Terminology

While the terms “physical activity” and “exercise” are often used interchangeably, there is an important distinction between the two. Physical activity has been defined as “any bodily movement produced by skeletal muscles that results in energy expenditure, and increases heart rate and breathing”.[83] Importantly, physical activity does not need to be deliberate and can include activities of daily living such as household chores. Conversely, exercise has been defined as a subtype of

physical activity that is "planned, structured, repetitive and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective".[83]

Another important term that must be defined is "physical fitness", which is defined as a set of attributes or characteristics that a person has that describes their ability to perform physical activity and complete daily activities without substantial fatigue.[83] Health-related physical fitness is comprised of three main components: cardiorespiratory fitness (CRF), muscular fitness, and body composition.[84] CRF refers to the delivery, extraction, and use of oxygen during prolonged activity requiring aerobic metabolism.[84] Muscular fitness is described as the ability to generate and maintain muscular force via muscle contractions.[84] Lastly, body composition refers to the relative proportion of body tissues including fat, fat-free (muscle), and bone.[84]

### 1.9 – Physical Activity, Fitness and Disability Progression in People with Multiple Sclerosis

Objective data has demonstrated that people with MS engage in less physical activity compared to the general population and other neurologically-impaired populations.[85,86] Levels of physical activity further decline with disability accumulation, as people with MS who have the highest disability are typically the least active.[85] Low levels of physical activity have been associated with increased neurological impairment, risk of comorbidity, diminished functional capacity, and reduced QoL among individuals with MS.[87–89] Reduced levels of physical activity further contribute to physiological deconditioning in people with MS. Previous investigations have reported that people with MS demonstrate significantly lower CRF and muscular fitness compared to healthy controls.[90–92] Unfortunately, these relatively low levels of physiological fitness further decline as disability accumulates.[93]

Importantly, physiological fitness (particularly CRF) has been associated with neurological impairment, brain structure and integrity, mobility, cognitive function, body composition, MS

symptoms, quality of life, and participation in daily activities.[88,94–97] Unfortunately, as disability accumulates, individuals with MS tend to engage in less physical active and experience physiological deconditioning. This results in a problematic 'spiral', as physical activity engagement becomes more difficult with increasing disability, resulting in further physiological deconditioning and disability accumulation.[88] It has also been reported that people with MS with severe disability consume approximately three times more oxygen when performing daily movement tasks compared to controls, suggesting increased energetic costs of bodily movements.[98] Collectively, these data demonstrate the loss of physiological fitness and hindered engagement in daily activities in people with MS as the disease progresses and disability accumulates. This highlights the necessity for interventions that increase activity levels and improve physiological fitness to maintain meaningful engagement in daily life for people with MS.

The decision to engage in exercise within the MS population is complex, with the complexity of this decision being compounded by the unpredictable and ongoing disease pathology.[99] As a result, efforts have been made to explore factors which influence the decision to engage in exercise for people with MS.[99–101] Previous investigations exploring benefits and barriers of exercise engagement have identified improved health outcomes and feelings of accomplishment as perceived benefits of exercise among people with MS.[100–102] Furthermore, previous studies have acknowledged symptoms of fatigue, physical exertion, physical impairment, lack of support and advise, and environmental limitations as prominent barriers to exercise engagement among people with MS.[100–102] While informative, these previous investigations have primarily included individuals with mild-to-moderate disability, limiting our understanding of the unique benefits and barriers of exercise engagement for nonambulatory people with MS. A recent qualitative study involving people with MS who use wheelchairs for mobility reported high interest in exercise engagement, but cited difficulties engaging in and maintaining exercise engagement due to the

limited availability of informative exercise resources.[103] While few previous studies have explored factors that influence exercise engagement in nonambulatory people with MS,[11,104] there have been no comprehensive evaluations of perceived exercise benefits and barriers in this population. Such an evaluation would provide valuable insight into the complexity of exercise engagement for nonambulatory people with MS and would help inform the development of strategies aimed at promoting exercise engagement in this population.

### 1.10 – Exercise Training for People with Multiple Sclerosis

Despite early concerns regarding the safety of exercise for individuals with MS, exercise training has emerged as an efficacious strategy for managing MS disability.[105] Historically, exercise was thought to be detrimental for people with MS with concerns regarding possible symptom exacerbation with exercise.[105] Fortunately, research conducted in recent decades has determined that exercise training is safe and well-tolerated by people with MS.[106] A systematic review of 26 RCTs reported that exercise training was not associated with an increased risk of relapse among those with RRMS, and the frequency of adverse events with exercise training in people MS was comparable to that reported in healthy populations.[106] Numerous systematic reviews and meta-analyses have now summarized the benefits of exercise training for people with MS. These benefits span the ICF, as improvements in 'body functions', 'activities', and 'participation' outcomes have been observed in people with MS after exercise training.[107]

Perhaps the most consistent benefit reported of exercise training for people with MS is improvements in cardiorespiratory and muscular fitness. One meta-analysis of 20 randomized controlled trials (RCTs) concluded that exercise training promoted moderate (Hedge's $g$ = 0.47) improvements in CRF and small improvements in muscular fitness (Hedge's $g$ = 0.27) in people with MS.[108]

Importantly, improvements in symptomatic outcomes in response to exercise training have also been reported. To date, there have been three reviews exploring the effects of exercise training on fatigue in people with MS.[109–111] The first of these reviews concluded that exercise therapy had the potential to induce a positive changes in fatigue for people with MS, but noted limitations in retrieved studies hindered definitive conclusions.[109] One meta-analysis involving 17 RCTs and reported that exercise training was associated with a small reduction in fatigue (Hedge's $g$ = 0.45).[110] Similarly, findings from a meta-analysis of 10 exercise trials reported exercise training was associated with a moderate reduction in fatigue in people with MS (Hedge's $g$ = 0.57).[111] Additionally, one meta-analysis reported reduced symptoms of depression in people with MS after exercise training interventions (ES = -0.37).[112] A separate meta-analysis reported reduced symptoms of anxiety in people with MS following exercise training (SMD = -0.16).[113]

To date, two meta-analyses have investigated the effects of exercise training on walking and mobility in those with MS. The first of these meta-analyses involved 22 studies and reported that exercise training (aerobic and resistance) was associated with a small improvement in walking (Hedge's $g$ = 0.19).[114] A more recent meta-analysis involved 13 RCTs and reported significant improvements in walking speed and endurance in people with MS after exercise (aerobic and resistance).[115] Additionally, one meta-analysis reported small, significant improvements in balance in people with MS after exercise training (SMD = 0.22).[116]

One meta-analysis conducted in 2008 reported that exercise training was associated with small, significant improvements in QoL among people with MS;[117] however, a more recent systematic review reported inconclusive findings,[118] leaving the effect of exercise training on QoL uncertain.[107] Further, while previous reviews have provided insight into the effects of exercise training on outcomes that capture some aspects of 'participation' (e.g., QoL), the effects of

exercise on measures that reflect other aspects of engagement in daily life have yet to be characterized.

### 1.11 – Physical Activity and Exercise Training Recommendations for People with Multiple Sclerosis

The abundance of literature demonstrating the benefits of exercise training has resulted in the development of evidence-based physical activity and exercise guidelines for persons living with MS.[10] The earliest iteration of these guidelines were published in 2013, and recommended 30 minutes of moderate intensity aerobic exercise 2x/week, in addition to resistance training 2x/week for persons with MS who have mild-to-moderate disability.[107] Since 2013, this literature base has evolved considerably, resulting in updated lifestyle physical activity and exercise recommendations.[10] The most recent guidelines provide disability-specific recommendations for lifestyle physical activity and exercise training, resulting in separate recommendations for those with mild (EDSS 0-4.5), moderate (EDSS 5-6.5), and severe (EDSS 7-9) disability levels.

It is recommended that people with MS of all ability levels engage in 150 minutes of lifestyle physical activity per week or 30 minutes of daily physical activity, 5 days a week.[10] Further, those with severe disability who cannot tolerate 150 minutes are recommended to engage in as much weekly physical activity as tolerable.

Current exercise guidelines for people with mild and moderate MS are primarily informed by published evidence and recommend aerobic exercise 2-3x/week for 10-30 minutes.[10] These exercise guidelines further recommend resistance training 2-3x/week, neuromotor exercise 3-6x/week, and daily flexibility training.[10] The current exercise guidelines for people with severe MS (EDSS 7-9) are primarily based on expert opinion, rather than published evidence.[10] These recommendations include aerobic exercise 3–7x/week for approximately 10-20 minutes, resistance

exercise (focused on extremities and core), breathing exercises every second day, and daily flexibility training.[10]

### 1.12 – Exercise Training in People with Multiple Sclerosis with Severe Disability

While the safety and efficacy of exercise training has been well-established in people with MS with mild-to-moderate disability,[119,120] there is limited evidence for the role of exercise in people with MS with higher disability levels. One systematic review conducted in 2012 investigated the benefits of rehabilitation interventions, including exercise training, for nonambulatory people with MS.[9] This review included five exercise interventions (three case studies and two RCTs) involving nonambulatory people with MS (EDSS ≥ 7.0). Findings from this review suggested potential benefits of aerobic and resistance exercise training on some aspects of fatigue, muscular fitness, and spasticity among nonambulatory people with MS. However, the authors acknowledged that definitive conclusions regarding the benefits of exercise training for nonambulatory people with MS could not be made due to insufficient quantity and quality of the evidence.[9] This systematic review highlighted the discrepancy between the evidence needed and evidence available regarding exercise training for nonambulatory people with MS.

Following this review, a systematic review of 18 controlled and uncontrolled exercise training interventions involving people with MS with mobility impairment (EDSS ≥ 6.0) was published in 2017.[119] While this review did not examine the role of exercise training for nonambulatory people with MS exclusively, this review reported improvements in physiological fitness, physical function, mobility, and symptomatic/participatory outcomes following exercise training.[119] Importantly, both reviews were limited by small sample sizes, lack of control conditions, variability in exercise prescriptions, and inconsistent disability grouping of participants (i.e., EDSS cut points), highlighting the low methodological quality of this work to date. Further,

these reviews highlighted the substantial gap in research pertaining to exercise training for people with MS with higher disability (EDSS ≥ 7.0) who rely on wheelchairs for mobility.[24]

Unfortunately, the literature involving exercise training in nonambulatory people with MS remains understudied, as few studies have been published since the 2017 review.[121–125] While these additional studies (Summarized in Table1) are relatively small in terms of sample size (n =9– 24), they provide further evidence for the safety, feasibility, and potential benefits of exercise training for nonambulatory people with MS. Collectively, these additional studies report slight reductions in symptoms of fatigue, pain, and depression, while also reporting slight improvements in functional capacity among nonambulatory people with MS.[121–125] However, several key evidence gaps remain and should be addressed using high-quality research designs. Fortunately, the importance of exercise training for nonambulatory individuals with MS is becoming increasingly acknowledged and there have been calls to action to address this research and practice gap.[9,10, 108]

### 1.13 – Current Literature Gaps

Several literature gaps must be addressed in order to inform exercise prescription, intervention development and evaluation, and ultimately promote exercise engagement for people with MS who are nonambulatory. An important first step in developing exercise recommendations for people with MS who are nonambulatory, is to establish the safety of exercise responses. Further, as the efficacy of exercise training for improving health outcomes is dependent upon a sufficient exercise stimulus, characterizing the acute exercise response in people with MS represents a critical step to inform exercise prescription.[84] No studies to date have examined the safety of exercise for nonambulatory people with MS or how these individual respond to an acute bout of exercise from a physiological perspective. Given the limited exercise modalities that can be applied with this population, a thorough examination of the safety, symptomatic, cardiorespiratory

response, and participant experience with accessible exercise modalities is essential for informing and optimizing exercise prescription for this population.

Next, an exploration into which outcome measures are most appropriate for this population will be imperative for evaluating the success of any future exercise intervention. Given the physical disability and limitations experienced by nonambulatory individuals with MS, determining the success of an exercise intervention for this population may be a surprisingly difficult task. Outcome measures describing 'participation' provide valuable insight into the impact of MS on everyday living and have been identified as highly important and relevant outcomes for people with MS.[51,53] Such 'participation' outcomes are particularly advantageous for nonambulatory people with MS as they can be used regardless of an individual's level of disability or impairment.[51,53,126] However, the influence of exercise training on 'participation' outcomes has not been fully examined in the MS population.

Lastly, a key literature gap is the lack of investigation of perceived exercise benefits, barriers, and needs of nonambulatory people with MS. An examination of exercise benefits and barriers in nonambulatory people with MS would provide important information that could help promote exercise initiation and maintenance within this population. Additionally, a comprehensive assessment of exercise needs among nonambulatory people with MS is another valuable strategy for promoting exercise engagement in this population. Such an evaluation would provide informative feedback from nonambulatory people with MS that can be used to design targeted and pragmatic exercise programs and interventions.[127] Further, such an evaluation would be valuable for informing the development of community exercise programming and resource allocation. To date, only one comprehensive needs assessment involving people with moderate-to-severe MS disability and their family caregivers has been conducted.[128] This study acknowledged that a "one-size-fits-all" approach to exercise prescription is not appropriate for those with MS with higher

disability and identified the need for flexible strategies to increase co-participation in exercise for people with MS-care and their care-partners. Notably, no such assessment has been conducted involving nonambulatory people with MS.

Collectively, exercise research involving nonambulatory people with MS is largely undeveloped relative to those with lower MS disability, and many questions remain unanswered. Specifically, understanding the safety and acute response to adapted exercise, the influence of exercise training on 'participation' outcomes, and directions for promoting exercise engagement (i.e., exercise benefits, barriers and needs) in nonambulatory people with MS are important literature gaps that warrant investigation. Addressing such gaps will provide direction to facilitate the development of evidence-informed exercise interventions, promote measurable health improvements, and ultimately increase engagement in exercise for nonambulatory people with MS.

### 1.14 – Purpose of the thesis dissertation

This dissertation research is presented across four primary manuscripts with the goal of addressing the aforementioned gaps in current MS and exercise literature. The purpose of the four manuscripts include to:

1) Evaluate the safety of adapted exercise for nonambulatory people with MS (Chapter 2);
2) Characterize and compare the acute cardiorespiratory response of nonambulatory people with MS to three adapted exercise modalities (Chapter 3);
3) Describe outcome measures used to capture participation in exercise training studies involving persons with MS, and to quantify the effect of exercise training on participation outcomes (Chapter 4); and

4) Identify and describe perceived exercise benefits, barriers, and needs among nonambulatory people with MS (Chapter 5).

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**Table 1**: Summary of exercise training studies involving nonambulatory people with MS following 2017

| **Study [Design]** | **Participant Characteristic** | **Intervention** | **Results** |
|---|---|---|---|
| Grubić Kezeleet al. 2019<br>[RCT] | Training: 5 (age: NR)<br>Control: 5 (age: NR)<br><br>Disease duration: NR<br><br>EDSS: 7.0 – 8.0<br>MS type: NR | Aerobic Exercise<br>3 x/ week for 4 weeks<br>≥ 20 min/session | ↓ Fatigue<br>↔ QoL |
| Barclay et al. 2019<br>[RCT] | Training: 6 male, 9 females (age: 55yrs)<br>Control: 3 males, 6 females (age: 53yrs)<br>Disease duration:<br>Training: 15yrs / Control: 17yrs<br><br>EDSS: 6.0 – 8.5<br>MS type:<br>Training: 13 PMS, 2 RRMS<br>Control: 8 PMS, 1 RRMS | Aerobic Exercise<br>5 x/week for 4 weeks<br>30 min/session | ↑ Average speed,<br>↑ Power output<br>↑ Distance cycled |
| Williams et al. 2020<br>[Pre-Post] | 6 males, 3 females (age: 59yrs)<br>Disease duration: 17yrs<br><br>EDSS: 6.5 – 8.5 (7.5 median)<br>MS type: 4 RRMS, 5 PMS | Aerobic Exercise<br>6-8 training sessions with minimum 1 day of rest between each session (4-8 weeks) | ↓ Spasticity<br>↔ Pain |
| Grubić Kezele et al. 2020<br>[RCT] | Training: 5 (age: NR)<br>Control: 5 (age: NR)<br><br>Disease duration: NR<br><br>EDSS: 7.0 – 8.0<br>MS type: NR | Aerobic Exercise<br>3 x/ week for 4 weeks<br>≥ 20 min/session | ↓ Pain<br>↑ Functional Independence |

| | | | |
|---|---|---|---|
| Backus et al. 2020<br>[RCT] | Training: 3 male, 3 females (age: 55yrs)<br>Control: 2 males, 4 females (age: 56yrs)<br><br>Disease duration: NR<br><br>EDSS: 7.2 (median)<br>MS type:<br>Training: 13 PMS, 2 RRMS<br>Control: 8 PMS, 1 RRMS | Aerobic Exercise<br>2-3x week for 12 weeks<br>30 minutes/session | ↓ Fatigue<br>↑ Functional Capacity<br>↓ Depression |

EDSS, Expanded disability status scale; MS, Multiple Sclerosis; NR; Not Reported; PPMS, primary progressive multiple sclerosis, QoL, Quality of life; RCT, Randomized controlled trial; RRMS: relapsing-remitting multiple sclerosis; SPMS, Secondary progressive multiple sclerosis.

# CHAPTER 2

## The Safety of Exercise for Nonambulatory People with Multiple Sclerosis

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**Acknowledgments**: This study was supported, in part, by finding from the National Multiple Sclerosis Society [PP 1904-33937], the Canadian Foundation for Innovation [CFI-37079], and the Ontario Research Fund [MRIS-37079].

***Note*:** Chapters 2 and 3 present data from the same study and participant sample.

**ABSTRACT**

**Background:** The safety and benefits of exercise training for people with multiple sclerosis (MS) who have mild-to-moderate disability have been established. However, the effects of exercise in people with multiple sclerosis (MS) who are nonambulatory (i.e., Expanded Disability Status Scale ≥ 7.0) are largely unknown. Current exercise guidelines for people with MS who are nonambulatory are primarily derived from expert opinion. A key limitation to developing evidence-based exercise recommendations is the lack of understanding and characterization of the acute response to exercise in this population.

**Objectives:** To characterize the safety, acute symptomatic response, and participant experience associated with aerobic exercise in nonambulatory people with MS.

**Methods:** Twelve nonambulatory people with progressive MS (mean age=62.6; median EDSS=7.5; mean disease duration=22.3 years) completed three submaximal exercise sessions using adapted aerobic exercise modalities including an arm-cycle ergometer (ACE), a recumbent stepper (RS), and a functional electrical stimulation (FES) cycle. Adverse events (AE), changes in neurological function, symptoms of pain and fatigue, cognitive performance, and skin temperature in response to exercise were recorded and described. The participant experience (affective response and satisfaction) with the different modalities was also characterized.

**Results:** Six AE were reported across the 36 exercise sessions (ACE=4; RS=2; FES=0), none of which were classified as 'severe'. There was a main effect of exercise modality on sensory function, acute pain and fatigue, and cognitive performance (all $p<0.05$). Overall, participants reported increased sensory impairment and elevated pain with ACE exercise compared to both RS and FES exercise (all $p<0.05$). There was an increase in self-reported fatigue and diminished objective cognitive performance with ACE compared to FES exercise overall (all $p<0.05$). There

was a main effect of time on sensory function and acute pain (both $p<0.05$), as participants experienced a temporary increase in sensory impairment and pain in immediately following to exercise. Participants reported better overall experiences with RS and FES exercise compared to ACE exercise ($p<0.05$). Lastly, there was a main effect of time on participant experience, as participants reported higher levels of positive experience 30 minutes following exercise compared to pre-exercise and immediate-post exercise levels (both $p<0.05$).

**Conclusions:** Both RS and FES may be safe exercise options for nonambulatory individuals with MS. The high frequency of AEs and elevated symptomatic burden associated with ACE exercise suggest it may not be well-tolerated by untrained individuals with MS who are nonambulatory. Further, this study demonstrated transient changes in sensory function and pain in response to acute exercise in nonambulatory people with MS; however, this response was alleviated within 24 hours. Lastly, participants reported overall positive experiences with both RS and FES exercise compared to ACE exercise.

**Keywords:** multiple sclerosis, disability, wheelchair, exercise, safety, pain, fatigue, cognition.

## INTRODUCTION

Multiple sclerosis (MS) is an immune-mediate disorder of the central nervous system that involves the progressive accumulation of neurological disability, often reflected as the loss of ambulation.[1,2] Approximately 30% of people living with MS are nonambulatory and rely primarily on wheelchairs for mobility.[3] In additional to mobility disability, people with MS who are non-ambulatory experience substantial disease burden, as reflected by increased cognitive impairment, fatigue, depression and anxiety, and reduced quality of life (QOL), compared to those who have less disability.[4–7] Given the current lack of efficacy of disease-modifying therapies in preventing the accumulation of disability in MS,[2] it is critical that we look to alternative approaches, such as exercise, for disease management at the upper end of the disability spectrum. Despite established benefits of exercise training for people with MS who have mild-to-moderate disability (i.e., Expanded Disability Status Scale (EDSS) scores=1.0-6.5),[8] the role of exercise for people with MS who experience greater mobility impairment is largely unknown.[3] Consequently, current exercise guidelines for nonambulatory people with MS (EDSS=7.0-9.0) are primarily based on expert opinion.[9]

There is a clear need for evidence-based exercise prescription for people with MS who are nonambulatory. One challenge to exercise prescription and delivery for this population is the need for exercise modalities that are adapted. There is growing evidence for the application and potential benefits of adapted exercise options (e.g., arm cycle ergometer, recumbent stepper, body-weight supported treadmill walking) for people with MS with mobility impairment (EDSS≥5.0).[10] One systematic review involving five exercise trials reported that aerobic and resistance exercise improved some aspects of fatigue, muscular fitness, and spasticity among nonambulatory people with MS (EDSS≥7.0). Importantly, the authors of this review acknowledged that the exercise

literature involving nonambulatory people with MS is underdeveloped and called for further research of appropriate exercise options for this population.[3] As such, an investigation of adapted exercise modalities would be a valuable first step to inform exercise recommendations for people with MS who are nonambulatory.

A key consideration in developing prescriptive recommendations is to establish the safety profile of exercise. Among nonambulatory people with MS, perceived risk of injury, increased symptomatic burden, and heat sensitivity have been cited as potential barriers to physical activity and exercise engagement.[11,12] Research to date has demonstrated the safety of exercise training for people with MS with mild-to-moderate disability. One review of 26 exercise trials reported that the frequency of adverse events (AE) associated with exercise training was not higher in people MS compared to the general population, and that people with MS did not experience an increased risk of relapse with exercise training (relative risk=0.73).[13] Another study involving 34 people with MS (mode EDSS=1.0) reported few, temporary symptomatic changes (e.g., slight increase in fatigue, sensory abnormalities) in response to acute exercise.[14] Further, one study with 14 people with MS (median EDSS=1.75) reported that cooling the environment limited heat sensitivity during exercise for people with MS.[15] Together, these findings support the safety of exercise for people with MS who have mild-to-moderate disability. However, no such investigations have been conducted in people with MS who are nonambulatory.

In addition to safety, understanding user experiences with different exercise modalities provides relevant information for optimizing and individualizing exercise prescriptions. Participant experience with exercise, specifically exercise enjoyment, has been identified as an important aspect of exercise prescription to consider in exercise adoption and maintenance.[16,17] A previous exercise trial involving healthy individuals reported that greater exercise enjoyment was

associated with increased exercise adherence and increased post-intervention exercise engagement.[16] A similar finding was reported in a small trial of exercise training involving patients recovering from stroke, reinforcing the importance of exercise enjoyment for adherence and maintenance long-term.[18] Therefore, a characterization of experiences with different exercise modalities in people with MS who are nonambulatory would provide insight to promote exercise adherence at the individual level, and direction for resource allocation in community exercise settings.[19]

As such, we conducted a cross-sectional characterization of the safety profile and participant experience associated with exercise in nonambulatory people with MS (EDSS 7.0-8.0). The objectives of this study were to: (1) characterize the safety and acute response associated with three adapted exercise modalities by describing adverse events, changes in neurological function, symptoms of pain and fatigue, cognitive performance, and skin temperature; and (2) describe participant experiences and level of satisfaction with the different modalities. Findings from this study will address fundamental knowledge gaps regarding the acute exercise response in nonambulatory people with MS that can be used to guide exercise prescription in research and practice settings.

## METHODS

### Participants

The criteria for inclusion were: (a) age 18-75; (b) self-reported diagnosis of MS; (b) EDSS 7.0-8.0 based on neurological examination;[1] (c) relapse-free in the past 30 days; (d) stable course of disease modifying therapy over past 6 months; and (e) asymptomatic (i.e., no signs or symptoms of acute or uncontrolled cardiovascular or metabolic diseases) based on the Get Active

Questionnaire (GAQ).[20] Criteria for exclusion were: (a) other neurological or musculoskeletal conditions; (b) contraindications to FES cycling; and (c) pregnancy.

**Baseline Outcome Measures**

*Anthropometrics, Demographic and Clinical Characteristics*

Participants' height and mass were measured in the laboratory to the nearest 0.1 cm and 0.1 kg, respectively. To measure height, participants were transferred to an examination table and laid in a supine position. A measuring tape was then used to measure the participants' height. Mass was measured using a platform scale (Sartorius AG, Göttingen, Germany) under supervision of the research team. Demographic and clinical characteristics were collected using a questionnaire.

*Neurological function*

Neurological function was assessed using the Expanded Disability Status Scale (EDSS) by a Neurostatus-certified assessor (TE; Level C) to characterize the disability level of the sample.[1] The EDSS assesses neurological function within seven functional systems as well as ambulation, with overall scores ranging between 0 (*normal neurological function*) and 10 (*death due to MS*).

*MS Symptoms and Impact Questionnaires*

Baseline symptomatic variables included fatigue, pain, anxiety and depression, and were captured using a questionnaire battery. Fatigue was assessed with the Fatigue Severity Scale (FSS)[21] and the Modified Fatigue Impact Scale (MFIS).[22] Pain was assessed using the short form McGill Pain Questionnaire (SF-MPQ).[23] The impact of MS on everyday life and was assessed with the 29-item

Multiple Sclerosis Impact Scale (MSIS-29).[24] The MSIS-29 consists of two subscales that describe the physical and psychological impact of MS.

*Cognitive Performance*

Baseline cognitive performance was assessed with the Symbol Digit Modalities Test (SDMT)[25] and the Stroop Color-Word Test (SCWT).[26] The SDMT is used to measure information processing speed and involves associating numbers with specific symbols. Participants were asked to provide as many correct numbers as possible within 90-seconds.[25] The SDMT was expressed as the total number of correct responses within 90-seconds. The SCWT is used to assess selective attention and executive cognitive control.[26] Participants were asked to identify specific visual stimulus while an incongruent visual stimulus was simultaneously present (e.g., the word "Green" displayed in a red coloured font).[26,27] While participant completed a Stroop Word-Test and Stroop Color Test, only the SCWT was scored and expressed as the total number of correct responses in 45-seconds.

**Submaximal Outcome Measures**

*Adverse Events*

Adverse events (AE) that occurred during and/or after submaximal exercise were characterized using the National Institutes of Health Terminology and Classification scheme.[28] AEs were characterized based on severity, expectedness and relatedness. The severity of AEs were graded from Grade 1 (*mild*) through Grade 5 (*death*).[28] Expectedness (*expected, unexpected*) was described as the predictability of an AE in relation to the exercise stimulus. If an AE was documented or occurred in a previous exercise trial, it was characterized as "expected".[29] Conversely, if an AE occurred that was unobserved or undocumented in previous exercise

literature involving those with MS, it was characterized as "unexpected".[29] Relatedness (*not related, possibly related, or study-related)* was characterized as the likelihood that an AE was caused by the exercise stimulus. The assessment of AE relatedness was based on factors such as plausibility, prior participant experiences with exercise, and temporal relationship between exercise and AE onset.[29] This approach for characterizing AE has been used in previous clinical trials, including those involving people with MS with mobility impairment.[30]

*Neurological Function*

Change in neurological function in response to exercise was assessed using an abridged version of the EDSS.[1] Four functional systems (visual, brainstem, cerebellar, and sensory) were assessed.[15] These four functional systems were selected as they have been previous examined in other investigations of acute exercise responses in people with MS.[14,15]

*Symptoms of Pain and Fatigue*

Change in acute pain was assessed using a modified version of the Brief Pain Inventory (BPI) consisting of three questions.[31] Items were scored on a 7-point scale, with scores ranging between 1 (*no pain*) and 7 (*severe pain*). Change in acute fatigue was assessed using the Daily Fatigue Impact Scale (DFIS), an eight-item scale used to capture momentary fatigue.[32] Participants were asked to rate how their fatigue affected them in the moment and items were scored on a 5-point scale with scores ranging between 0 (*no problem due to fatigue*) and 4 (*extreme problem due to fatigue*).

*Cognitive Performance*

Change in cognitive performance was assessed with the SDMT[25] and the SCWT.[26] The testing protocols were the same as at baseline. In order to minimize practice effects, different versions of the SDMT and SCWT were used at teach time point.

*Skin Temperature*

Skin temperature was measured with heat flux transducers (iButton Technologies) placed on 12 different sites on the right side of the participants' body: the forehead, chest, biceps, forearm, abdomen, lower and upper back, front and back of the calf, quadriceps, hamstrings, and finger.[33] Temperature was recorded every minute at each site and was expressed in degrees Celsius (°C). Overall skin temperature was expressed as the mean temperature of all 12 sites.

*Participant Experience*

Participant experience was characterized as the affective response to exercise and satisfaction with using the exercise modality. The affective response was captured using the single-item Feeling Scale and the 12-item Exercise-induced Feeling Inventory (EFI).[34] The single-item Feeling scale consists of an 11-point scale ranging between −5 (*feeling very bad*) and 5 (*feeling very good*). The EFI captures four distinct feeling states including revitalization, tranquility, positive engagement, and physical exhaustion.[35] Each item of the EFI was scored on a scale between 0 (*do not feel*) and 4 (*feel very strongly*). Participant satisfaction with using each exercise modality was measured with a 6-item scale that captures equipment enjoyment, confidence in equipment use, perceived fitness benefits of the equipment, and recommendations and expected use of the equipment in community exercise settings. Each item was scored between 1 (*reflects negative*

*experience/recommendation of the modality*) and 7 (*reflects positive experience/recommendation of the modality*).[36]

**Exercise Modalities**

The submaximal exercise bouts were performed on an arm-cycle ergometer (ACE), a recumbent stepper (RS), and a functional electrical stimulation (FES) cycle. Participants used the arm-cycle ergometer (ACE; SCIFIT Systems Inc; Tulsa, OK) by propelling their arms around a central axis from a seated position.[37] Participants exercised on the recumbent stepper (RS; SCIFIT Systems Inc; Tulsa, OK), using both their upper and lower extremities moving their limbs in a bilateral, reciprocal motion.[38] Lastly, participants used an FES cycle ergometer (FES; Restorative Therapies Inc; Baltimore, MD) and were asked to voluntarily cycle with their lower limbs to the best of their ability.[30] Participants received mild superficial stimulation during voluntary leg cycling via self-adhering surface electrodes placed over muscle groups of the lower extremities (quadriceps, hamstrings, and calves). The intensity of leg muscle stimulation was adjusted per muscle group according to each participants' sensory tolerance.

**Procedures**

The study protocol was approved by the Health Sciences and Science Research Ethics Board at the University of Ottawa [REB H03-19-3436]. A visual representation of the protocol timeline is presented in Figure 1. Eligible participants completed one baseline testing session (Session 1) and three subsequent submaximal exercise sessions (Sessions 2-4). All exercise bouts were performed in a temperature-controlled room set to 18 degrees Celsius (°C). Participants arrived at the laboratory for Session 1 and completed the informed consent process. Participants then underwent

assessment of anthropometric outcomes, neurological function, and completed the questionnaire battery.

Following baseline assessment, participants completed Sessions 2-4 on the three exercise modalities in a counterbalanced order. Sessions 2-4 were each separated by 7 days and occurred at approximately the same time of day. Participants were asked to maintain a consistent medication schedule and refrain from exercise, caffeine and alcohol 24-hours prior to testing. Upon arrival, participants were fitted with 12 heat flux transducers, placed on the right side of the participants' body for continuous skin temperature measurement.

Before submaximal exercise (PRE EXE), participants underwent an initial assessment of neurological function, pain, fatigue, cognition, and affect. Participants then completed 15-minutes of submaximal exercise at an intensity of 12-13 on the Borg Rating of Perceive Exertion (RPE) scale.[39] AEs were continuously monitored by a member of the research team both during and after each submaximal exercise bout. Neurological function, pain, fatigue, cognition, and affect were measured immediately after exercise (IMD POST). These same outcomes were measured again 30-minutes post-exercise (30-min POST). Participants' experience with the exercise equipment was measured once at the IMD POST time point. Lastly, a follow-up phone call was conducted 24 hours after exercise to measure pain, fatigue, and affect, and to capture any adverse events that occurred within 24-hrs post-exercise (24-hr POST).

**Data Analysis**

Data analysis was performed using IBM SPSS Statistics (Version 27.0, IBM Corp., Armonk, NY). Descriptive statistics were used to characterize the sample at baseline. AEs experienced during/after submaximal exercise and within 24-hours of exercise were summarized using

descriptive statistics and were compared between modalities with Chi-squared tests. Differences in the acute response (neurological function, pain, fatigue, cognitive performance, skin temperature and affect) across the exercise modalities were tested using a mixed model analysis of variance (ANOVA) with exercise modality (3 levels: ACE, RS and FES) and time as within-subjects factors (3-4 levels: PRE EXE, IMD POST, 30-min POST and 24-hour POST). Differences in participant experience across modalities were compared with a one-way ANOVA. Significant effects were decomposed using Bonferroni *post-hoc* comparisons. Statistical significance was set at $p<0.05$. Values are reported within the text as mean (SD), unless specified otherwise.

## RESULTS

### Participants

Fourteen participants were recruited, 12 of which completed all testing sessions. Baseline demographics, clinical characteristics, symptomatic and cognitive variables are summarized in Table 1. The mean age of the sample was 62.6 (9.5) years, and the mean disease duration was 22.3 (6.3) years. The median (IQR) EDSS of the sample was 7.5 (0.6). All participants had either primary or secondary progressive MS.

### Acute Response

*Adverse Events*

Overall, six AE were reported during and immediately after the 36 submaximal exercise sessions (ACE=4; RS=2; FES=0). Participants reported significantly more AEs during and after ACE exercise compared to RS exercise ($p=0.02$) and FES exercise ($p<0.01$). Additionally, participants reported significantly more AEs during and after RS exercise compared to FES exercise ($p=0.02$)

Four participants reported upper-limb discomfort during ACE exercise. One of these AEs was classified as Grade 1, expected, and study-related. The remaining three AEs were classified as Grade 2, expected, and study-related. These Grade 2 AEs resulted in premature exercise cessation. Two participants reported lower-limb discomfort during RS exercise (Grade 1, expected, and study-related).

Ten AEs were reported at 24-hours POST (ACE=6; RS=2; FES=2). Participants reported significantly more AEs 24 hours after ACE exercise compared to RS exercise ($p$=0.02) and FES exercise ($p$=0.02). One participant reported increased fatigue (Grade 1, expected and possibly related), two participants reported mild upper-limb discomfort (Grade 1, expected, and study-related AEs), and three participants reported moderate upper-limb discomfort (Grade 2, expected, and study-related AEs), 24-hours after ACE exercise. One participant reported mild upper-limb discomfort (Grade 1, expected, and study-related AE) and one participant reported moderate lower-limb discomfort (Grade 2, expected, and study-related) 24-hours after RS exercise. Two participants reported skin irritation 24-hours after FES exercise (Grade 1, expected, and study-related).

*Neurological Function*

Changes in acute neurological function in response to submaximal exercise are presented in Figure 3 and Supplementary Tables A and B. There was a significant modality by time interaction on sensory function ($p$<0.01). There was a significant main effect of exercise modality on sensory function, such that individuals experienced less sensory impairment with RS and FES exercise compared to ACE (both $p$>0.01). There was also a significant main effect of time on sensory function, as participants reported increased sensory impairment IMD-POST compared to PRE-

EXE ($p$=0.04) and compared to 30-min POST ($p$=0.01). There were no modality effects, time effects, or modality by time interactions on any other functional system score (i.e., visual, brainstem, and cerebellar) (all $p$>0.05).

*Symptoms of Pain and Fatigue*

Acute pain and fatigue changes in response to submaximal exercise are presented in Figure 3 and Supplementary Tables A and B. There was a significant modality by time interaction on pain ($p$<0.01). There was a significant main effect of exercise modality on acute pain, as participants reported less with pain in response to RS and FES exercise compared to ACE exercise (both $p$=0.05; >0.01, respectively). There was a significant main effect of time on acute pain, as participants reported an increase in acute pain IMD-POST compared to PRE-EXE ($p$=0.04).

There were no modality by time interactions on acute fatigue ($p$=0.08). There was a significant main effect of exercise modality on acute fatigue, as participants reported less fatigue with FES exercise compared to ACE exercise ($p$=0.03). There was no effect of time on acute fatigue symptoms ($p$=0.08).

*Cognitive Performance*

Changes in cognitive performance in response to submaximal exercise are presented in Figure 3 and Supplementary Tables A and B. There was no modality by time interactions on SDMT ($p$=0.48) performance. There was a significant main effect of exercise modality ($p$=0.04) on SDMT performance, such that participants performed worse on the SDMT in response to ACE exercise compared to FES exercise ($p$=0.046). There were no significant main effects of time on SDMT performance ($p$=0.23). There was no modality by time interactions on SCWT performance

($p$=0.69), and there were no significant main effects of modality ($p$=0.53) or time ($p$=0.09) on SCWT performance.

*Skin Temperature*

A graphical representation of the change in skin temperature in response to submaximal exercise for each modality is presented in Figure 4. Overall, skin temperature increased from 31.6 °C PRE-EXE to 31.9 °C IMD-POST, before lowering to 31.7 °C 30-min POST. There were no modality by time interactions ($F_{(1,11)} = 1.5$, $p = 0.22$, $\eta p^2 = 0.13$), or main effects for exercise modality ($F_{(1,11)} = 1.4$, $p = 0.26$, $\eta p^2 = 0.06$) or time ($F_{(1,11)} = 0.8$, $p = 0.47$, $\eta p^2 = 0.07$) on skin temperature.

**Participant Experience**

*Affective Response*

Changes in the affective response to submaximal exercise presented in Figure 5 and Supplementary Tables A and B. There was a significant modality by time interaction on FS scores ($p<0.01$). There was a significant main effect of exercise modality on FS scores, as participants reported higher FS scores in response to RS and FES exercise compared to ACE exercise ($p$=0.02; 0.05, respectively). There was a significant main effect of time on FS scores, as participants reported higher FS scores 30-min POST compared to PRE EXE ($p$=0.02) and IMD POST ($p<0.01$). Additionally, FS scores were greater 24-hr POST compared to IMD POST ($p$=0.03).

There were no modality by time interactions on any domains of the EFI (all $p>0.05$). There was a significant main effect of time on Revitalization, as participants felt greater revitalization 30-min POST and 24-hr POST compared to IMD POST ($p$=0.02; <0.01, respectively). There was a significant main effect of exercise modality on Tranquility, as participants felt more tranquil in

response to RS and FES exercise compared to ACE (both $p<0.01$). There was a significant main effect of time on Positive Engagement, as participants reported greater positive engagement IMD POST, 30-min POST and 24-hr POST compared to PRE EXE ($p=0.04$; <0.01; 0.02, respectively).

*Participant Experience*

A summary of the participants' experiences with each exercise modality is reported in Table 2. There was a significant difference in mean rating of the exercise experience between modalities ($F_{(1,11)} = 10.73$, $p < 0.01$, $\eta p^2 = 0.39$), such that participant reported a more positive experience with RS and FES exercise compared to ACE exercise (both $p < 0.01$).

## DISCUSSION

This is the first study to characterize the safety profile and acute response to aerobic exercise in nonambulatory people with MS. Overall, observed AEs and negative symptomatic responses were less frequent with RS or FES exercise compared to ACE exercise. Participants reported more positive affective responses and experiences with using both RS and FES equipment compared with ACE equipment. Collectively, our results suggest that RS and FES exercise are better tolerated by nonambulatory people with MS. There was also a temporary increase in sensory impairments and symptoms of pain after exercise. Further, participants generally reported a positive experience with the submaximal aerobic exercise sessions, as affect and feeling improved after exercise. Results from this study can be used to inform expected responses to exercise in nonambulatory people with MS and the design of future exercise training interventions for this population.

The increased prevalence of AEs, specifically upper-limb discomfort, observed during and after ACE exercise may be the result of greater fatigability of the upper limb musculature required for ACE exercise. It has been reported that muscles exercising in a state of exhaustion are more prone to damage and acute injury.[40] As the muscles of the upper-limbs are much smaller and weaker compared to those of the lower-limbs, it is plausible that overexertion of the upper-limb musculature during ACE exercise may have resulted in more frequent AEs. Similar types of AEs were reported in an exercise intervention involving 23 untrained people with spinal cord injury (SCI), as temporary increases in shoulder pain were common following ACE exercise.[41] That study noted that poor technique and low fitness levels likely contributed to the observed AEs and reported that the frequency of AEs decreased as the intervention progressed. Similar factors likely explain the increased frequency of AEs with ACE exercise in the current nonambulatory MS sample.

In addition to AEs, concerns surrounding increased symptomatic responses to exercise has been cited as a safety concern among both ambulatory and nonambulatory people with MS.[12,42] Findings from the current study demonstrate that symptomatic responses associated with RS and FES exercise were minimal, with overall time effects noted only for sensory function and acute pain. A similar finding was reported in a study involving 34 people with MS with minimal disability (mode EDSS=1.0), which reported slight increases in sensory impairment and fatigue symptoms after combined aerobic and resistance exercise that were alleviated within 24-hours.[14] These findings suggest that RS and FES exercise are well-tolerated by nonambulatory individuals with MS, and temporary changes in sensation and increases in acute pain may be expected in response to adapted aerobic exercise in this population.

Conversely, there were greater increases in sensory impairment as well as symptoms of pain and fatigue in response to ACE exercise compared to the other two modalities, and this is consistent with the increased frequency and type of AEs reported in response to this type of exercise. Further, ACE exercise was the only modality associated with a decrease in cognitive performance, as SDMT scores decreased immediately after ACE exercise and remained lower 30-min POST exercise. Due to the relatively low cost and high accessibility, ACE is one of the more common forms of adapted exercise available in clinical and community settings.[19] Given the AEs, symptomatic and cognitive response observed in the current sample, experiences associated with this modality might deter exercise engagement within this population. Further, as adapted exercise options are often limited in these settings due to resource contraints,[43] nonambulatory people with MS may have few options for engaging in aerobic exercise, further discouraging exercise participation. Findings from the current study demonstrate that RS and FES are viable modality options for nonambulatory people with MS. These results can be used to inform the design, development, and implementation of exercise programs which are better tolerated by nonambulatory people with MS, and will be valuable for directing resource allocation, and potentially, promoting long-term exercise engagement in community settings.

There were no significant effects of submaximal exercise on skin temperature in the current sample. Importantly, the exercise sessions in the current study were performed in a temperature-controlled environment to alleviate heat sensitivity. A previous investigation involving 14 people with MS with varying degrees of disability reported temperature-controlled environments were associated with reduced fatigue during exercise, relative to non-temperature-controlled environments.[15] Future exercise programs involving nonambulatory people with MS should consider similar methods of temperature control in order to avoid heat sensitivity and improve

exercise tolerance for this population. These findings further address potential concerns regarding temperature sensitivity in response to exercise in this population.

In addition to the safety profile, participant experience and level of satisfaction with exercise are important to consider when developing exercise recommendations.[16] In the current study, participants generally had positive affect and high satisfaction with both RS and FES equipment in comparison with ACE, mirroring the more positive safety profile associated with these exercise modalities. Notably, while participants reported positive affect and enjoyment with FES exercise, many expressed low confidence in their ability to use the FES cycle in an unsupervised setting. This concern was not conveyed with RS exercise, suggesting that RS exercise may be more feasible in settings where supervision and direct assistance may not be readily available (e.g., community exercise facility).

Given the frequency of AEs and the symptomatic response observed during/after ACE, it is unsurprising that participants reported less positive affect and satisfaction with ACE. Interestingly, the opposite response was observed in an acute exercise study involving 36 adults with SCI, as no differences in equipment enjoyment or preference were reported comparing ACE, RS, arm glider, and arm–leg cycle ergometer.[19] This discrepancy suggests that nonambulatory individuals with MS may have different exercise needs compared to other neurologically-impaired populations who are nonambulatory and that must be considered when designing exercise programs and promoting exercise engagement. As positive affective and exercise equipment enjoyment have been associated with exercise adherence,[19] exercise programs that are well enjoyed by nonambulatory people with MS are vital for long-term exercise participation. When examining the effects of exercise on affect over time, participants reported overall positive experience in response to acute exercise, despite increased sensory impairment and symptoms of

pain. These findings suggest that nonambulatory people with MS enjoyed engaging in aerobic exercise and further reinforces the feasibility of adapted exercise in this population.

**Limitations**

There are several limitations of this study that must be considered. First, the sample size of the study was small, which may limit the applicability of the findings to a larger population. While the sample size was relatively small, it is important to note that this is the first investigation of acute exercise responses in this population. Additionally, the use of RPE to standardize exercise intensity is also a limitation given the inherit subjectivity associated with using the RPE scale. While the RPE scale is not without flaws, it has been used in similar investigations of exercise modalities involving other neurologically impaired populations.[19,37] This investigation also only evaluated three adapted exercise modalities. Future investigation would be prudent to explore the safety and feasibility of other adapted exercise modalities for nonambulatory people with MS. Lastly, given the physiological deconditioning of the current sample, it is reasonable to suspect that many of the AEs experienced were due to an unfamiliar exercise stimuli. Future investigation examining AEs over a longer time-period are needed to better characterize the safety associated with exercise training for nonambulatory people with MS.

**Conclusion**

The high frequency of AEs, elevated symptomatic burden, and negative experiences associated with ACE exercise suggest that this modality may not be well-suited for untrained individuals with MS who are nonambulatory. Fortunately, RS and FES exercise were well-tolerated by nonambulatory individuals with MS and represent viable exercise modality options for this

population. Further, this study demonstrated that nonambulatory people with MS can expect transient changes in sensory function and pain, but these experiences were alleviated within 24 hours. Participants also reported overall positive experiences with both RS and FES exercise compared to ACE exercise. Both RS and FES represent safe and viable exercise options for nonambulatory individuals with MS. The findings from this study can be used by clinicians and researchers to inform safe and enjoyable exercise prescription for nonambulatory people with MS. Further, these results provide nonambulatory people with MS, fitness professionals and facilities with information for selecting exercise options and equipment in community settings.

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**Table 1:** Baseline demographic, clinical and symptomatic variables for the sample (n=12). Values are reported as mean (SD), unless specified otherwise.

| **Demographic and Clinical Characteristics** | |
|---|---|
| Age (years) | 62.6 (9.5) |
| Height (cm) | 164.1 (6.4) |
| Mass (kg) | 69.9 (17.2) |
| BMI (kg/m$^2$) | 25.6 (6.6) |
| Sex* | |
| Male | 1 (8.3) |
| Female | 11 (91.7) |
| EDSS# | 7.5 (0.6) |
| Disease duration (years) | 22.3 (6.3) |
| MS Type* | |
| PPMS | 5 (41.7) |
| SPMS | 7 (58.3) |
| **MS Symptoms and Impact** | |
| MFIS | 31.3 (20.0) |
| FSS | 4.3 (1.8) |
| SF-MPQ | 7.8 (6.1) |
| MSIS-29 | |
| Physical | 49.0 (18.6) |
| Psychological | 15.8 (5.5) |
| SDMT | 45.9 (10.8) |
| SCWT | 30.6 (7.8) |

EDSS, Expanded Disability Status Scale; PPMS, Primary Progressive MS; SPMS, secondary progressive MS; MFIS, Modified Fatigue Impact Scale; FSS, Fatigue Severity Scale; HADS, Hospital Anxiety and Depression Scale; MSIS-29, 29-item Multiple Sclerosis Impact Scale; SDMT, Symbol digit modalities test; SCWT, Stroop Color-Word Test.

*Indicates values presented as *n* (%).
#Indicates values presented as median (interquartile range)

**Table 2**: Participant experience and satisfaction with each adapted exercise modality. Experience and satisfaction were scored with a 7-point Likert Scale, with a score of 1 reflecting a negative experience with the modality) and a score of 7 reflecting a positive experience with the modality. Values are reported as mean (SD).

| **Item** | **Modality** | | |
|---|---|---|---|
| | **ACE** | **RS** | **FES** |
| 1. How much did you enjoy using this exercise modality? | 4.1 (1.3) | 6.0 (1.0) | 6.6 (0.8) |
| 2. How confident are you that you can use this exercise modality without assistance | 4.8 (1.2) | 4.9 (2.4) | 3.2 (2.0) |
| 3. How confident are you that you can use this exercise modality safely without causing injury | 5.0 (1.7) | 6.0 (1.2) | 6.4 (0.8) |
| 4. How useful would this piece of equipment be for improving your fitness? | 5.3 (2.1) | 6.1 (0.8) | 6.3 (1.1) |
| 5. Would you recommend an exercise facility purchase this exercise modality? | 5.0 (1.7) | 6.6 (0.7) | 6.2 (1.5) |
| 6. If an exercise facility you attended had this piece of equipment, how often would you use it? | 3.9 (1.8) | 6.0 (0.9) | 6.1 (1.2) |
| **Mean item score** | **4.5 (1.3) ^*** | **5.9 (1.0)** | **5.8 (1.0)** |

ACE, Arm Cycle Ergometer; RS, Recumbent Stepper; FES, Functional Electrical Stimulation Cycle.

*Significant difference between ACE and RS exercise.
^Significant difference between ACE and FES exercise.

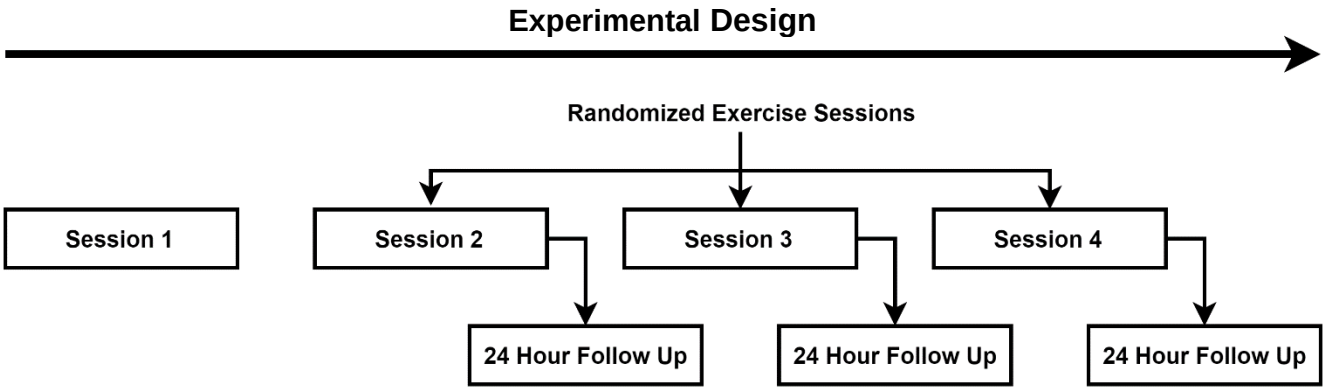


**Figure 1:** Experimental protocol for the study.

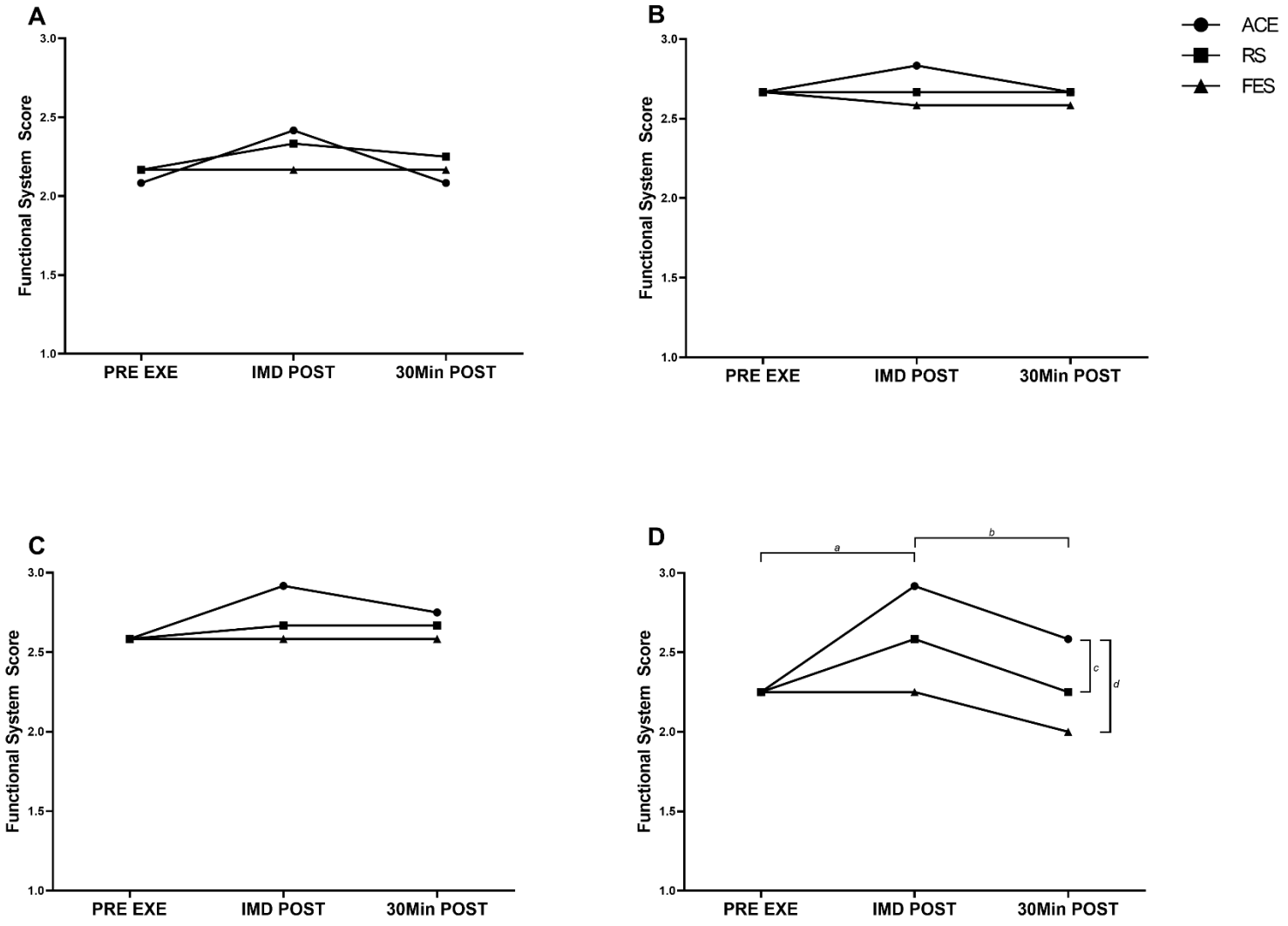


**Figure 2:** Changes in neurological function for each exercise modality across the submaximal exercise sessions: (A) Visual function; (B) Brainstem function; (C) Cerebellar function; and (D) Sensory function.

ACE, Arm Cycle Ergometer; RS, Recumbent Stepper; FES, Functional Electrical Stimulation Cycle; PRE EXE, Pre-exercise; IMD POST; immediately post-exercise; 30min POST, 30 minutes post-exercise

*a* - significant difference between PRE EXE & IMD POST
*b* - significant difference between IMD POST & 30-min POST
*c* - significant difference between ACE & RS
*d* - significant difference between ACE & FES

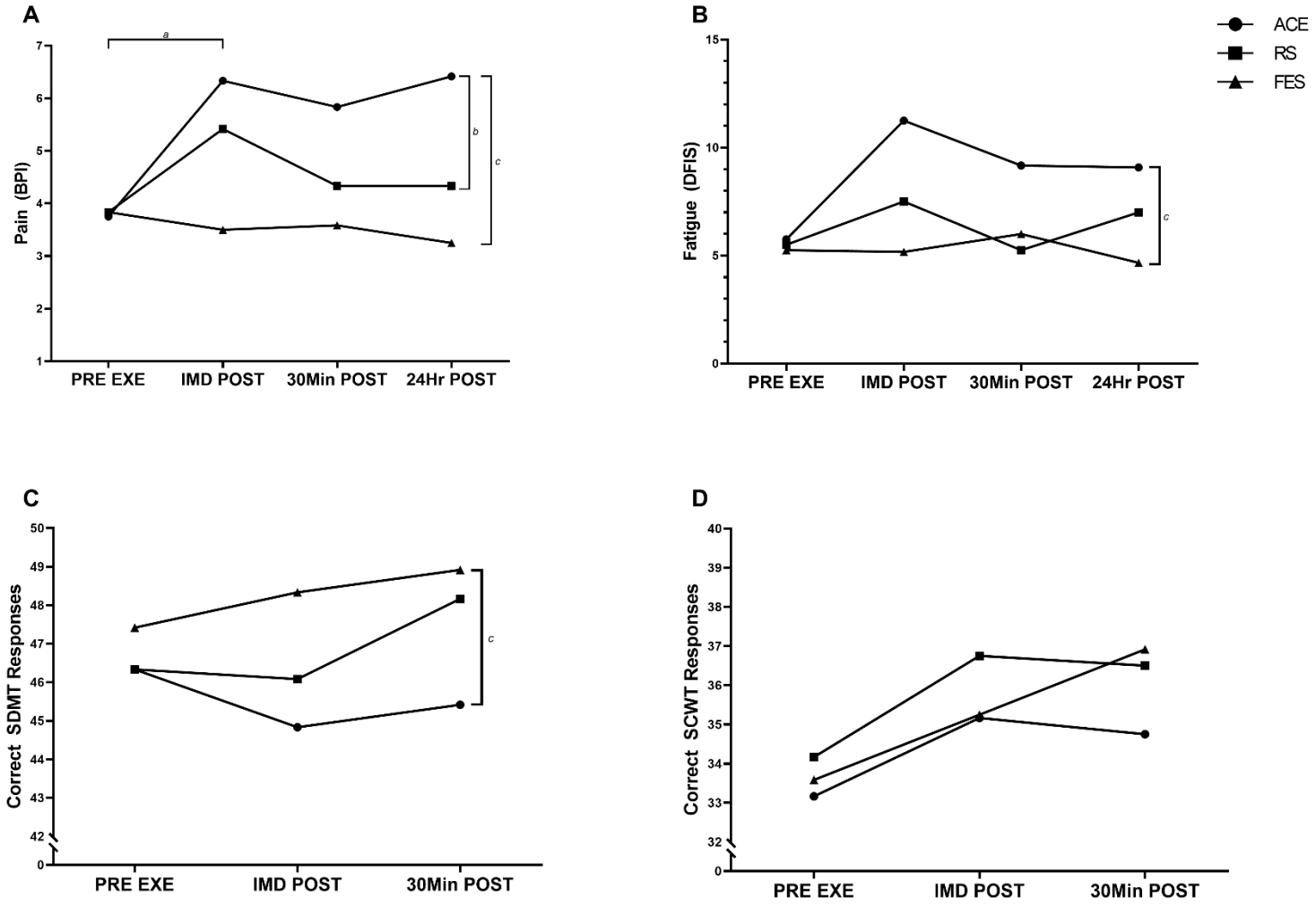


**Figure 3:** Changes in acute pain and fatigue symptoms, and cognitive performance for each exercise modality across the submaximal exercise sessions: (A) Brief Pain Inventory (BPI); (B) Daily Fatigue Impact Scale (DFIS); (C) Symbol Digit Modalities Test (SDMT); and (D) Stroop Color-Word Test (SCWT).

ACE, Arm Cycle Ergometer; RS, Recumbent Stepper; FES, Functional Electrical Stimulation Cycle; PRE EXE, Pre-exercise; IMD POST; immediately post-exercise; 30min POST, 30 minutes post-exercise; 24Hr POST, 24 hours post-exercise

*a* - significant difference between PRE EXE & IMD POST
*b* - significant difference between ACE & RS
*c* - significant difference between ACE & FES

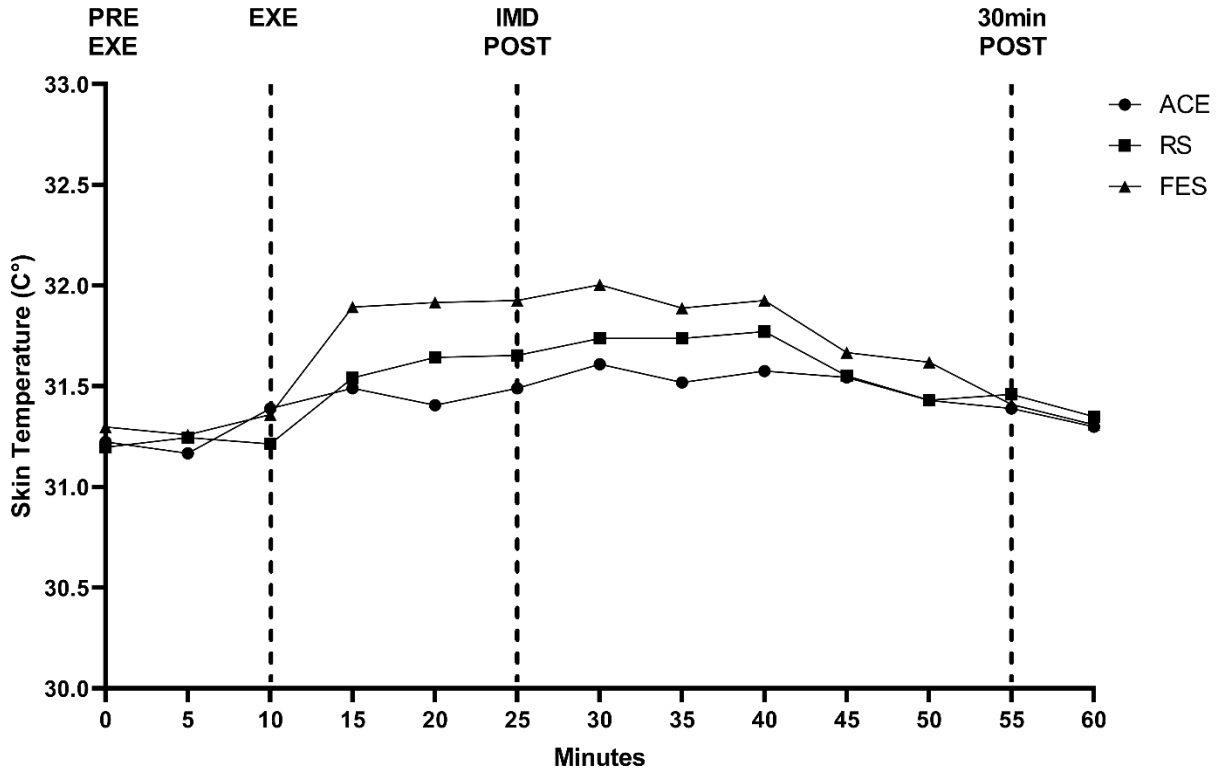


**Figure 4**: Change in skin temperature (°C) across the submaximal exercise session for each exercise modality. ACE, Arm Cycle Ergometer; RS, Recumbent Stepper; FES, Functional Electrical Stimulation Cycle; PRE EXE, Pre-exercise; EXE, exercise; IMD POST; immediately post-exercise; 30min POST, 30 minutes post-exercise

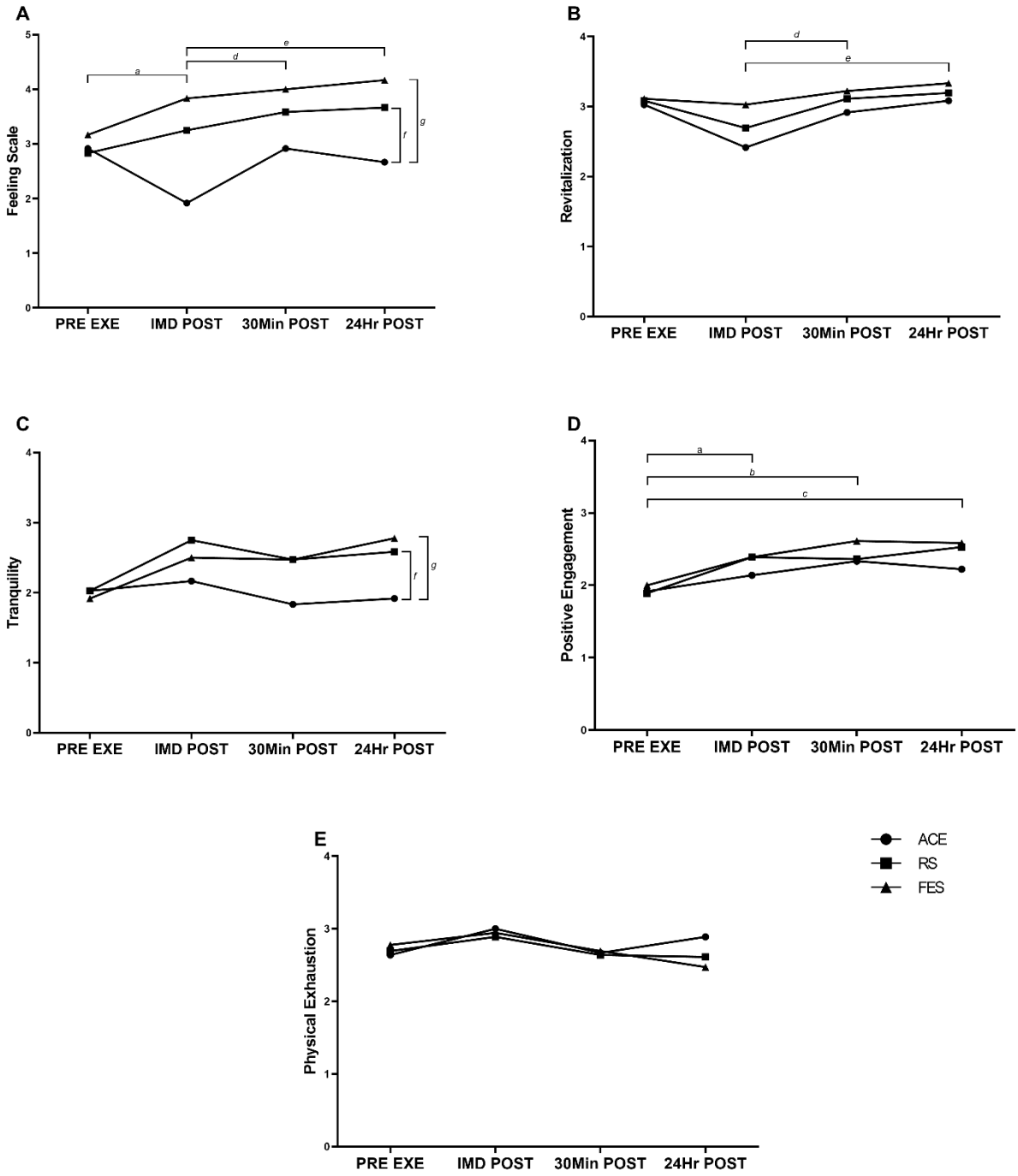


**Figure 5:** Changes in acute pain, acute fatigue, and cognitive performance, for each exercise modality across the submaximal exercise sessions; (A) Feeling Scale, (B) Revitalization, (C) Tranquility, (D) Positive Engagement, (E) Physical Exhaustion. ACE, Arm Cycle Ergometer; RS, Recumbent Stepper; FES, Functional Electrical Stimulation Cycle; PRE EXE, Pre-exercise; IMD POST; immediately post-exercise; 30min POST, 30 minutes post-exercise; 24Hr POST, 24 hours post-exercise.

*a* - significant difference between PRE EXE & IMD POST
*b* - significant difference between PRE EXE & 30-min POST
*c* - significant difference between PRE EXE & 24-hr POST
*d* - significant difference between IMD POST & 30-min POST
*e* - significant difference between IMD POST & 24-hr POST
*f* - significant difference between ACE & RS
*g* - significant difference between ACE & FES

# CHAPTER 3

## Characterizing the Cardiorespiratory Response to Exercise in Nonambulatory People with Multiple Sclerosis

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**Acknowledgments**: This study was supported, in part, by finding from the National Multiple Sclerosis Society [PP 1904-33937], the Canadian Foundation for Innovation [CFI-37079], and the Ontario Research Fund [MRIS-37079].

***Note*:** Chapters 2 and 3 present data from the same study and participant sample.

**ABSTRACT**

**Background:** Individuals with multiple sclerosis (MS) with higher disability experience physiological deconditioning, notably the loss of cardiorespiratory fitness (CRF). Exercise training has been effective in managing the loss of CRF in people with mild-moderate MS; however, the effect of exercise training on CRF in nonambulatory people with MS remains unclear. As the efficacy of exercise training for improving CRF is contingent upon a sufficient exercise stimulus, understanding the cardiorespiratory response to exercise is paramount for informing exercise recommendations across all ability levels in MS.

**Objectives:** To characterize the acute cardiorespiratory response of nonambulatory people with MS (Expanded Disability Status Scale score 7.0-8.0) to three accessible aerobic exercise modalities.

**Methods:** Twelve nonambulatory individuals with multiple sclerosis completed three submaximal exercise sessions (15 min; Rating of Perceived Exertion [RPE] = 12–13) using an arm-cycle ergometer (ACE), a recumbent stepper (RS), and a functional electrical stimulation (FES) cycle. Cardiorespiratory variables including oxygen consumption ($VO_2$), heart rate (HR), work rate (WR), respiratory exchange ratio (RER), and rating of perceived exertion (RPE) were recorded throughout the submaximal session.

**Results:** All participants were able to complete the submaximal exercise session using the RS and FES cycle. Three participants were unable to complete the ACE exercise session. There was a significant difference in RER during exercise, such that RER during ACE exercise was significantly higher than FES exercise ($p$=0.02). There were no significant differences between the exercise modalities in submaximal $VO_2$, HR, WR, and RPE (all $p$>0.05). All exercise modalities

elicited a cardiorespiratory response that corresponded with moderate-to-vigorous intensity aerobic exercise (mean $VO_2$ = 69.0% [14.0%], mean HR = 84.1% [9.9%]).

**Conclusion:** The current investigation supports the potential for improvements in cardiorespiratory fitness with aerobic exercise training in nonambulatory people with MS. This investigation provides much needed evidence that can better inform exercise prescription for nonambulatory people with MS.

**Keywords:** multiple sclerosis, cardiorespiratory, exercise, wheelchair, nonambulatory

## INTRODUCTION

Multiple sclerosis (MS) is a progressive neurological condition affecting approximately 2.8 million people worldwide.[1] It is estimated that 30% of people living with MS are nonambulatory and rely on wheelchairs for mobility.[2–4] Individuals with MS with higher disability levels engage in less physical activity and experience substantial physiological deconditioning, notably the loss of cardiorespiratory fitness (CRF).[5,6] In persons with MS, CRF has been associated with neurological impairment, mobility, brain structure and integrity, cognitive function, body composition, symptoms, quality of life, and participation in daily activities.[7–11] Further, it has been reported that persons with MS who use walking aids consume almost three times more oxygen when performing daily movement tasks (e.g., rolling in bed, lying to sitting, sitting to standing) compared to controls, suggesting an increased energetic cost of everyday movements.[12] Collectively, these data support the loss of CRF among persons with severe MS and the need for interventions that improve aerobic capacity as an approach for improving function and maintaining participation in daily life.

Exercise training has been effective in managing the loss of CRF in people with MS. Indeed, meta-analytic data support a significant, moderate improvement (Hedge's $g$ = 0.47) in CRF after exercise training in people with MS who have mild-to-moderate disability.[13,14] However, the effect of exercise training on CRF in nonambulatory people with MS (Expanded Disability Status Scale (EDSS) score $\geq$ 7.0) remains unclear, given the limited research to date and challenges to exercise delivery in this population.[15] Indeed, nine trials of exercise training in nonambulatory people with MS have been conducted to date, none of which have examined the efficacy of exercise on CRF variables.[16–19] Such lack of evidence has limited the development of

evidence-based exercise recommendations for this population, as current exercise guidelines for nonambulatory people with MS (EDSS = 7.0-9.0) are primarily derived from expert opinion.[20]

As the efficacy of exercise training for improving CRF is contingent upon a sufficient exercise stimulus and an appropriate modality for delivery in nonambulatory people with MS, understanding the acute cardiorespiratory response to adapted exercise is paramount to inform exercise recommendations for this population.[16,21] Previous studies have demonstrated that people with MS with mobility impairment (EDSS = 5.5–6.5) can engage in acute adapted exercise (recumbent stepper and functional electrical stimulation cycling exercise) at a sufficient intensity (i.e., moderate-to-vigorous) for promoting improvements in CRF.[22,23] Notably, these studies did not include nonambulatory people with MS. As such, characterizing the acute cardiorespiratory response of nonambulatory people with MS during adapted exercise represents a critical step for informing the design of exercise training interventions for improving CRF and other important health outcomes, and the development of evidence-based exercise recommendations for this population.[20]

Consequently, the objective of this study was to acutely characterize and compare the cardiorespiratory response to three accessible aerobic exercise modalities in nonambulatory people with MS (EDSS≥7.0). Findings from this study can inform expected responses to aerobic exercise in nonambulatory people with MS and can contribute to the development of evidence-based exercise prescription for this population.

## METHODS

### Participants

The inclusion criteria were: (a) age 18-75; (b) self-reported diagnosis of MS; (c) Expanded Disability Status Scale (EDSS) of 7.0-8.0; (d) relapse-free in the past 30 days; (e) stable course of disease modifying therapies over past 6 months; and (f) asymptomatic (i.e., no signs or symptoms of acute or uncontrolled cardiovascular, metabolic, or renal diseases) based on the Get Active Questionnaire (GAQ).[24] Additionally, participants were excluded if they were: (a) diagnosed with other neurological or musculoskeletal conditions; (b) unable to complete FES cycling due to contraindications; or (c) pregnant or planned to become pregnant. Given the level of disability of the sample, we did not exclude participants based on clinical course (relapsing vs. progressive) or use of medications.

**Protocol**

The study protocol was approved by the Health Sciences and Science Research Ethics Board at the University of Ottawa [REB H03-19-3436]. Eligible participants completed one baseline testing session and three submaximal exercise sessions. For all testing sessions, participants were asked to maintain a consistent medication schedule and refrain from consuming caffeine or alcohol 24-hours prior to the session. Participants were also asked to refrain from exercise 24-hours prior to each testing session. All exercise bouts were performed in a temperature-controlled room set to 18 degrees Celsius (°C). At the baseline testing session, participants underwent the informed consent process and completed assessment of anthropometrics, neurological function, a symptom-limited cardiopulmonary exercise test, and demographics and clinical characteristics.

Following the baseline assessment, participants completed the submaximal exercise sessions on three adapted exercise modalities in a counterbalanced order. The three submaximal exercise sessions took place seven days apart, at approximately the same time each day. Each

submaximal exercise bout consisted of four phases (see Figure 1): (i) 5-min period of monitored rest (RE); (ii) 1-min transition/warm-up period (WU); (iii) 15-min period of exercise (EXE); and (iv) 5-min cool-down period (CD). The submaximal exercise bouts were performed on an arm-cycle ergometer (ACE; SCIFIT Systems Inc; Tulsa, OK), a recumbent stepper (RS; SCIFIT Systems Inc; Tulsa, OK), and a functional electrical stimulation cycle (FES; Restorative Therapies Inc; Baltimore, MD). These modalities were selected based on their use in previous research,[5,25,26] potential for improving CRF,[27] and potential for access in home, community and/or clinical settings. All exercise modalities were used from a seated position and did not require participants to transfer from their wheelchairs.

**Baseline Outcome Measures**

*Anthropometrics, Demographic and Clinical Characteristics*

To measure height, participants were transferred to an examination tabled and laid in a supine position. A measuring tape was then used to measure the height of the participant to the nearest 0.1 cm. Mass was measured using a platform scale (Sartorius AG, Göttingen, Germany) to the nearest 0.1 kg under the supervision of members of the research team. Demographic and clinical characteristics were collected using questionnaires.

*Neurological function*

Neurological impairment was assessed with the Expanded Disability Status Scale (EDSS),[28] a standard neurological examination for persons with MS. The EDSS assesses neurological function within seven functional systems (visual; brainstem; pyramidal; cerebellar; sensory; bowel/bladder; cerebral) and ambulation. The EDSS scale ranges between 0 (*normal neurological function*) and

10 (*death due to MS*). The examination was conducted by a Neurostatus-certified assessor (TE; Level C).[28]

*Peak Cardiorespiratory fitness ($VO_{2peak}$)*

Peak CRF was measured using a cardiopulmonary exercise test on a recumbent stepper and a metabolic measurement system for analyzing expired gases (TrueOne 2400, Parvo Medics, Sandy, UT, USA). The exercise testing protocol was informed by previous trials involving people with MS with mobility impairments and was modified for nonambulatory people with MS.[5,25] Each participant was fitted with a facemask designed for collecting expired gases. The exercise test began with a 1-minute warm-up at 0 Watts. Participants were then asked to maintain a stepping rate of 40-50 steps/min for the duration of the test.[29] The initial work rate (WR) was set to 0 Watts and gradually increased at a rate of 2 Watts every 30-seconds until volitional fatigue (i.e., inability to continue exercising). The participant then performed a 5-minute cool down at 0 Watts. Oxygen consumption ($VO_2$), respiratory exchange ratio (RER), and WR were monitored continuously throughout the exercise test. Heart rate (HR) was monitored continuously using a Polar (Polar Electro, Kempele, Finland) heart rate monitor. Participants were asked to rate their perception of exercise intensity each minute using the Borg Rating of Perceived Exertion (RPE)[30] scale. Peak oxygen consumption ($VO_{2peak}$) was determined when at least one of the following criteria were recorded: (1) respiratory exchange ratio (RER) $\geq 1.10$; (2) peak HR within 10 bpm of age-predicted maximum (i.e., 220 − age); or (3) RPE $\geq 17$.[5,25]

**Submaximal Outcome Measures**

*Cardiorespiratory response*

The intensity of each submaximal exercise session was adjusted per participant to maintain an RPE of 12–13 ("*Somewhat hard*", i.e., moderate intensity).[31] The submaximal cardiorespiratory response associated with each adapted exercise modality was measured continuously using the same approach as during peak cardiopulmonary exercise testing. The cardiorespiratory variables recorded included $VO_2$, HR, WR, and RER and were expressed as a mean value for the 15-minute AE period.

**Data Analysis**

Data analysis was performed using IBM SPSS Statistics (Version 27.0, IBM Corp., Armonk, NY, USA). Descriptive statistics were used to characterize baseline demographic and clinical characteristics, and peak cardiorespiratory fitness variables. Descriptive statistics were also used to characterize the cardiorespiratory response during submaximal exercise. The cardiorespiratory variables were averaged per minute and expressed as a mean value for each phase of the submaximal exercise session. Cardiorespiratory variables including $VO_2$, HR, and WR were further expressed as a percentage of peak values, as these variables are commonly used indicators of exercise intensity.[31] To determine if there were any differences in the acute cardiorespiratory response across the exercise modalities, a one-way analysis of variance (ANOVA) was performed using exercise modality (ACE, RS, and FES) as the within-subjects factor. If significant modality effects were identified, a Tukey's *post-hoc* analysis was performed. Statistical significance was set at $p < 0.05$. Values within the text are presented as mean (SD), unless indicated otherwise.

**RESULTS**

*Baseline Assessment*

Baseline demographics, clinical characteristics, and peak cardiorespiratory variables are summarized in Table 1. The median EDSS score of the sample was 7.5 (IQR = 0.6) (i.e., unable to take more than a few steps), indicating a high level of mobility impairment. The mean disease duration was 22.3 (6.3) years and all participants had a progressive MS course (primary progressive MS = 5; secondary progressive MS n = 7). Mean $VO_{2peak}$, $HR_{peak}$, and $WR_{peak}$ for the sample were 9.6 (3.0) ml/kg/min, 119.0 (19.0) bpm, and 41.2 (12.6) Watts, respectively. All peak cardiorespiratory tests satisfied at least one criterion for attaining peak values.

*Submaximal Exercise Response*

All participants were able to complete 15-min of submaximal exercise using the RS and FES cycle. Three participants were unable to complete the full submaximal exercise session using the ACE. Table 2 provides a summary of the cardiorespiratory variables at rest and during submaximal exercise for each modality. A graphic representation of the minute-by-minute $VO_2$, HR, and WR responses are also presented in Figure 2. Mean RPE of the submaximal exercise sessions ranged between 10.8-12.0 across the modalities, indicating that participants perceived the exercise intensity as light-to-moderate. RPE was consistent across the modalities ($p$ = 0.22), as intended. There was a significant difference in mean submaximal RER (range = 0.80–0.88), as RER during ACE exercise was higher that RER during FES exercise ($p$=0.02). Mean submaximal $VO_2$ (range = 6.1–7.0 ml/kg/min), HR (range = 94–103 bpm), and WR (range = 9.0–18.1 Watts) were similar across the exercise modalities, with no statistically significant differences observed (all $p$ >0.05). Expressed as a percentage of peak values, mean submaximal $VO_2$ (range = 63.6%–73.1%), HR (range = 79.6%–86.6%), and WR (range = 20.0%–41.3%) were similar across the exercise modalities, with no statistically significant differences (all $p$ >0.05). Across all exercise modalities,

mean $VO_2$, HR, and WR expressed as a percentage of peak values were 69.0% (14.0%), 84.1% (9.9%), 30.8% (23.8%), respectively, in the nonambulatory MS sample.

## DISCUSSION

Nonambulatory people with MS have limited options for engaging in aerobic exercise and lack evidence-based guidance for directing exercise participation. This cross-sectional study was the first to characterize the cardiorespiratory response of nonambulatory people with MS to three different adapted aerobic exercise modalities. All modalities examined elicited cardiorespiratory responses at sufficient exercise intensities for promoting improvements in CRF. Findings from this study can be used to inform expected responses to aerobic exercise, the design of future exercise interventions, and evidence-based exercise recommendations for nonambulatory people with MS.

All modalities evaluated in the current study appear to be capable of promoting improvements in CRF with ongoing exercise training. The American College of Sport Medicine (ACSM) recommends moderate-to-vigorous intensity physical activity for promoting improvements in CRF among adults.[31] Further, individuals with low CRF (i.e., $VO_{2peak}$<40 ml/kg/min), such as individuals in our sample ($VO_{2peak}$ = 9.3 ml/kg/min), can experience improvements in CRF at even lower exercise intensities of approximately 30% of $VO_{2peak}$.[36] In the current study, participants were capable of exercising at an intensity that satisfied the ACSM criteria for MVPA on all modalities, indicating that all modalities are viable options for nonambulatory individuals with MS that are capable of providing a moderate-vigorous intensity exercise stimulus. These findings will enable clinicians and researchers to make evidence-based recommendations for nonambulatory people with MS, particularly with regards to exercise modality selection.

While there were no significant differences in the majority of cardiorespiratory variables across exercise modalities, there was a significant difference in RER across the exercise modalities, with a higher RER observed in response to ACE exercise compared to FES cycling. As use of the ACE relies solely on upper-limb exertion, smaller/weaker upper-limb musculature used during arm cycling may have contributed greater peripheral fatigue and reliance on anaerobic metabolism to maintain physical exertion during the submaximal exercise session.[37] This increased reliance on anaerobic energy production would explain a higher RER observed during ACE exercise.

While the cardiorespiratory response was comparable between ACE and RS exercise, FES cycling generally elicited the weakest cardiorespiratory response compared to the other adapted exercise modalities. Given FES cycling exercise relies on lower-limb exertion coupled with external stimulation, the current sample may have struggled to exercise efficiently using this modality, due to substantial lower-limb muscle atrophy and motor impairment.[32] However, it is foreseeable that some nonambulatory individuals with MS (particularly those with EDSS > 7.5) may struggle to use ACE or RS due to substantial upper-limb impairment.[33] This is particularly problematic as nonambulatory individuals with MS who experience considerable upper-limb impairment have limited choices for aerobic exercise modalities. By combing electrical stimulation of the muscles of the lower limbs and passive leg cycling, FES enables individuals with extremely high levels of neurological impairment, such as those with tetraplegia, to benefit from exercise training.[34] As a result, FES represents a viable option for nonambulatory individuals with MS to exercise at an intensity that is sufficient for promoting health benefits, regardless of upper or lower limb impairment that they may experience.

Additionally, differences in WR during exercise approached statistical significance ($p$ = 0.08), with the highest mean WR observed in response to RS exercise. A similar trend was observed among 64 individuals with MS (median EDSS = 4.25), as exercise testing conducted on a RS elicited a greater cardiorespiratory response compared to exercise testing performed on an ACE.[38] The increased WR during RS is likely due to the fact that this modality involves recruitment of more active muscle mass (i.e., upper and lower extremities) during exercise compared to ACE and FES exercise.[29] Herein lies one of the primary advantages of RS exercise for nonambulatory individuals with MS as the combined use of both the upper and lower-limbs can provide a more substantial cardiorespiratory challenge compared to other adapted modalities.[26]

Regardless of the exercise modality, the current nonambulatory sample demonstrated low peak CRF levels in comparison to other MS samples with lower disability and compared to other neurologically impaired populations. One previous study involving 22 individuals with MS with moderate disability (EDSS = 5.5-6.5) reported higher peak CRF levels ($VO_{2peak}$ = 13.9 ml/kg/min) compared to the current sample, despite the two samples being similar in age and disease duration, and using the same testing modality.[23] The current sample also had lower peak CRF levels compared to a sample of individuals with tetraplegia ($VO_{2peak}$ = 15.1 ml/kg/min), despite those with tetraplegia having drastically greater muscular impairments, atrophy, and paralysis.[35] Significant, negative associations ($r$ = -0.42) have been reported between peak CRF and EDSS scores in persons with MS.[10] Further, associations between peak CRF and activities of daily living ($r$ = 0.28) have been establish in those with MS, suggesting low CRF levels may limit activities of daily living.[11] These findings highlight the potential severity of physiological deconditioning experienced by people with MS who are nonambulatory, and the necessity for effective strategies that improve CRF in this population.

## Limitations

There are several important limitations of this study that must be considered when interpreting the findings. First, the sample size of the study was relatively small, which may limit the applicability of the findings to a larger population. While the sample size was relatively small, participants were homogenous in terms of disability level (EDSS 7.0-8.0) and disease course (all progressive MS). Another limitation of this study the ability to determine peak CRF in this sample. Given the high level of physiological deconditioning, coupled with the lack of experience with the adapted exercise modalities, it is foreseeable that the peak values obtained from the exercise test may not accurately reflect the fitness level of the current sample. Additionally, baseline cardiorespiratory fitness variables were determined on a RS and these variables were used to characterize the submaximal exercise sessions on the different modalities relative to peak values. Lastly, a limitation to this study was the fact that not all participants were able to complete all bouts of submaximal exercise using the ACE. While this provides important information on the feasibility of ACE, it may ultimately skew the mean values obtained across the ACE sessions.

## Conclusion

The current investigation is the first examination of the acute cardiorespiratory response of nonambulatory people with MS during submaximal exercise performed on adapted aerobic exercise modalities. All modalities examined elicited a cardiorespiratory response sufficient for improving health outcome with ongoing exercise participation. This investigation represents a critical step in addressing the evidence gap involving nonambulatory people with MS and provides much needed evidence that can be used to better inform exercise prescription for this population.

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**Table 1:** Baseline demographic, clinical and peak cardiorespiratory variables for the sample. Values reported as mean (SD), unless specified otherwise.

| **Demographic and Clinical Characteristics** | |
|---|---|
| Age (years) | 62.6 (9.5) |
| Height (cm) | 164.1 (6.4) |
| Mass (kg) | 69.9 (17.2) |
| BMI (kg/m2) | 25.6 (6.6) |
| Sex***** | |
| Male | 1 (8.3%) |
| Female | 11 (91.7%) |
| EDSS[#] | 7.5 (0.6) |
| Disease Duration (years) | 22.3 (6.3) |
| MS Type* | |
| PPMS | 5 (41.7%) |
| SPMS | 7 (58.3%) |
| **Peak Cardiorespiratory Fitness** | |
| $VO_{2peak}$ (ml/kg/min) | 9.6 (3.0) |
| $HR_{peak}$ (bpm) | 119.0 (19) |
| $WR_{peak}$ (Watts) | 41.2 (12.6) |
| $RER_{peak}$ | 0.89 (0.10) |
| TTE (sec) | 543.2 (131.0) |
| $RPE_{peak}$ [#] | 17.0 (1.8) |

EDSS, expanded disability statue scale; PPMS, primary-progressive multiple sclerosis; SPMS, secondary-progressive multiple sclerosis; VO2peak, peak oxygen consumption; HRpeak, peak heart rate; WRpeak, peak work rate; RERpeak, peak respiratory-exchange ratio; TTE; time to exhaustion; RPEpeak, peak rating of perceived exertion.

*Denotes value reported as *n* (%); [#]Denotes value reported as median (IQR).

**Table 2:** Mean cardiorespiratory response at rest and during submaximal exercise for each exercise modality. Values reported as mean (SD), unless specified otherwise.

| **Variable** | **ACE** | **RS** | **FES** | **ANOVA Output** | | |
|---|---|---|---|---|---|---|
| **Rest** | | | | **F value** | ***p* value** | **$\eta p^2$** |
| $VO_2$ (ml/kg/min) | 3.1 (0.04) | 3.0 (0.08) | 3.3 (0.07) | 0.80 | 0.46 | 0.05 |
| HR (bpm) | 78.8 (0.8) | 79.4 (0.6) | 79.3 (0.6) | 0.01 | 0.99 | 0.00 |
| **Submaximal exercise** | | | | | | |
| $VO_2$ (ml/kg/min) | 6.6 (2.2) | 7.0 (2.1) | 6.1 (2.2) | 1.5 | 0.60 | 0.03 |
| $\%VO_{2peak}$ | 70.3 (15.6) | 73.1 (12.7) | 63.6 (15.8) | 1.5 | 0.24 | 0.08 |
| HR (bpm) | 102.5 (19.3) | 102.6 (18.5) | 93.6 (11.7) | 1.0 | 0.40 | 0.05 |
| $\%HR_{peak}$ | 86.4 (9.3) | 86.6 (8.5) | 79.6 (8.2) | 1.9 | 0.16 | 0.10 |
| WR (Watts) | 13.0 (8.3) | 18.1 (13.9) | 9.0 (10.1) | 2.0 | 0.15 | 0.11 |
| $\%WR_{peak}$ | 31.4 (19.4) | 41.3 (27.5) | 20.0 (19.8) | 2.8 | 0.08 | 0.14 |
| RER ($CO_2/O_2$) ***** | 0.88 (0.08) | 0.85 (0.07) | 0.80 (0.05) | **3.9** | **0.03** | **0.20** |
| RPE | 11.8 (1.2) | 12.0 (0.7) | 10.8 (2.5) | 1.6 | 0.22 | 0.10 |

ACE, arm-cycle ergometer; RS, recumbent stepper; FES, functional electrical stimulation cycle;$VO_2$,oxygen consumption; $\%VO_{2peak}$ , percentage of peak oxygen consumption; HR, heart rate; $\%HR_{peak}$, percentage of peak heart rate; WR, work rate; $\%WR_{peak}$, percentage of peak work rate; RER, respiratory-exchange ratio; RPE, rating of perceived exertion.

* Indicates significant difference between ACE and FES

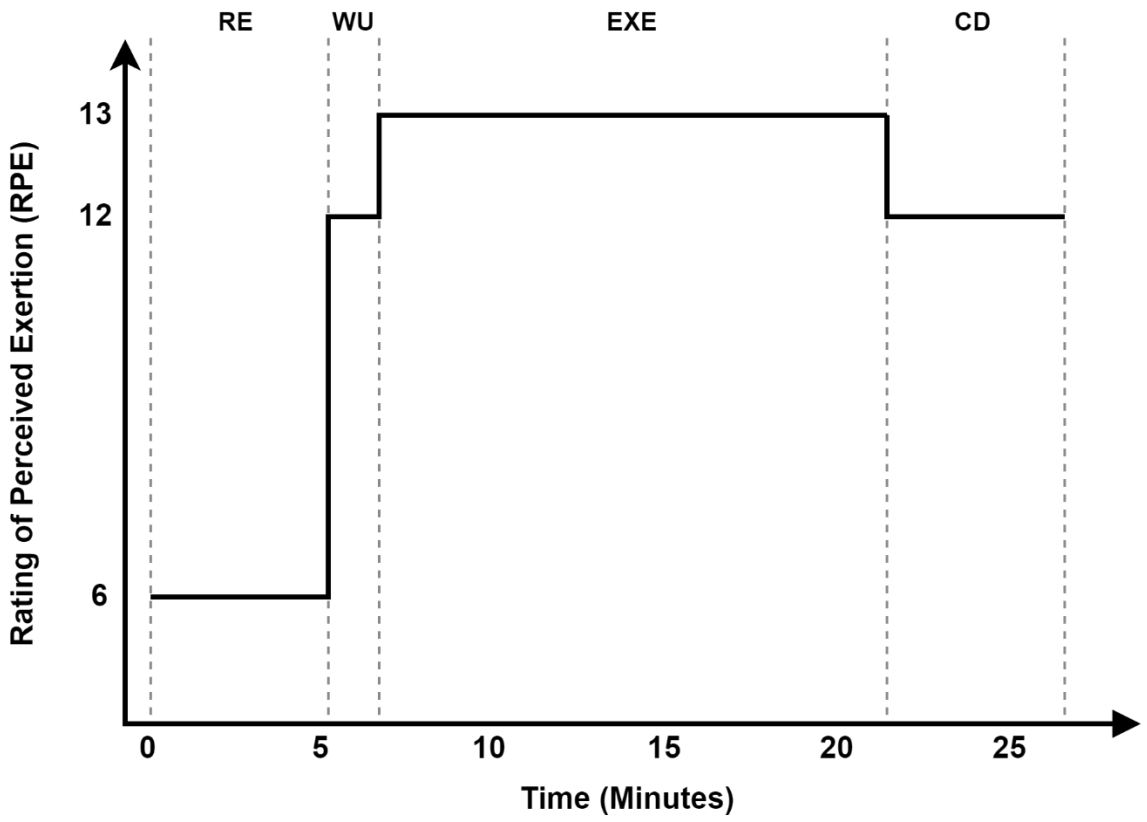


**Figure 1:** Protocol for the submaximal exercise session consisting of 4 phases: (i) Rest (RE): 5-min period of monitored rest; (ii) Warm-up (WU): 1-min transition/warm-up period; (iii) Exercise (EXE): 15-min period of exertion; (iv) Cool-down (CD): 5-min cool-down period.

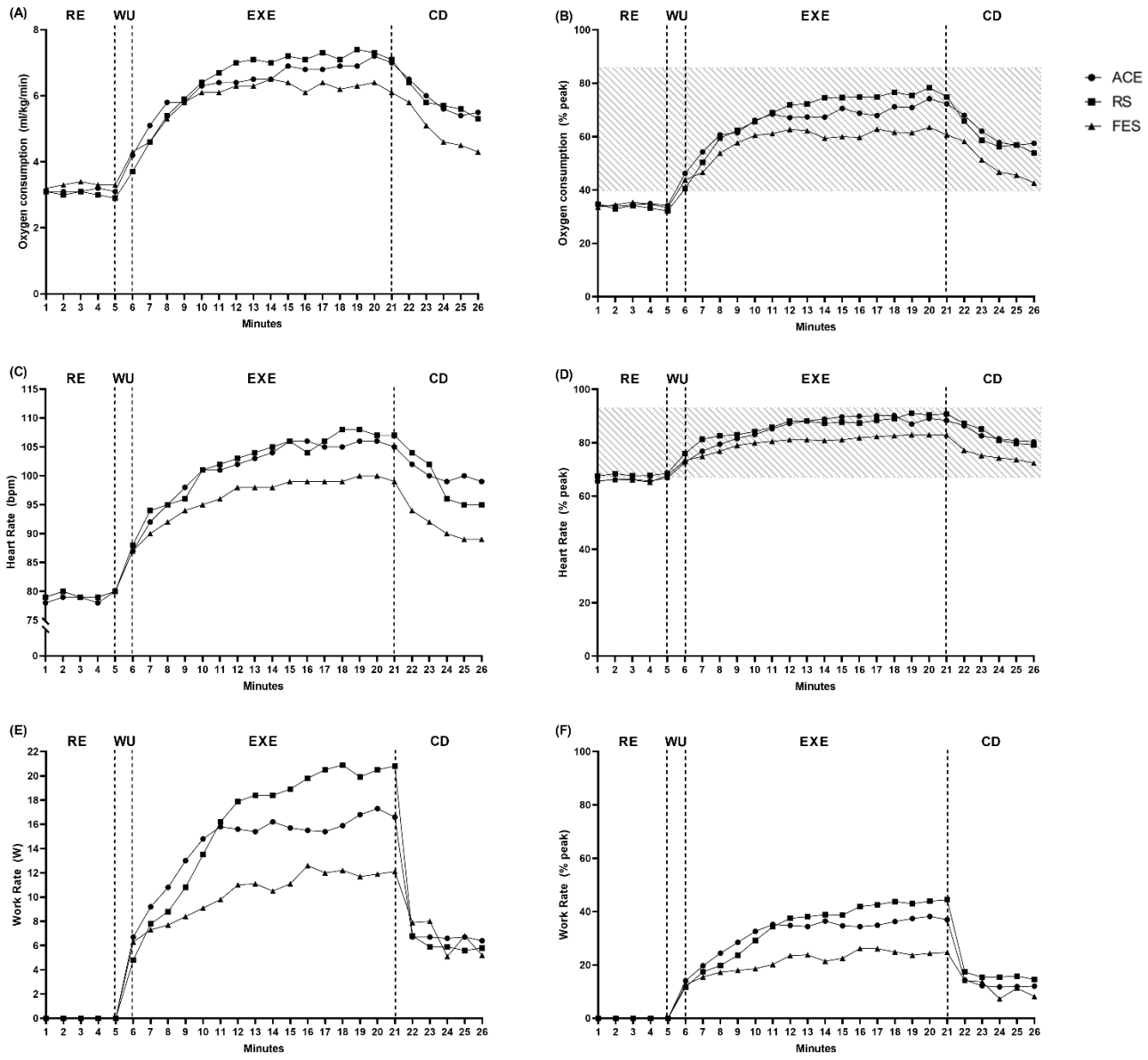


**Figure 2:** Minute-by-minute cardiorespiratory response measured during submaximal exercise: (A) Oxygen consumption (ml/kg/min); (B) Oxygen consumption (% peak); (C) Heart rate (bpm); (D) Heart rate (% peak); (E) Work rate (Watts); and (F) Work rate (% peak). Grey hashed area denotes exercise intensity range for moderate-to-vigorous physical activity (MVPA).[28] ACE, arm-cycle ergometer; RS, recumbent stepper; FES, functional electrical stimulation cycle.

# CHAPTER 4

## Exercise training improves participation in persons with multiple sclerosis: A systematic review and meta-analysis

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**Running head: Exercise and Participation in MS**

## ABSTRACT

**Objectives:** While previous studies have examined the effects of exercise training on other International Classification of Functioning, Disability and Health (ICF) component levels in persons with multiple sclerosis (MS), the effects of exercise training on participation remains unclear. The objectives of this review were to: (1) systematically characterize the use of outcome measures that capture participation in exercise training studies; (2) quantify the effect of exercise training on participation in persons with MS.

**Methods:** A search of 6 electronic databases (CINAHL, Sport Discuss, EMBASE, MEDLINE, CENTRAL, Scopus) was conducted to identify controlled and non-controlled trials involving exercise training and participation in persons with MS. Search strings were built from Medical Subject Headings (MeSH) and "CINAHL headings". ICF linking rules were used to identify participation chapters and categories captured. Meta-analysis was used to quantify the effect of exercise training on participation in randomized controlled trials (RCTs) comparing exercise effects to no intervention/usual care.

**Results:** Forty-nine articles involving controlled and non-controlled exercise trials were included in the systematic review of outcome measures. Sixteen different outcome measures that captured all 9 participation chapters and 89 unique participation categories were identified. Across these 16 outcome measures, "mobility" was the most represented participation chapter, with 108 items. A subsample of 23 RCTs were included in the meta-analysis. An overall effect of 0.60 (standard error = 0.12, 95% confidence interval (0.37, 0.84), $z = 4.9$, $p < 0.001$) was calculated, indicating a moderate, positive effect of exercise training on participation.

**Conclusion:** The current review provides information that can be used to guide the selection of outcome measures that capture participation in studies of exercise training in persons with MS. Exercise training has a positive effect on outcomes that capture participation, providing further evidence for the role of exercise training in promoting and maintaining engagement in everyday life.


**Keywords:** exercise training, ICF framework, multiple sclerosis, participation

## 1. Introduction

The pathology of multiple sclerosis (MS) involves chronic neuroinflammation and neurodegeneration within the central nervous system,[1,2] often resulting in symptoms and physical limitations that impact an individual's ability to participate in society.[3,4] According to the International Classification of Functioning, Disability and Health (ICF),[5] "participation" and associated restrictions have been described as the involvement in, and problems experienced with life situations. Given the broad nature of participation, efforts have been made to identify participation categories that may be particularly relevant for persons living with MS.[6] The brief ICF core set for MS identifies involvement in situations related to "solving problems", "carrying out daily routines", "walking", "family relationships", and "remunerative employment" as key categories of relevance for understanding and describing disability in persons with MS.[6] Additionally, "recreation and leisure", "socializing", and "community life" are aspects of participation that have been reported to be of relevance to persons with MS.[3] Outcomes that capture participation provide insight into the impact of MS on everyday living and have been identified as outcomes of high importance to people living with MS.[6,7] Importantly, persons with MS demonstrate significant impairment in multiple participation categories, with greater impairment experienced as disability increases.[8] Despite this, there has been an underutilization of study end-points that capture participation in clinical trials involving persons with MS.[9] Consequently, understanding the potential of interventions to improve participation is of utmost importance.

Exercise training has emerged as a safe, effective, low-cost, non-pharmacological intervention for managing disability experienced by persons with MS.[10] Previous systematic reviews and meta-analyses have reported that exercise training promotes improvements in aerobic capacity, muscular strength, balance, walking performance, and gait kinematics, while also

reducing fatigue and depression.[10–13] Within the context of the ICF, these effects primarily reflect improvements within "body structures", "body functions", and "activities" component levels. Previous studies of exercise training have used a variety of measures that capture different aspects of participation in everyday life, such as carrying out daily tasks and self-care, walking and movement, interpersonal relationships, and recreation and leisure. Such measures are rarely the primary outcome of intervention studies,[9] and are often not included with the intention of capturing changes in everyday life that may occur in response to exercise training.

Previous reviews have examined the effects of exercise and physical activity interventions on some aspects of participation, such as quality of life and physical activity levels. One meta-analysis conducted in 2008 reported that exercise training was associated with small, significant improvements in quality of life among persons with MS;[14] however, a systematic review conducted in 2013 reported inconclusive findings.[15] Another meta-analysis supported the efficacy of behavioral interventions, including those involving exercise and physical activity, for increasing self-reported physical activity behavior in persons with MS.[16] While previous research provides insight on the effects of exercise training on some aspects of participation, they do not represent the entire scope of outcome measures that capture different elements of participation. As a result, the effect of exercise training on many categories of participation has not been described. The extent to which outcomes that capture participation have been included in studies of exercise training, and which aspects of participation are captured by these tools, also remain unclear.

Given the importance of participation for describing the impact of MS on daily life and the significance of such outcomes to persons with MS, and in order to gain a preliminary understanding of the effects of exercise training on participation, a review of the current literature is warranted. Consequently, the objectives of this review were to: (1) systematically characterize

the use of outcome measures that capture participation in studies of exercise training involving persons with MS; and (2) quantify the effect of exercise training on participation in persons with MS. Results from this review can be used be researchers and clinicians to guide the selection of relevant participation outcomes as endpoints of exercise and rehabilitation interventions. This review will further provide evidence for the role of exercise training in improving involvement in everyday life for persons with MS.

## 2. Methods

The protocol for the current review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[17] recommendations and was submitted, accepted, and published in the international database of prospectively registered systematic reviews in health and social care (PROSPERO, ID number: CRD42020155721).[18]

### *2.1 Search strategy and screening*

This review focused on published studies examining the effect of exercise training on participation in persons with MS. As per the ICF framework, participation outcome measures were defined as those that capture the "involvement of people in all areas of life".[5] Exercise training was defined as a "form of leisure-time physical activity that was performed repeatedly over an extended period of time with a specific external objective".[19]

A search of 6 electronic databases (CINAHL, Sport Discuss, EMBASE, MEDLINE, CENTRAL, Scopus) was initially conducted on August 16, 2019, and then updated on August 31, 2020. The following PICO (i.e., Population/Patient, Intervention, Comparison, Outcome) question[18] guided the search strategy: "Amongst persons with MS, to what extent does exercise

training, in comparison to a non-exercise condition, effect participation?" Searches were conducted using database-specific terms based on Medical Subject Headings (MeSH) and "CINAHL headings" used to identify keywords related to "multiple sclerosis" (Term 1), "exercise training" (Term 2), and "participation" (Term 3; Supplementary Table 1). The database search was supplemented with hand-searches of the authors' personal databases, relevant reviews, meta-analyses, and reference lists of the included articles. Results from the literature search were exported to Covidence (Covidence, Veritas Health Innovation, Melbourne, Australia), which was then used to de-duplicate the retrieved articles.

After removal of duplicates, an initial screening at the title/abstract level was conducted using the following inclusion criteria to identify studies involving: (a) adults (>18 years of age) with a diagnosis of MS; and (b) exercise training. Following the initial screening, full-text articles were evaluated and excluded using the following criteria: (a) non-English; (b) animal models; (c) non-primary research; (d) non-MS population; (e) no exercise intervention (≥2 weeks in length); and (f) no participation outcome. At this stage of the screening process, all eligible articles (controlled and non-controlled trials) were included in the systematic review for the purpose of characterizing the use of outcome measures that capture participation. Articles were further screened for inclusion in the meta-analysis using the following criteria: (a) randomized controlled trial (RCT) design; (b) control group involving no exercise intervention or usual care; and (c) sufficient data to calculate effect sizes. TE and ASM individually reviewed each article during the title/abstract screening, full-text screening, and meta-analysis screening stages. Upon the completion of each stage of the screening process, discrepancies between the authors regarding article inclusion were discussed. If consensus could not be reached, a third author (LAP) served as a tiebreaker.

*2.2 Data extraction*

Following the screening process, relevant data from the included articles were extracted into Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA, USA) by 2 members of the research team (TE and ASM). Data were initially extracted by TE, with ASM ensuring the accuracy of extracted data. Extracted data included study characteristics (study design, sample size, and country of origin), participant characteristics (age, body mass index, and sex distribution), clinical characteristics (disease duration, MS type, and disability status), exercise prescription (modality, setting, duration, frequency, and intensity), and participation outcome values (pre-post mean, significance of change). Any discrepancies or errors in data extraction were settled by consensus.

*2.3 Quality assessment*

The Tool for the Assessment of Study Quality and Reporting in Exercise (TESTEX) scale, was used to evaluate the quality of each article.[20] The TESTEX scale was selected to evaluate study quality as it has demonstrated reliability in scoring exercise training studies, has been used in other systematic reviews/meta-analysis involving exercise trials, and was designed specifically for the evaluation of exercise training studies.[20] The TESTEX overcomes some limitations of other quality evaluation tools by accounting for aspects of study design unique to exercise training studies, allowing a more nuanced evaluation of study quality.

The TESTEX scale has a maximum possible score of 15 points, with a higher score indicating better methodological quality.[20] Each article was independently evaluated by TE and ASM. Any scoring discrepancies between the raters were discussed and resolved when possible.

A third author (LAP) acted as a tiebreaker when discrepancies could not be resolved. A breakdown of the TESTEX scores per item for each article are presented in Supplementary Table 2.

*2.4 Characterization of participation outcomes*

Outcome measures used to capture participation were identified and quantified per study. Established ICF linking rules and protocols were then used to identify the participation chapters and categories captured within each outcome measure.[21,22] Each individual item within the retrieved outcome measure was linked to the corresponding ICF participation chapter and category code. If an item could not be linked to a participation chapter, it was described as a "non-participation" item. Each item was linked independently by TE and AOF. Any discrepancies in the ICF linking process were discussed among the authors and resolved when possible. A third author (LAP) acted as a tiebreaker if discrepancies could not be resolved. Items were linked to the lowest possible ICF participation code.

*2.5 Descriptive analytic approach*

Descriptive statistics were used to calculate the median (IQR) sample size and TESTEX score of the included studies. The type and frequency of participation outcome measures used across all studies were summarized using descriptive statistics. Additionally, studies reporting a participation outcome as their primary outcome measure were identified and tabulated. To identify which aspects of participation were captured within each measure, the linked ICF chapters (d1–d9) were tabulated, and the frequencies of items representing each ICF chapter were summarized. Items that could not be linked to a participation chapter were also tabulated.

*2.6 Meta-analytic approach*

Mean (SD) values for participation outcomes per study were extracted and entered into the Comprehensive Meta-Analysis software (Version 2.0; Biostat, Englewood, New Jersey, USA). For each study, the effect sizes represent the pre–post change in participation outcomes in the exercise group compared to the non-exercise control group. When multiple measures of participation were included within a single study, an overall mean effect size was generated for that study. The aggregate effect size was estimated using a random-effects model. The random-effects model was selected due to the variance in participant and exercise-training characteristics across the studies.[23] Additionally, separate effect sizes were calculated by exercise type (i.e., aerobic training, resistance training, and mixed/other training). Heterogeneity of the overall effect size was examined using the *Q* statistic, with a significance level of $p < 0.05$ indicating study heterogeneity. An investigation of the potential modifying effects of participant and/or study characteristics (covariates) on the mean overall effect size was explored using meta-regression.[23] Disability status, disease duration, exercise modality, TESTEX scores, and clinical improvement (i.e., reported significant improvement) in physiological fitness outcomes (i.e., aerobic and muscular fitness) were input as categorical variables and tested as potential moderator variables.

## 3. Results

*3.1 Literature search and quality assessment*

Fig. 1 provides a breakdown of the literature search and screening process. The initial database search yielded 4272 articles and was supplemented by the addition of 4 articles from the authors' personal libraries. Following the removal of duplicates and irrelevant articles, 419 full-text articles were assessed for eligibility. Following the full-text screening process, 49 articles were eligible

and were included in the systematic review.[24–72] For the purpose of presenting the findings of the literature search, these 49 articles were subdivided into 3 categories based on exercise type: aerobic training,[24–46] resistance training,[47–54] and mixed/other training (e.g., combination of aerobic and resistance training, yoga, Pilates).[55–72] A detailed description of the participants and exercise prescription per study is presented in Table 1. The median (interquartile range; IQR) sample size for the included studies was 38 (33), with sample sizes ranging from 6 to 314 participants. The median (IQR) TESTEX score for the included studies was 10 (4), with scores ranging from 3 to 14 points. The median TESTEX score of the current review was higher than the median TESTEX score reported in a previous review of 41 exercise trials involving people with MS (median = 8).[73]

*3.2 Participation outcomes*

A summary of the participation outcome measures used per study is reported in Table 2. Sixteen different measures capturing participation were included across the 49 studies. Most studies included in the review (*n* = 35, 71%) used a single outcome measure capturing participation, while the remaining 14 studies (29%) used multiple outcome measures capturing participation. Only 6 studies (12%)[31,33,36,61–63] identified an outcome measure capturing participation as the primary outcome of the study. Across all retrieved outcome measures, all 9 (d1-d9) participation chapters were captured in varying capacities (range: 1 to 7 chapters). Additionally, 89 unique participation categories were represented across the 16 included outcome measures (range: 3 to 54 categories). The 36-Item Short Form Survey (SF-36) was the most commonly used outcome measure capturing participation, reported in 16 (33%) studies. The SF-36 contains 22 items representing 5 different participation chapters. The Multiple Sclerosis Impact Scale (MSIS-29) was the most prevalent

MS-specific outcome measure capturing participation, reported in 14 (29%) studies. The MSIS-29 contains 14 items representing 6 unique participation chapters.

A visualization of the frequency of linked ICF participation chapters are presented in Figure 2. "Mobility" was the most represented ICF participation chapter, captured in 108 items across 14 different outcome measures. There were 34 unique ICF participation categories represented across the 108 items capturing "mobility". Conversely, "communication" was the least frequently represented ICF participation chapter, captured with only four items across two outcome measures. Non-participation items accounted for 143 items across the 16 outcome measures.

*3.3 Meta-analytic approach*

A subsample of 23 articles was included in the meta-analysis. Mean values for participation outcomes (pre and post) for all 23 randomized controlled trials (RCT) are presented in Supplementary Table 4. Overall, 78 individual effect sizes were retrieved from 1093 individuals with MS (exercise training = 558; control = 535). The overall weighted mean effect size (Hedges's *g*) was 0.60 (standard error; SE = 0.12, 95% confidence interval; CI (0.37 - 0.84), $z = 4.9$, $p < 0.001$), indicating a moderate, positive effect of exercise training on participation (Fig. 3). The overall effect was heterogeneous ($Q = 79.7$, $I^2 = 72.4$, $p < 0.001$). The mean effect size for aerobic training (n = 13 studies), resistance training (n = 4 studies), and mixed/other training (n = 6 studies) was 0.68 (SE = 0.21, 95% CI (0.27, 1.1), $z = 3.3$, $p = 0.001$), 0.47 (SE = 0.15, 95% CI (0.14, 0.97), $z = 3.1$, $p = 0.002$), and 0.56 (SE = 0.21, 95% CI = (0.18, 0.77), $z = 2.6$, $p = 0.009$), respectively. The heterogeneity of effect sizes ($I^2$) for aerobic training, resistance training, and mixed/other

training were 80.2 ($Q$ = 60.7, $p$ < 0.001), 0.00 ($Q$ = 0.8, $p$ = 0.86) and 71.8 ($Q$ = 17.8, $p$ = 0.003), respectively.

Meta-regression indicated that clinical improvements in physiological fitness accounted for a significant amount of the variation in the observed effect of exercise training on participation ($R^2$ = 0.42, $p$ < 0.01). Conversely, baseline disability status ($R^2$ = 0.00, $p$ = 0.68), disease duration ($R^2$ = 0.01, $p$ = 0.58), study quality ($R^2$ = 0.00, $p$ = 0.18), and exercise type ($R^2$ = 0.01, $p$ = 0.60) accounted for minimal variation in the observed effect of exercise training on participation.

## 4. Discussion

The findings from this review indicate considerable breadth and variability in how participation is captured in studies of exercise training involving persons with MS, as reflected by the number of outcome measures and heterogeneity of participation categories represented across the retrieved studies. Further, mobility was the most represented participation chapter. The meta-analysis of 23 RCTs determined a moderate, positive effect of exercise training on participation when compared to a non-exercise control condition. While there is variability in how participation is captured in the MS exercise literature, there appears to be an overall positive effect of exercise training for improving involvement in daily life for persons with MS.

### *4.1 Systematic review*

The 49 retrieved studies included 16 different outcome measures that capture participation to some extent. Given the broad definition of participation within the ICF framework,[7] such variability in how participation has been captured in exercise studies involving persons with MS is unsurprising. While all participation chapters (d1 through d9) were represented across the

retrieved outcomes measures, there was a noticeable disparity in the frequency of these chapters. For example, mobility (chapter d4) was by far the most represented participation chapter (108 items), while communication (chapter d3) was represented by only four items. There was further variability in the number of participation categories captured across outcome measures, ranging between 3 (Godin Leisure-Time Exercise Questionnaire; GLTEQ) and 54 (Sickness Impact Profile; SIP), which suggests that some tools may capture participation in a more comprehensive manner than others. The heterogeneity in ICF chapter representation across the retrieved outcome measures reflects that these tools capture different aspects of participation. Such variability in participation chapter and category representation may impact interpretations of how interventions, including exercise training, influence participation in daily life. Given the heterogeneity in the presentation of MS, certain outcome measures may have greater relevance than others based on clinical disease characteristics. For instance, an outcome measure composed primarily of mobility items (e.g., Late Life Function and Disability Inventory) would not be relevant for those with MS with substantial mobility impairment. Instead, an outcome measure composed of a variety of participation chapters (e.g., Functional Independence Measure or Barthel Index) may be more appropriate. Future studies may benefit from including multiple tools when attempting to capture different aspects of participation. Collectively, when selecting outcome measures intended to capture participation, it is important to consider which chapters and categories are represented, and whether a selected tool is aligned with intervention content and participant characteristics.

The participation chapters and categories captured in the retrieved outcome measures have considerable overlap with those identified in the brief and comprehensive ICF core sets for persons with MS.[6] Indeed, the brief ICF core set for MS identifies “solving problems”, “carrying out daily

routines", "walking", "family relationships", and "remunerative employment" as the essential participation categories that should be used when characterizing participation in those with MS.[6]

When examining the most represented participation chapters across included outcomes, "walking" and "family relationships" are adequately represented as chapter d4 (mobility) and chapter d7 (interpersonal interactions & relationships) were the first and third most represented participation chapters, respectively. This suggests that outcome measures capturing participation in studies of exercise training are covering some relevant aspects of participation as identified by expert consensus. However, other relevant aspects of participation may not be reflected within these outcome measures. For example, chapter d1 (learning and applying knowledge) and chapter d8 (major life areas) were the second and third least represented chapters across outcome measures in our review, respectively, despite being represented on the brief ICF core set for MS.[6] This seems to indicate that while many relevant categories of participation are being adequately captured, there remain some categories of participation that may be overlooked by existing tools. While the ICF core and comprehensive sets for MS provide direction on potential categories of relevance, it is also important to consider participant perspectives when selecting outcome measures as endpoints for research and clinical practice.

One cross-sectional study involving 113 persons with MS sought to identify the patient-reported aspects of participation most impacted by MS.[7] In that study, community, social and civic life (chapter d9), mobility (chapter d4), and domestic life (chapter d6) were identified as the most impacted aspects from a patient's perspective. Conversely, communication (chapter d3) was cited as the least impacted. Interestingly, while mobility categories were adequately represented in items across the outcome measures retrieved in our review, items representing community, social and civic life (chapter d9), and domestic life (chapter d6) were relatively scarce. The incongruence

between categories identified as most impacted by persons with MS and those captured by current outcome measures highlights the potential need for inclusion of different or new tools to capture participation and the impact of interventions on engagement in daily life. For instance, an outcome measure describing community, social and civic life (chapter d9), or domestic life (chapter d6) may capture more meaningful changes in participation from a participant's perspective compared to some of the currently used outcome measures.

Despite the importance of participation outcomes, 85 articles of 419 full-text articles were excluded from the current review due to the absence of any outcome capturing participation. Further, only ~10% of the included articles identified an outcome capturing participation as their primary outcome, indicating that these outcomes have been largely overlooked in the existing MS exercise training literature. Ideally, the results from this review can facilitate more frequent inclusion of outcomes that capture participation in future studies of exercise training in MS by providing a detailed breakdown of which participation chapters and categories are captured within current outcome measures. Results from this review can be further cross-referenced with the established ICF core set for MS[6] as well as with patient-reported chapters and categories of relevance.[7] Our analysis can be used by clinicians and researchers to identify which outcome measures capture the most relevant aspects of participation. Ultimately, the strategic inclusion of these outcomes can provide greater insight into the benefits of exercise training on everyday life for persons with MS.

### *4.2 Meta-analytic approach*

This review is the first to demonstrate the effects of exercise training on participation in persons with MS. The magnitude of the effect size reported herein is somewhat larger than

previous meta-analyses examining the effects of exercise training on physical fitness, symptoms of fatigue, and mobility.[11,74,75] From a clinical perspective, this novel finding is particularly important as persons with MS have demonstrated restricted levels of participation compared to controls without MS.[4] Indeed, a cross-sectional study involving 105 people with MS reported that approximately 77% of the sample had significantly restricted societal participation—as measured by the Community Integration Questionnaire (CIQ)—when compared to age- and sex-matched controls without MS.[8] The findings from our review provide evidence for the role of exercise training in increasing and maintaining engagement in everyday life, and consequently, they add to the body of literature supporting exercise training as a disease-management strategy for MS.[76]

In the current analysis, clinical variables, such as baseline disability and disease duration, had no statistically significant influence on the effect of exercise training on participation, which suggests that improvements in participation may be possible, irrespective of disability or disease burden. Studies involving aerobic exercise training had the largest effect size when compared to resistance and mixed/other exercise types, although there were no statistically significant differences in the overall effect by exercise type. Further, clinically relevant improvements in physiological fitness accounted for significant variation (>40%) in the observed effect of exercise training on participation, suggesting a relationship between improved physiological fitness and increased participation. Interestingly, people with progressive MS have demonstrated greater oxygen requirements when completing activities of daily life compared to controls without MS.[77] Further, cross-sectional associations have been reported between cardiorespiratory capacity and instrumental activities of daily living in persons with MS.[78] Importantly, we recognize the potential bi-directional nature of the relationship between physiological fitness and participation, and such associations should be examined in future intervention trials.

*4.3 Limitations*

The current systematic review and meta-analysis have limitations that must be considered when interpreting the results. First, the identification of outcome measures that capture participation can be challenging, with potential for overlap with other component levels, particularly activities. Therefore, there may have been reviewer bias in the selection of studies included in the review. As a result, measures that capture some elements of participation may not have been included in the final analysis. Additionally, many of the retrieved studies included participation outcome measures as a secondary outcome, likely resulting in many studies that were underpowered to detect potential changes in these outcomes. It is also important to acknowledge that despite widespread use, there are no published cut-points for the TESTEX scale, limiting the classification of articles in terms of study quality. The sample size of many of the retrieved studies was relatively small, which may be problematic in terms of power and responsiveness, as the time-course of changes in participation outcomes may differ from other outcomes (i.e., may respond more slowly). Finally, there was a small number of heterogeneous studies within each exercise-type subgroup. Consequently, these effects should be interpreted with caution at this stage.

## 5. Conclusion

The findings from this review demonstrate considerable variability in how participation has been captured in MS exercise studies. A range of participation categories was represented across the identified outcome measures, with a notable focus on involvement in mobility. Our characterization of outcome measures that capture participation using established ICF coding rules can be used to inform the selection of outcomes in future studies of exercise training in people

with MS. Additionally, exercise training had a moderate, positive effect on participation. Given the importance of participation for people living with MS, such outcomes deserve more attention and inclusion in future exercise studies with people who have MS.

**Authors' contributions**

TE conceptualized the idea and objective of the review, performed the literature searches, data extraction, methodological quality assessment, ICF coding, meta-analysis, and was responsible for drafting the manuscript. ASM performed data extraction and methodological quality assessment. AOF performed data extraction and ICF coding. UD conceptualized the idea and objective of the review. LAP conceptualized the idea and objective of the review and assisted in methodological quality assessment and ICF coding. All authors provided feedback and critically revised the manuscript. All authors approved the final version of the manuscript.

**Conflict of interest**

No authors have conflicts of interests.

**Acknowledgement**

Funding for this review and collaboration were provided by the Canadian Institutes of Health Research Canada Graduate Scholarship and the Michael Smith Foreign Study Supplement program.

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**Table 1:** Summary of the 49 articles included in the systematic review separated by exercise type. Values are reported as means ± SD unless specified otherwise.

| Study | Design | Modality/ method | *n* | Age (year) | Diagnosis (year) | Male/ Female | EDSS | Duration (week) | Frequency (sessions/week) | Time (mins) | Intensity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Aerobic training (*n* = 23)** | | | | | | | | | | | |
| Backus et al. (2017)[24] | Pre-post | EX:FES | 14 | 55.3 ± 11.0 | 15.3 ± 7.4 | 7/7 | NR | 4 | 3 | 30 | 35-50rpm |
| Baquet et al. (2018)[25] | RCT | EX: Cycling | 34 | 38.2 ± 9.6 | 6.8 ± 5.5 | 13/21 | 1.7 ± 0.9 | 12 | 2 or 3 | 30–60 | Watts corresponding to 60%$VO_{2peak}$ |
| | | CON: NI | 34 | 39.6 ± 9.7 | 5.7 ± 6.3 | 9/25 | 1.8 ± 1.0 | – | – | – | – |
| Barclay et al. (2019)[26] | RCT | EX: Cycling | 15 | 38.2 ± 9.6 | 6.8 ± 5.5 | 6/9 | 7.2 ± 0.2 | 4 | 5 | 30 | RPE: 12–14 / 20 |
| | | CON: UC | 9 | 39.6 ± 9.7 | 5.7 ± 6.3 | 3/6 | 7.3 ± 0.2 | – | – | – | - |
| Beer et al. (2008)[27] | RCT | EX1: RAGT | 19 | 49.7 ± 11.0 | 15.0 ± 8.0 | 7/12 | 6.5 (6–7.5)^ | 3 | 5 | 30 | 1.0–2.8 km/h |
| | | EX2: CWT | 19 | 51.0 ± 15.3 | 15.0 ± 9.0 | 5/11 | 6.5 (6–7.5)^ | | | | |
| Cakt et al. (2010)[28] | RCT | EX1: Cycling | 14 | 36.4 ± 10.5 | 9.2 ± 5.0 | 5/9 | NR | 8 | 2 | NR | EX1: 15 sets of 40% $WR_{peak}$ (2 min/set) |
| | | EX2: Cycling | 10 | 43.0 ± 10.2 | 6.2 ± 2.2 | 2/8 | NR | 8 | 2 | NR | EX2: 15 sets of 40% $WR_{peak}$ (2 min/set) |
| | | CON: NI | 9 | 35.5 ± 10.9 | 6.6 ± 2.4 | 3/6 | NR | – | – | – | – |
| Calabrò et al. (2017)[29] | RCT | EX1: RAGT | 20 | 41 (38-47)^ | 11.5 (8-14)^ | 8/12 | 3.8 ± 1.5 | 8 | 5 | 40 | 70%BWS |
| | | EX2: RAGT-VR | 20 | 44 (40-48)^ | 11.5 (8-16)^ | 7/13 | 3.8 ± 1.5 | 8 | 5 | 40 | 70%BWS |
| Collett et al. (2011)[30] | RCT | EX1: Cycling | 20 | 52.0 ± 8.0 | 15.0 ± 8.0 | 4/16 | NR | 12 | 2 | 20 | EX1: 45% WRpeak (interval) |
| | | EX2: Cycling | 18 | 50.0 ± 10.0 | 11.0 ± 7.0 | 4/14 | NR | 12 | 2 | 20 | EX2: 30s 90% WR, 30s rest (continuous) |
| | | EX3: Cycling | 17 | 55.0 ± 10.0 | 12.0 ± 11 | 8/9 | NR | 12 | 2 | 20 | EX3: 10min interval / 10min continuous |
| Heine et al. (2017)[31] | RCT | EX: Cycling | 43 | 43.0 ± 9.8 | 7.0 ± NR | 11/32 | NR | 16 | 3 | 6×3 min | $WR_{peak}$:40–80%, interval training |
| | | CON: UC | 46 | 48.2 ± 9.2 | 12.0 ± NR | 13/13 | NR | | | | |
| Jackson et al. (2012)[32] | Pre-post | EX: Kickboxing | 15 | 49.5 ± 11.7 | 12.1 ± 5.5 | 2/9 | 4.1 ± 2.1 | 5 | 3 | 60 | RPE <5 / 10 |
| Kargarfard et al. (2012)[33] | RCT | EX: Aquatic | 16 | 33.7 ± 8.6 | 4.9 ± 2.3 | NR | 2.9 ± 0.9 | 8 | 3 | 60 | $HR_{peak}$:50–75% |
| | | CON: NI | 16 | 31.6 ± 7.7 | 4.6 ± 1.9 | NR | 3.0 ± 0.7 | – | – | – | – |
| Learmonth et al. (2011)[34] | RCT | EX: Cycling | 20 | 51.4 ± 8.1 | 13.4 ± 6.4 | 5/15 | 6.1 ± 0.4 | 12 | – | 60 | interval training |
| | | CON: NI | 12 | 51.8 ± 8.0 | 12.6 ± 8.1 | 4/8 | 5.8 ± 0.5 | – | – | – | – |
| McAuley et al. (2007)[35] | RCT | EX: AT | 13 | NR | NR | NR | NR | 12 | 3 | 60 | 50% age-predicted $HR_{max}$ |
| | | CON: NI | 13 | NR | NR | NR | NR | | | | |
| McCullagh et al. (2008)[36] | RCT | EX: AT | 17 | 40.5 ± 12.7 | 5.4 ± 4.3 | 3/10 | NR | 12 | 2 | 60 | RPE: 11–13 / 20 |
| | | CON: NI | 13 | 33.6 ± 6.1 | 5.0 ± 3.5 | 3/14 | NR | | | | |
| | RCT | EX: Cycling | 25 | 32.0 ± 2.8 | 2.7 ± 1.8 | 0/25 | 1.8 ± 0.4 | 8 | 3 | 42–66 | $WR_{peak:}$ 60%, interval training |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mokhtarzade et al. (2017)[37] | | CON: NI | 20 | 31.3 ± 3.3 | 3.5 ± 1.3 | 0/20 | 1.6 ± 0.6 | | | | |
| Mostert et al. (2002)[38] | RCT | MS-EX | 13 | 45.2 ± 8.7 | 11.2 ± 8.5 | 3/10 | 4.6 ± 1.2 | 4 | 5 | 30 | – |
| | | MS-NI | 13 | 43.9 ± 13.9 | 12.6 ± 8.1 | 2/11 | 4.5 ± 1.9 | – | – | – | – |
| | | CG-EX | 13 | 44.7 ± 10.0 | – | 3/10 | – | | | | |
| | | CG-NI | 13 | 41.7 ± 11.2 | – | 2/11 | – | – | – | – | – |
| Niwald et al. (2017)[39] | RCT | EX: Cycling | 21 | 57.2 ± 7.6 | 13.9 ± 11.5 | 8/13 | 6.3 ± 0.9 | 4 | 5 | 3x10 | 25W/min |
| | | CON: NI | 32 | 59.7 ± 4.2 | 12.2 ± 10.5 | 11/21 | 6.2 ± 1.1 | – | – | – | – |
| Oken et al. (2004)[40] | RCT | EX1: Yoga | 26 | 49.8 ± 7.4 | NR | NR | 3.2 ± 1.7 | 24 | 1 | 90 | – |
| | | EX2: Cycling | 21 | 48.8 ± 10.4 | NR | NR | 2.9 ± 1.7 | 24 | 1 | NR | RPE = 2–3 / 10 |
| | | CON: NI | 22 | 48.4 ± 9.8 | NR | NR | 3.1 ± 2.1 | – | – | - | – |
| Petajan et al. (1996)[41] | RCT | EX: Cycling | 21 | 41.1 ± 2.0 | 9.3 ± 1.6 | 6/15 | 3.8 ± 0.3 | 15 | 3 | 40 | 60% $VO_{2peak}$ |
| | | CON: NI | 25 | 39.0 ± 1.7 | 6.2 ± 1.1 | 9/16 | 2.9 ± 03 | – | – | – | – |
| Pilutti et al. (2011)[42] | Pre-post | EX: Stepper | 6 | 48.2 ± 9.3 | 11.5 ± 6.6 | 2/4 | 6.9 ± 1.1 | 12 | 2 | 45 | 1.1–1.6 km/h |
| Pilutti et al. (2019)[43] | RCT | EX: FES | 4 | 57.3 ± 6.0 | 22.3 ± 5.3 | 3/1 | 6.25 ± 0.9^ | 24 | 3 | 10–40 | 50 rpm |
| | | CON: PLC | 4 | 48.5 ± 7.7 | 20.8 ± 8.5 | 4/0 | 6.25 ± 0.5^ | | | | |
| Rietberg et al. (2014)[44] | RCT | EX: MDR | 23 | 45.0 ± 9.9 | 7.0 ± 6.6 | 9/14 | 3.0 ± 3.0^ | 12 | 2 | 45 | 50–70% $VO_{2peak}$ |
| | | CON: UC | 25 | 47.0 ± 8.6^ | 8.0 ± 6.1^ | 8/17 | 4.0 ± 2.0^ | – | – | – | – |
| Straudi et al. (2016)[45] | RCT | EX1: RAGT | 30 | 52.3 ± 11.1 | 13.3 ± 6.6 | 10/17 | 6.4 ± 0.4 | 6 | 2 | NR | 0.1–3.0 km/h |
| | | EX2: CWT | 28 | 54.1 ± 11.4 | 17.8 ± 8.7 | 8/17 | 6.5 ± 0.4 | 6 | 2 | NR | 0.1–3.0 km/h |
| Straudi et al. (2020)[46] | RCT | EX1: RAGT | 36 | 56.0 ± 11.0 | 12.0 (6–19)^ | 12/24 | 6.5 (6–6.5)^ | 4 | 3 | 40 | 50% body-weight support |
| | | EX2: CT | 36 | 55.0 ± 11.0 | 18.0 (9–25)^ | 11/25 | 6.5 (6–6.5)^ | 4 | 3 | 40 | NR |
| **Resistance training (*n* = 9)** | | | | | | | | | | | |
| Aydin et al. (2014)[47] | RCT | EX1:Calisthenics | 16 | 32.6 ± 3.2 | 6.4 ± 2.8 | 7/9 | 3.6 ± 1.3 | 12 | 3 | 60 | NR |
| | | EX2:Calisthenics | 20 | 33.0 ± 4.1 | 7.4 ± 3.4 | 9/11 | 3.4 ± 2.1 | 12 | 3 | 60 | NR |
| Dalgas et al. (2010)[48] | RCT | EX: PRT | 15 | 47.7 ± 10.4 | 6.6 ± 5.9 | 5/10 | 3.9 ± 0.9 | 12 | 2 | – | 3 sets / 8–10 repetitions (8–15RM) |
| | | CON: NI | 16 | 49.1 ± 8.4 | 8.1 ± 6.0 | 6/10 | 3.7 ± 0.9 | – | – | – | – |
| Dodd et al. (2011)[49] | RCT | EX: PRT | 36 | 47.7 ± 10.4 | NR | 5/10 | NR | 10 | 2 | NR | 2 sets / 10–12 repetitions (10–12 RM) |
| | | CON: NI | 35 | 49.1 ± 8.4 | NR | 5/10 | NR | – | – | – | – |
| Ertekin et al. (2012)[50] | Pre-post | EX: PRT | 31 | 43.6 ± 8.2 | NR | 15/16 | 4.6 ± 1.3 | 12 | NR | NR | 2 sets / 10–12 repetitions |
| Kierkegaard et al. (2016)[51] | Pre-post | EX: PRT | 20 | 36.3 ± 7.6 | 5.4 ± 3.4 | 4/16 | 1.5^ | 12 | 2 | 60 | 2 sets / 10–12 repetitions (15RM) |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Kjølhede et al. (2018)[52] | RCT | EX: PRT | 18 | 43.0 ± 8.0 | 7.0 ± 7.0 | NR | 2.9 (2.0–4.0)^ | 24 | NR | NR | 3 sets / 6–10 repetitions (6–15RM) |
| | | CON: NI | 17 | | | | | – | – | – | – |
| Mutluay et al. (2008)[53] | RCT | EX: Calisthenics | 22 | 42.7 ± 7.7 | 11.8 ± 7.6 | 7/15 | 5.4 ± 1.4 | 6 | 1 | 50 | NR |
| | | CON: NI | 21 | 40.6 ± 7.3 | 10.7 ± 4.9 | 7/14 | 4.8 ± 1.4 | – | – | – | – |
| Taylor et al. (2006)[54] | Pre-post | EX: PRT | 9 | 45.6 ± 10.7 | 6.0 ± 4.1 | 2/7 | NR | 10 | 2 | – | 2 sets / 10–12 repetitions |
| **Mixed training & other (*n* = 18)** | | | | | | | | | | | |
| Bansi et al. (2013)[55] | RCT | EX1: Cycling | 28 | 52 ± NR | NR | 10/18 | 4.7 ± NR | 3 | 2 | 30 | 70% $HR_{peak}$ /60%$VO_{2peak}$ |
| | | EX2: Aquatic | 24 | 50 ± NR | NR | 17/8 | 4.6 ± NR | 3 | 2 | 30 | 70% $HR_{peak}$ / 60%$VO_{2peak}$ |
| Bjarnadottir et al. (2007)[56] | RCT | EX1: AT/RT | 6 | 38.7 ± NR | 8.7 ± NR | 3/3 | 2.1 ± NR | 5 | 3 | 30 | AT: 55% $VO_{2peak}$<br>RT: 1 set / 10 repetition |
| | | CON: NI | 10 | 36.1 ± NR | 8.3 ± NR | 2/8 | 1.8 ± NR | – | – | – | – |
| Bulguroglu et al. (2017)[57] | RCT | EX1: Pilates | 12 | 45 (39-50)^ | 5 (3-13) | NR | 1.8 (1.1-1.3)^ | 8 | 2 | 60–90 | NR |
| | | EX2: Pilates | 13 | 37 (30-40)^ | 5 (2-10) | NR | 2.0 (1.0-3.0)^ | 8 | 2 | 60–90 | NR |
| | | CON: NI | 13 | 40 (26-43)^ | 3 (1-8.5) | NR | 1.0 (0.5-2.0) | – | – | – | – |
| Carter et al. (2013)[58] | RCT | EX: AT/RT | 15 | 39.5 ± 6.5 | NR | 2/14 | 3.0 ± 1.1 | 10 | 3 | 15 | 50%–70% $HR_{peak}$ |
| | | CON: UC | 13 | 40.9 ± 8.7 | NR | 2/12 | 3.1 ± 1.7 | – | – | – | – |
| Carter et al. (2014)[59] | RCT | EX: AT/RT | 60 | 45.7 ± 9.1 | 8.4 ± 7.4 | 17/43 | 3.8 ± 1.5 | 12 | 3 | 15 | AT: 50%–70% $HR_{peak}$<br>RT: 1–3 sets / 5-20 repetitions |
| | | CON: UC | 60 | 46.0 ± 8.4 | 9.2 ± 7.9 | 17/43 | 3.8 ± 1.5 | – | – | – | – |
| Coote et al. (2017)[60] | RCT | EX1: AT/RT + SCT | 33 | 43.3 ± 9.9 | 6.7 ± 5.7 | 4/29 | 3.3 ± 0.7 | 10 | 6 sessions | – | – |
| | | EX2: AT/RT | 32 | 41.9 ± 9.3 | 7.0 ± 6.1 | 6/26 | 3.3 ±0.7 | 10 | 6 sessions | – | – |
| Garrett et al. (2013)[61] | RCT | EX1: Yoga | 77 | 49.6 ± 10.0 | 11.6 ± 8.0 | 44/19 | NR | 10 | 1 | 60 | NR |
| | | EX2: RT/ AT | 80 | 51.7 ± 10.0 | 9.8 ± 7.0 | 50/13 | NR | 10 | 1 | 60 | AT: 65% $HR_{peak}$<br>RT: 3 sets / 12 repetitions |
| | | EX3: AR/RT | 86 | 50.3 ± 10.0 | 10.5 ± 6.9 | 45/22 | NR | 10 | 1 | 60 | AT: NR<br>RT: NR |
| | | CON: NI | 71 | 48.8 ± 11.0 | 10.6 ± 8.2 | 6/43 | NR | – | – | – | – |
| Gobbi et al. (2016)[62] | Pre-post | EX: AT/RT | 8 | 46.5 ± 8.4 | 8.2 ± 5.2 | 4/4 | 3.3 ± 0.8 | 7 | 3 | 20 | AT: 65–75% $HR_{peak}$<br>RT: 2 sets / 10 repetitions |
| Kahraman et al. (2018)[63] | Pre-post | EX1: Yoga (MS) | 27 | 39.0^ | 6^ | 6/21 | 2.0^ | 24 | 1 | 60 | NR |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | EX2: Yoga (Non-MS) | 17 | 42.0^ | – | 2/15 | | 24 | 1 | 60 | NR |
| Kerling et al. (2015)[64] | RCT | EX1: AT/RT | 30 | 45.6 ± 11.4 | NR | 10/20 | 3.1 ± 1.3 | 12 | 2 | AT:20<br>RT:20 | EX1: 50% WRpeak, RPE ≥ 13<br>2 Sets / 10–15 repetitions, RPE ≥ 13 |
| | | EX2: AT | 30 | 42.3 ± 9.0 | NR | 6/24 | 2.6 ± 1.1 | 12 | 2 | 40 | EX2: 50% $WR_{peak}$, RPE ≥ 13 |
| Konečný et al. (2010)[65] | Pre-post | EX: AT/RT | 15 | 50.7 ± 13.1 | 15.7 ± 14.4 | 3/12 | 2.8 ± 0.7 | | | | |
| Learmonth et al. (2017)[66] | RCT | EX: AT/RT | 29 | 48.7 ± 10.4 | 13.9 ± 8.1 | 1/28 | NR | 15 | AT:2<br>RT:2 | AT:<br>10-30 | AT: NR<br>RT: 1–2 sets / 10–15 repetitions |
| | | CON: NI | 28 | 48.2 ± 9.1 | 13.0 ± 7.7 | 1/27 | NR | | | | |
| McAuley et al. (2015)[67] | RCT | EX: AT/RT | 24 | 59.6 ± 1.4 | 18.1 ± 9.4 | 6/18 | NR | 24 | 3 | NR | |
| | | CON: NI | 24 | 59.8 ± 1.5 | 19.9 ± 9.4 | 6/18 | NR | – | – | – | – |
| Romberg et al. (2005)[68] | RCT | EX: AT/RT | 47 | 43.8 ± 6.3 | 6.0 ± 6.5 | 17/30 | 2.0 (1.5–3.5) | 26 | AT:1<br>RT:3 | NR | NR |
| | | CON: NI | 48 | 43.9 ± 7.1 | 5.5 ± 6.4 | 17/31 | 2.5 (2.0–3.5) | – | – | – | – |
| Sabapathy et al. (2011)[69] | RCT | EX1: AT | 6 | 55.0 ± 7.0 | 10.0 ± 10.0 | 4/12 | | 8 | 2 | | |
| | | EX2: RT | 15 | | | | | 8 | 2 | | |
| Sangelaji et al. (2014)[70] | RCT | EX1: AT/RT | 39 | 33.1 ± 7.7 | NR | 15/24 | NR | 10 | 3 | 40 | AT: 40% $HR_{peak}$ |
| | | CON: NI | 22 | 32.1± 6.4 | NR | 7/15 | NR | – | – | – | – |
| Straudi et al. (2014)[71] | RCT | EX: TOCT | 12 | 49.9 ± 7.5 | 12.2 ± 6.9 | 5/7 | 5.0 ± 0.6 | 2 | 5 | 120 | NR |
| | | CON: UC | 12 | 55.3 ± 13.8 | 18.3 ± 9.5 | 2/10 | 4.8 ± 0.5 | – | – | – | – |
| van der Linden et al. (2014)[72] | Pre-post | EX: Pilates | 15 | 51.0 ± 8.0 | NR | 7/8 | NR | 12 | 1–2 | 60 | NR |

Abbreviations: AT = aerobic training; BWS = body weight support; CON = control group; CWT = conventional walking training; EX = exercise group; FES = functional electrical stimulation; HR = heart rate; $HR_{peak}$ = peak heart rate; MDR = multidisciplinary rehabilitation; MS = multiple sclerosis; NI = no intervention; NR = not reported; PLC = passive leg cycling; PRT = progressive resistance training; RAGT = robot-assisted gait training; RCT = randomized controlled trial; RM = repetition maximum; RPE = Rating of Perceived Exertion; rpm = revolutions per minute; RT = resistance training; TOCT = task-oriented circuit training; UC = usual care; $VO_2$ = oxygen consumption; $VO_{2peak}$ = peak oxygen consumption; VR = virtual reality; $WR_{peak}$ = peak work rate

^ Indicates values reported as median and interquartile range (IQR) or range

**Table 2:** Summary of the 16 participation outcome measures used across the included studies and of the frequency of ICF chapters represented in these 16 measures.

| Participation outcome | Items, subscales | ICF chapter [items] | |
|---|---|---|---|
| **36-Item Short Form Survey** *(SF-36)*<br><br>*Studies:16* | 36 items, 8 subscales<br>(1) Physical function<br>(2) Role physical<br>(3) Bodily pain<br>(4) General health<br>(5) Vitality<br>(6) Social function<br>(7) Emotion role<br>(8) Mental health | **d2 – General tasks and demands [7]**<br>d299 – General tasks and demands, unspecified [7]<br><br>**d4 – Mobility [8]**<br>d4102 – Kneeling [1]<br>d4105 – Bending [1]<br>d4309 – Lifting and carrying, unspecified [1]<br>d4500 – Walking short distances [1]<br>d4501 – Walking long distances [2]<br>d4551 – Climbing [2] | **d5 – Self-care [2]**<br>d5109 – Washing oneself, unspecified [1]<br>d5409 – Dressing, unspecified [1]<br><br>**d8 – Major life areas [1]**<br>d859 – Work and employment, other unspecified [1]<br><br>**d9 – Community, social and civic life [4]**<br>d9201 – Sports [2]<br>d9205 – Socializing [2]<br><br>**Non-participation items [16]** |
| **Multiple Sclerosis Impact Scale** *(MSIS-29)*<br><br>*Studies:14* | 29 items, 2 subscale<br>(1) Physical<br>(2) Phycological | **d1 – Learning and applying knowledge [1]**<br>d1609 – Focusing attention, unspecified [1]<br><br>**d2 – General tasks and demands [4]**<br>d299 – General tasks and demands, unspecified [4]<br><br>**d4 – Mobility [6]**<br>d4458 – Hand and arm use, other specified [1]<br>d4401 – Grasping [1]<br>d4309 – Lifting and carrying, unspecified [1]<br>d4609 – Moving around in different locations, unspecified [1]<br>d4708 – Using transportation, other specified [1]<br>d499 – Mobility, unspecified [1] | **d5 – Self-care [1]**<br>d5309 – Toileting, unspecified [1]<br><br>**d8 – Major life areas [1]**<br>d859 – Work and employment, other unspecified [1]<br><br>**d9 – Community, social and civic life [1]**<br>d9308 – Recreation and leisure, other specified [1]<br><br>**Non-participation items [15]** |
| **Multiple Sclerosis Quality of Life-*54*** *(MSQoL-54)*<br><br>*Studies:10* | 54 items, 12 subscales<br>(1) Physical function<br>(2) Limitations-physical<br>(3) Limitations-emotional<br>(4) Pain<br>(5) Emotional wellbeing<br>(6) Energy<br>(7) Health perceptions<br>(8) Social function<br>(9) Cognitive function<br>(10) Health distress<br>(11) Overall quality of life | **d1 – Learning and applying knowledge [3]**<br>d1609 – Focusing attention, unspecified [3]<br><br>**d2 – General tasks and demands [7]**<br>d299 – General tasks and demands, unspecified [7]<br><br>**d4 – Mobility [8]**<br>d4102 – Kneeling [1]<br>d4105 – Bending [1]<br>d4309 – Lifting and carrying, unspecified [1]<br>d4500 – Walking short distances [1]<br>d4501 – Walking long distances [2] | **d5 – Self-care [3]**<br>d5109 – Washing oneself, unspecified [1]<br>d5309 – Toileting, unspecified [1]<br>d5409 – Dressing, unspecified [1]<br><br>**d7 – Interpersonal interactions and relationships [3]**<br>d7702 –Sexual relationships [3]<br><br>**d8 – Major life areas [1]**<br>d859 – Work and employment, other unspecified [1]<br><br>**d9 – Community, social and civic life [4]** |

| | | | |
|---|---|---|---|
| | (12) Sexual function | d4551 – Climbing [2] | d9201 – Sports [2]<br>d9205 – Socializing [3]<br><br>**Non-participation items [26]** |
| **Godin Leisure-Time Exercise Questionnaire** *(GLTEQ)* *Studies:5* | 3 items | **d9 – Community, social and civic life [3]**<br>d920 – Recreation and leisure [3] | |
| **Functional Independence Measure** *(FIM)* *Studies:4* | 18 items, 2 subscales<br>(1) Physical domain<br>(2) Cognition domain | **d3 – Communication [2]**<br>d329 Communicating – receiving, other unspecified [1]<br>d349 Communication – producing, other unspecified [1]<br><br>**d4 – Mobility [6]**<br>d4200 –Transferring oneself while sitting [3]<br>d4201 – Transferring oneself while lying [1]<br>d469 – Walking and moving, other unspecified [1]<br>d4551 – Climbing [1] | **d5 – Self-care [8]**<br>d5101 – Washing whole body [1]<br>d5109 – Washing oneself, unspecified [1]<br>d5300 – Regulating urination [1]<br>d5301 – Regulating defecation [1]<br>d5309 – Toileting, unspecified [1]<br>d5409 – Dressing, unspecified [2]<br>d550 – Eating [1]<br><br>**d7 – Interpersonal interactions and relationships [1]**<br>d7109 –Basic interpersonal interactions, unspecified [1]<br><br>**Non-participation items [2]** |
| **The Multiple Sclerosis International Quality of Life** *(MUSIQOL)* *Studies:2* | 31 items | **d1 – Learning and applying knowledge [1]**<br>d1609 – Focusing attention, unspecified [1]<br><br>**d2 – General tasks and demands [1]**<br>d2309 – Carrying out daily routine, unspecified [1]<br><br>**d4 – Mobility [3]**<br>d4509 – Walking, unspecified [3] | **d7 – Interpersonal interactions and relationships [11]**<br>d7500 – Informal relationships with friends [3]<br>d7608 – Family relationships, other specified [3]<br>d7700 – Romantic relationships [1]<br>d7701 – Spousal relationships [3]<br>d7702 – Sexual relationships [1]<br><br>**d8 – Major life areas [1]**<br>d859 – Work and employment, other unspecified [1]<br><br>**d9 – Community, social and civic life [1]**<br>d9209 – Recreation and leisure, unspecified [1]<br><br>**Non-participation items [15]** |
| **Leeds Multiple Sclerosis Quality of Life** *(LMSQoL)* *Studies:2* | 8 items | **d7 – Interpersonal interactions and relationships [4]**<br>d7609 – Family relationships, unspecified [4] | **d8 – Major life areas [2]**<br>d8508 – Remunerative employment, other specified [2]<br><br>**d9 – Community, social and civic life [4]**<br>d9201 – Sports [1]<br>d9204 – Hobbies [1] |

| | | | |
|---|---|---|---|
| | | | d9205 – Socializing [2]<br><br>**Non-participation items [7]** |
| **The World Health Organization Quality of Life** *(WHOQOL)* *Studies:2* | 26 items, 4 domains<br>(1) Physical health<br>(2) Psychological health<br>(3) Social relationships<br>(4) Environment | **d2 – General tasks and demands [2]**<br>d2309 – Carrying out daily routine, unspecified [1]<br>d299 – General tasks and demands, unspecified [1]<br><br>**d4 – Mobility [2]**<br>d4559 – Moving around, unspecified [1]<br>d4709 – Using transportation, unspecified [1] | **d7 – Interpersonal interactions and relationships [3]**<br>d7500 – Informal relationships with friends [1]<br>d7509 – Informal social relationships, unspecified [1]<br>d7702 – Sexual relationships [1]<br><br>**d8 – Major life areas [1]**<br>d859 – Work and employment, other unspecified [1]<br><br>**Non-participation items [18]** |
| **Impact of Participation and Autonomy Questionnaire** *(IPA)* *Studies:2* | 41 items, 5 subscales<br>(1) Autonomy indoors<br>(2) Family role<br>(3) Autonomy outdoors<br>(4) Social life/ relationships<br>(5) Work and education | **d4 – Mobility [5]**<br>d4100 – Lying down [1]<br>d4101 – Squatting [1]<br>d4600 – Moving around within the home [2]<br>d499 – Mobility, unspecified [1]<br><br>**d5 – Self-care [8]**<br>d5101 – Washing whole body [ 2]<br>d5309 – Toileting, unspecified [1]<br>d5409 – Dressing, unspecified [2]<br>d550 – Eating [1]<br>d560 – Drinking [1]<br>d599 – Self-care, unspecified [1]<br><br>**d6 – Domestic life [9]**<br>d6409 – Doing housework, unspecified [5]<br>d6509 – Caring for household objects, unspecified [1]<br>d6609 – Assisting others, unspecified [2]<br>d699 – Domestic life, unspecified [1] | **d7 – Interpersonal interactions and relationships [7]**<br>d7100 – Respect and warmth in relationships [1]<br>d7409 – Formal relationships, unspecified [1]<br>d7502 – Informal relationships with acquaintances [1]<br>d7509 – Informal social relationships, unspecified [3]<br>d7709 – Intimate relationships, unspecified [1]<br><br>**d8 – Major life areas [11]**<br>d825 – Vocational training [2]<br>d839 – Education unspecified [2]<br>d8459 – Acquiring, keeping and terminating a job, unspecified [3]<br>d859 – Work and employment, other specified and unspecified [2]<br>d8700 – Personal economic resource [2]<br><br>**d9 – Community, social and civic life [5]**<br>d9205 – Socializing [3]<br>d9209 – Recreation and leisure, unspecified [2]<br><br>**Non-participation items [2]** |
| **Barthel Index** *(BI)* *Studies:2* | 10 items | **d4 – Mobility [3]**<br>d4209 – Transferring oneself, unspecified [1]<br>d4551 – Climbing [1]<br>d465 – Moving around using equipment [1] | **d5 – Self-care [7]**<br>d5108 – Washing oneself, other specified [1]<br>d5208– Caring for body parts, other specified [1]<br>d5300 – Regulating urination [1]<br>d5301 – Regulating defecation [1]<br>d5309 – Toileting, unspecified [1]<br>d5409 – Dressing, unspecified [1]<br>d550 – Eating [1] |
| **Extended Barthel Index** | 16 items | **d3 – Communication [2]** | **d5 – Self-care [7]** |

| | | | |
|---|---|---|---|
| *(EBI)*<br>*Studies:2* | | d329 Communicating – receiving, other unspecified [1]<br>d349 Communication – producing, other unspecified [1]<br><br>**d4 – Mobility [3]**<br>d4209 – Transferring oneself, unspecified [1]<br>d4551 – Climbing [1]<br>d465 – Moving around using equipment [1] | d5108 – Washing oneself, other specified [1]<br>d5208– Caring for body parts, other specified [1]<br>d5300 – Regulating urination [1]<br>d5301 – Regulating defecation [1]<br>d5309 – Toileting, unspecified [1]<br>d5409 – Dressing, unspecified [1]<br>d550 – Eating [1]<br><br>**d7 – Interpersonal interactions and relationships [1]**<br>d729 – General interpersonal interactions [1]<br><br>**Non-participation items [3]** |
| **Functional Assessment of Multiple Sclerosis**<br>*(FAMS)*<br>*Studies:2* | 44 items, 6 domains<br>(1) Mobility<br>(2) Symptoms<br>(3) Emotional wellbeing<br>(4) General contentment<br>(5) Thinking/fatigue<br>(6) Family/social wellbeing | **d1 – Learning and applying knowledge [2]**<br>d1609 – Focusing attention, unspecified [1]<br>d159 – Basic learning, other specified and unspecified [1]<br><br>**d2 – General tasks and demands [3]**<br>d2100 – Undertaking a simple task [2]<br>d299 – General tasks and demands, unspecified [1]<br><br>**d4 – Mobility [3]**<br>d4201 – Transferring oneself while lying [1]<br>d4509 – Walking, unspecified [1]<br>d4601 – Moving around within buildings [1]<br><br>**d5 – Self-care [2]**<br>d5300 – Regulating urination [2] | **d6 – Domestic life [1]**<br>d6609 – Assisting others, unspecified [1]<br><br>**d7 – Interpersonal interactions and relationships [8]**<br>d7500 – Informal relationships with friends [2]<br>d7609 – Family relationships, unspecified [4]<br>d7701 – Spousal relationships [1]<br>d7702 – Sexual relationships [1]<br><br>**d8 – Major life areas [1]**<br>d859 – Work and employment, other specified and unspecified [1]<br><br>**d9 – Community, social and civic life [2]**<br>d9205 – Socializing [2]<br><br>**Non-participation items [2]** |
| **Hamburg Quality of Life Questionnaire Multiple Sclerosis**<br>*(HAQUAMS)*<br>*Studies:1* | 28 items, 5 subscales<br>(1) Fatigue/thinking<br>(2) Mobility lower limb<br>(3) Mobility upper limb<br>(4) Social function<br>(5) Mood | **d1 – Learning and applying knowledge [3]**<br>d159 – Basic learning, other specified & unspecified [1]<br>d1609 – Focusing attention, unspecified [1]<br>d1709 – Writing, unspecified [1]<br><br>**d2 – General tasks and demands [1]**<br>d2109 – Undertaking single tasks, unspecified [1]<br><br>**d4 – Mobility [7]**<br>d4105 – Bending [1]<br>d4500 – Walking short distances [1]<br>d4501 – Walking long distances [1]<br>d4509 – Walking, unspecified [1]<br>d4552 – Running [1] | **d6 – Domestic life [2]**<br>d6309 – Preparing meals, unspecified [1]<br>d6402 – Cleaning living area [1]<br><br>**d7 – Interpersonal interactions and relationships [8]**<br>d7702 – Sexual relationships [1]<br>d7509 – Informal social relationships, unspecified [3]<br>d7609 – Family relationships, unspecified [4]<br><br>**d9 – Community, social and civic life [2]**<br>d9201 – Sports [1]<br>d9205 – Socializing [1] |

| | | | |
|---|---|---|---|
| | | d4600 – Moving around within the home [1]<br>d4601 – Moving around within buildings [1]<br><br>**d5 – Self-care [5]**<br>d5300 – Regulating urination [2]<br>d5301 – Regulating defecation [1]<br>d5409 – Dressing, unspecified [1]<br>d550 – Eating [1] | **Non-participation items [16]** |
| **Baecke Physical Activity Questionnaire**<br>*(BAECKE)*<br>*Studies:1* | 17 items, 3 subscales<br>(1) Work<br>(2) Sport<br>(3) Leisure | **d4 – Mobility [5]**<br>d4509 – Walking, unspecified [3]<br>d4700 – Using human-powered vehicles [2] | **d9 – Community, social and civic life [4]**<br>d9201 – Sports [4]<br><br>**Non-participation items [9]** |
| **Sickness inventory Profile**<br>*(SIP)*<br>*Studies:1* | 68 items, 6 subscales<br>(1) Somatic autonomy<br>(2) Mobility control<br>(3) Psychological autonomy<br>(4) Emotional stability<br>(5) Mobility range<br>(6) Social behavior | **d1 – Learning and applying knowledge [4]**<br>d159 – Basic learning, other specified and unspecified [1]<br>d1709 – Writing, unspecified [1]<br>d1609 – Focusing attention, unspecified [2]<br><br>**d2 – General tasks and demands [1]**<br>d299 – General tasks and demands, unspecified [1]<br><br>**d4 – Mobility [22]**<br>d4100 – Lying down [1]<br>d4102 – Kneeling [1]<br>d4103 – Sitting [1]<br>d4104 – Standing [2]<br>d4109 – Changing basic body position, unspecified [1]<br>d4200 – Transferring oneself while sitting [1]<br>d4201 – Transferring oneself while lying [1]<br>d4408 – Fine hand use, other specified [2]<br>d4500 – Walking short distances [1]<br>d4502 – Walking on different surfaces [1]<br>d4508 – Walking, other specified [1]<br>d4509 – Walking, unspecified [3]<br>d4551 – Climbing [3]<br>d465 – Moving around using equipment [1]<br>d4600 – Moving around within the home [1]<br>d4601 – Moving around within buildings [1] | **d5 – Self-care [8]**<br>d5101 – Washing whole body [2]<br>d5409 – Dressing, unspecified [3]<br>d550 – Eating [2]<br>d560 – Drinking [1]<br><br>**d6 – Domestic life [7]**<br>d649 – Household tasks, other specified/ unspecified [2]<br>d6400 – Washing and drying clothes and garments [1]<br>d6200 – Shopping [1]<br>d6201 – Gathering daily necessities [1]<br>d6402 – Cleaning living area [1]<br>d6409 – Doing housework, unspecified [1]<br><br>**d7 – Interpersonal interactions and relationships [5]**<br>d7702 – Sexual relationships [1]<br>d7109 – Basic interpersonal interactions, unspecified [1]<br>d7609 – Family relationships, unspecified [3]<br><br>**d9 – Community, social and civic life [7]**<br>d9109 – Community life, unspecified [1]<br>d9204 – Hobbies [2]<br>d9205 – Socializing [3]<br>d9208 – Recreation and leisure, other specified [1]<br><br>**Non-participation items [11]** |
| **Late Life Function and Disability Inventory**<br>*(LLFDI)*<br>*Studies:1* | 48 items, 2 components<br>(1) Disability [16]<br>(2) Function [32] | **d2 – General tasks and demands [1]**<br>d2308 – Undertaking multiple tasks, other specified [1]<br><br>**d4 – Mobility [27]** | **d5 – Self-care [6]**<br>d5408 – Dressing, other specified [3]<br>d5701 – Managing diet and fitness [1]<br>d5708 – Looking after one's health, other specified [1] |

| | | | |
|---|---|---|---|
| | | d4103 – Sitting [1]<br>d4104 – Standing [3]<br>d4105 – Bending [1]<br>d4302 – Carrying in the arms [2]<br>d4401 – Grasping [2]<br>d4402 – Manipulating [1]<br>d4408 – Fine hand use, other specified [3]<br>d4450 – Pulling [1]<br>d4452 – Reaching [1]<br>d4501 – Walking long distances [4]<br>d4502 – Walking on different surfaces [3]<br>d4551 – Climbing [2]<br>d4552 – Running [2]<br>d4600 – Moving around within the home [1] | d598 – Self-care, other specified [1]<br><br>**d6 – Domestic life [5]**<br>d6309 – Preparing meals, unspecified<br>d649 – Household tasks, other specified and unspecified<br>d6609 – Assisting others, unspecified<br>699 – Domestic life, unspecified [2]<br><br>**d8 – Major life areas [1]**<br>d855 – Non-remunerative employment [1]<br><br>**d9 – Community, social and civic life [5]**<br>d9205 – Socializing [4]<br>d9209 – Recreation and leisure, unspecified [1]<br><br>**Non-participation items [1]** |

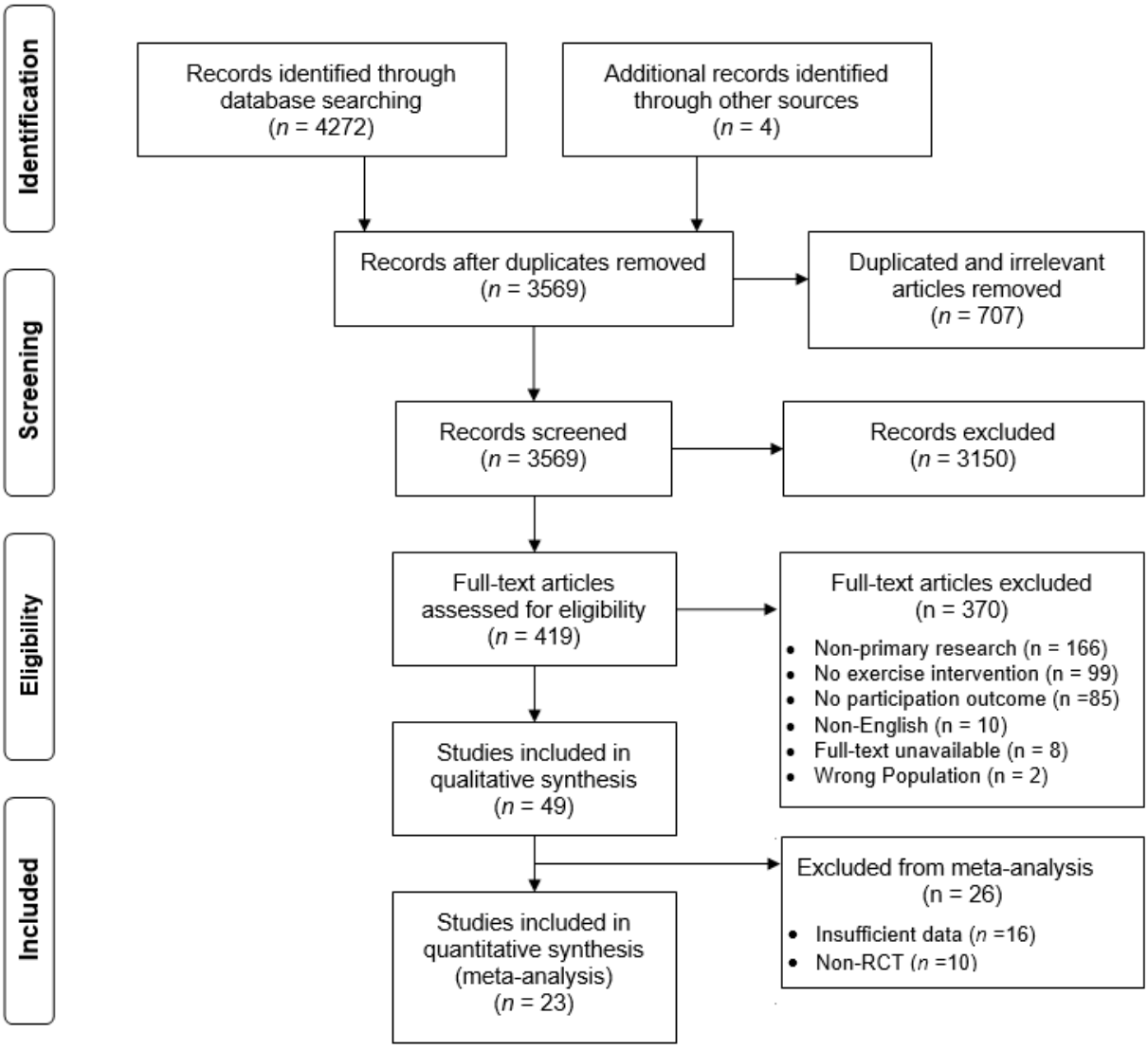


**Fig. 1:** The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of the review.

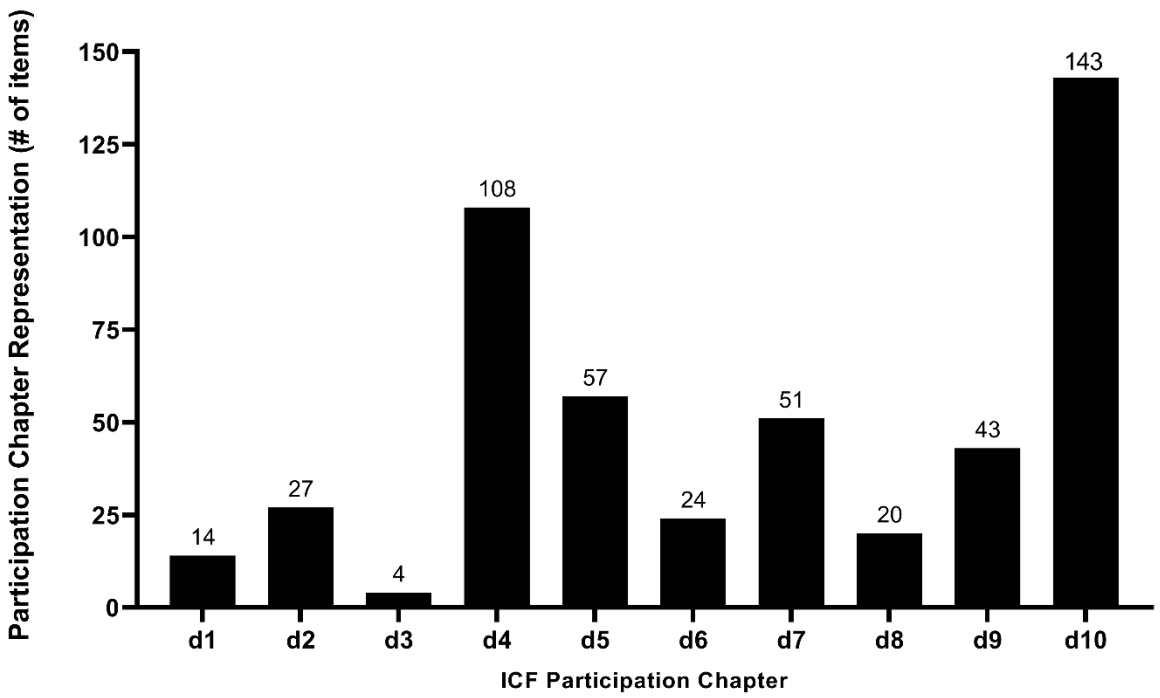


**Fig. 2:** Frequency of ICF participation chapters represented across the retrieved participation outcome measures. d1 = Learning and Applying Knowledge; d2 = General tasks and demands; d3 = Communication; d4 = Mobility; d5 = Self-care; d6 = Domestic life; d7 = Interpersonal Interactions & Relationships; d8 = Major life areas; d9 = Community, Social and Civic Life; d10 = Non-participation Item

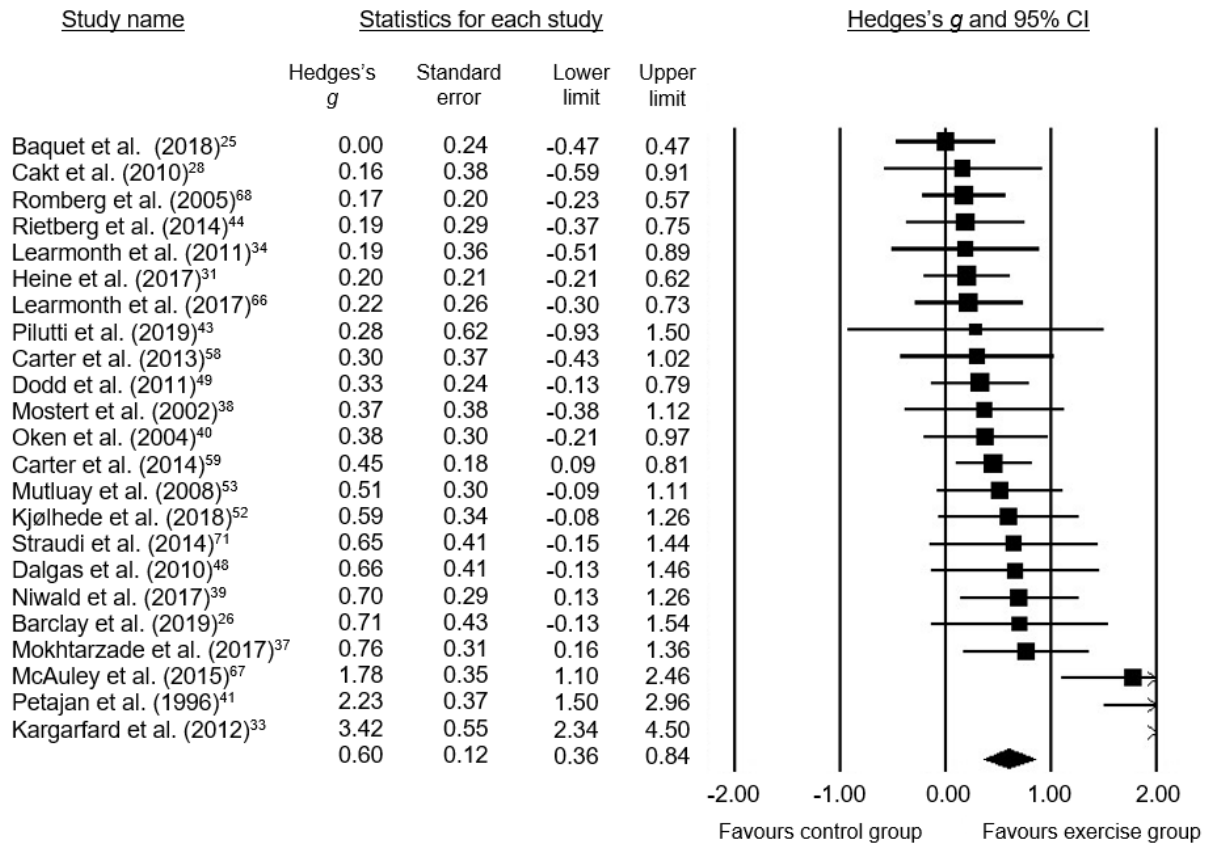


**Fig. 3:** A visual representation of the overall effect size (Hedges' *g*) for all 23 studies included in the meta-analysis.

# CHAPTER 5

## Understanding Exercise Benefits, Barriers, and Needs in Nonambulatory People with Multiple Sclerosis

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**Abstract**

**Purpose**: The purpose of this study was to identify perceived benefits of and barriers to exercise engagement in nonambulatory people with MS. This study further aimed to identify and rank needs for community exercise in nonambulatory people with MS.

**Methods:** 101 people with MS (Patient Determined Disease Steps score = 6–7; mean age = 60.1 years; disease duration = 25.6 years) participated in this cross-sectional survey study. Perceived exercise benefits and barriers were measured with the Exercise Benefits and Barriers Scale (EBBS). Needs for community exercise engagement were assessed using a comprehensive needs assessment protocol guided by the Concerns Report Methodology.

**Results:** Nonambulatory people with MS identified physical health improvements and personal accomplishment as the top benefits of exercise participation. Environmental barriers and perceived symptomatic changes were identified as the top challenges limiting exercise engagement. Nonambulatory people with MS reported that exercise facilities were failing to accommodate their needs, specifically citing exercise equipment shortcomings. Additionally, participants conveyed satisfaction with exercise professionals, specifically expressing that professionals were knowledgeable about exercise.

**Discussion:** Exercise promotion efforts in people with MS who are nonambulatory should reinforce the physical health benefits of exercise and promote opportunities for personal accomplishment. Knowledgeable exercise professionals may play a valuable role in the delivery of such initiatives in community settings. Results highlight the need to increase program and facility access and opportunities to support participation in community exercise for this population.

**Keywords:** Multiple sclerosis, exercise, nonambulatory, wheelchair users, needs assessment

## INTRODUCTION

It is estimated that approximately 30% of people with multiple sclerosis (MS) experience mobility limitations that require the use of a wheelchair for assistance in daily life [1]. This subset of the MS population experience greater symptomatic burden and have reported lower quality of life compared to people with MS with less disability [2–4]. Given the limited efficacy of pharmacological treatments for disease management in people with MS with progressed disability, alternative strategies such as exercise training are an important component of comprehensive care for nonambulatory people with MS [5].

There is substantial evidence for the benefits of exercise training for people with MS who have mild-to-moderate disability [6–8]. Few studies have examined the role of exercise training for nonambulatory people with MS, and report preliminary benefits on some aspects of fatigue, muscular fitness, and spasticity [9,10]. Importantly, low rates of exercise engagement after such interventions suggests current exercise opportunities may not meet the unique needs of this population [9,11]. This may be due to the fact that most exercise interventions have been conducted in highly controlled environments that do not account for practical factors that influence exercise engagement within a community setting. As a result, strategies to support long-term exercise engagement among people with MS who are nonambulatory are needed.

Understanding the perceived benefits of and barriers to exercise engagement is one approach for informing the development of strategies for promoting community exercise engagement. Previous investigations exploring the benefits of exercise have identified improved health outcomes and feelings of accomplishment as perceived benefits of exercise in people with MS [12–14]. Perceived barriers to exercise reported by people with MS have included symptoms of fatigue, physical exertion, impairment due to MS, lack of time, lack of support and advise, and

environmental limitations [12–14]. Importantly, these previous investigations have primarily included individuals with mild-to-moderate disability, limiting our understanding of the possible unique benefits of and challenges to exercise for nonambulatory people with MS.

Qualitative research has begun to characterize the lived experiences and perspectives of participation in physical activity and exercise in people with MS who are wheelchair users [9,15]. One qualitative study involving 15 nonambulatory people with MS highlighted a key role for mobility devices, environmental adaptations, and tangible supports in maximizing participation in daily physical activity [8]. Results from this study further highlighted the importance of accessible opportunities for physical activity and exercise, and the role of healthcare professionals as promoters of these opportunities [15]. Applying a Social Cognitive Theory lens, another qualitative study in 20 people with MS who used wheelchairs for mobility reported that increasing self-efficacy, knowledge accrual, education on outcomes of regular exercise engagement, and support through external and internal sources may support exercise participation in this population [2]. These studies provide key guidance for informing the development of targeted physical activity and exercise interventions for people with MS who are wheelchair users.

Another approach for informing health promotion initiatives is a comprehensive needs assessment. A needs assessment is a systematic process used to determine and address the needs of a population in order to better provide services or programming [16]. A comprehensive needs assessment includes the opportunity for input from the target population, and has been identified as an essential step for developing effective health programs [16,17]. To date, one comprehensive needs assessment of physical activity engagement in people with moderate-to-severe MS disability has been conducted [18]. Results from this study indicated that the lack of exercise resources and information were the top unmet physical activity needs for people with moderate-to-severe MS.

Notably, there have been no assessments of needs surrounding exercise engagement in nonambulatory people with MS. Such inquiry would be valuable to identify current unmet needs for community exercise in nonambulatory people with MS, and to provide key direction for increasing opportunities for exercise in this population.

To inform strategies for promoting community exercise engagement in nonambulatory people with MS, a cross-sectional survey study was undertaken. The objectives of this study were to: (1) identify the perceived benefits of and barriers to exercise engagement in nonambulatory people with MS; and (2) identify and rank the most important exercise needs for nonambulatory people with MS.

## Methods

### *Procedures*

The study protocol was approved by Health Sciences and Science Research Ethics Board [REB H-12-20-6324] at the University of Ottawa. Participants were recruited from online outlets including the MS Society of Canada's Research Portal, monthly MS Society of Canada newsletters, and social media platforms. A secure hyperlink containing access to the online survey was disseminated using these outlets. Interested participants were invited to follow the hyperlink to access the online survey administered through an institutional SurveyMonkey (SurveyMonkey, San Mateo, CA, USA) account. Interested participants were screened online to determine eligibility. Eligible participants were then invited to complete the informed consent process and the questionnaire items. The survey took approximately 25 minutes to complete and was administered between March-April 2021. Participants received a $10 online gift card for completing the study.

### *Participants*

The eligibility criteria were: (1) age ≥18 years; (2) currently residing in Canada; (3) ability to complete an online survey in English; (4) self-reported diagnosis of MS; (5) self-reported use of a wheelchair or scooter as primary method of mobility; and (6) no self-reported cognitive impairment that interferes with daily functioning.

### *Survey Measures*

#### *Sociodemographic characteristics*

Sociodemographic variables including age, gender, living situation (i.e., independent or assisted), annual income, employment status, and community population size were collected using a study-specific questionnaire. Community population size was characterised as rural, suburban, or urban using Statistics Canada definitions [19].

#### *Clinical characteristics*

Disease duration, MS clinical course, and use of assistive devices were collected using a study-specific questionnaire. Self-reported disability level was captured using the Patient Determined Disease Steps (PDDS) scale. The PDDS is a 9-item scale in which participants identify their level of disability, specifically their level of mobility impairment and symptom burden due to MS [20]. The PDDS scale is strongly correlated ($r$=0.78) with the Extended Disability Status Scale (EDSS), a clinically-administered metric of MS-related disability [20].

#### *Physical activity and exercise experience*

Current physical activity levels were measured using the Physical Activity Scale for Individuals with Physical Disabilities (PASIPD) [21]. The PASIPD is a 13-item questionnaire that captures the number of hours spent in recreational, household, and occupational physical activities during the last 7-days. Each item is multiplied by an associated metabolic equivalents (MET) value to an individual item score. Total PASIPD scores were calculated as the sum of all individual item scores, with higher PASIPD scores indicating greater physical activity engagement. Prior exercise experience was characterized with a study-specific questionnaire in which participants identified the type and duration of community exercise that they have engaged in previously.

*Perceived benefits of and barriers to exercise*

Perceived exercise benefits and barriers were measured with the Exercise Benefits and Barriers Scale (EBBS) [22]. The EBBS is a 43-item questionnaire that produces two scores: an EBBS benefits score and an EBBS barriers score. Items composing the EBBS benefits scale are scored from 1 (*item not believed to be a benefit*) to 4 (*item strongly believed to be a benefit*). Higher EBBS benefit scores indicate greater perceived benefits of exercise. Items composing the EBBS barrier scale are scored from 1 (item *strongly believed to be a barrier*) to 4 (*item not believed to be a barrier*). The EBBS barrier items are reverse scored, with lower values indicating greater perceived barriers to exercise.

*Exercise needs assessment*

Questions assessing community exercise needs were developed using the Concerns Report Methodology, a standardized protocol applied in previous needs assessments in people with MS [18,23]. Participants rated the perceived importance of and satisfaction with 28 different aspects

of exercise opportunities. Items were informed by previous qualitative studies involving nonambulatory people with MS and previous needs assessments with people with MS [15,18,24]. The 28 items were characterized into four distinct themes including: “exercise facilities and equipment needs”; “exercise program needs”; “personnel/professional needs”; and “education needs”. Each item was scored on a 5-point Likert scale with responses ranging from 1 (*very unimportant/unsatisfied*) to 5 (*very important/satisfied*). Participant responses were used to calculate a ‘Need Index’ which represents the magnitude to which a specific need is being unmet or fulfilled [23]. Need Index values were calculated per item using the following formula:

$$\left(\frac{4n(4)+\ 3n(3)+\ 2n(2)+\ 1n(1)+\ 0n(0)x\ 100}{N(4)} = \%\frac{\text{Importance}}{\text{Satisfaction}}\right)$$

where *4n* denotes the number of participants who score the item a 4, *3n* denotes the number of participants who score the item a 3, *2n* denotes the number of participants who score the item a 2, *1n* denotes the number of participants who score the item a 1, *0n* denotes the number of participants who score the item a 0, and *N* denotes the sample size [23]. The proportion of respondents who state an item is important and the proportion of respondents who state that they are satisfied with the item is then calculated using the formula. The Need Index for each item is calculated as the difference between the perceived importance and perceived satisfaction with the item, with larger values indicating a greater perception of the need being unmet.

***Data analysis***

Data were downloaded from SurveyMonkey and imported into IBM SPSS Statistics (Version 27.0, IBM Corp., Armonk, NY). Sociodemographic and clinical characteristics were summarized using descriptive and frequency statistics. Total EBBS benefits and barriers scores were computed and summarized with descriptive statistics. Mean values for individual EBBS and Needs Index items

were calculated and ranked. Values within the text are presented as mean (SD), unless noted otherwise.

## Results

### *Participants*

A flowchart of the study recruitment process is presented in Figure 1. A total of 216 individuals accessed the survey hyperlink, and 101 submitted the survey with complete data. A summary of the sociodemographic and clinical characteristics of participants is presented in Table 1. The sample was predominantly female (72.3%) with a mean age of 60.1 (8.4) years. Most participants reported independent living with a family member (71.3%). The mean disease duration of the sample was 25.6 (9.1) years, and most participants reported a progressive MS course (93.1%).

### *Physical activity and exercise experience*

The mean PASIPD score of the current sample was 16.5 (14.6), and was lower than that reported in previous studies involving neurologically impaired wheelchair users [25,26]. The majority of respondents (~87%) reported current or past participation in some form of community exercise. Exercise classes were the most common form of community exercise among respondents, with 61 people indicating current or past participation in exercise classes (Table 1).

### *Perceived benefits of and barriers to exercise*

The top five perceived benefits of and barriers to exercise in nonambulatory people with MS are presented in Table 2. The mean EBBS benefit score was 85.3 (10.5). Participants identified a "s*ense of personal accomplishment*" as the greatest perceived benefit associated with exercise

engagement with a mean score of 3.50 (0.56). The other top four benefits identified focused on physical health benefits. Conversely, the mean EBBS barrier score was 33.1 (4.6). Participants identified *"too few places to exercise"* as the greatest perceived barrier to exercise, with a mean barrier score of 1.56 (0.76). Limitations in accessing exercise facilities and perceived fatigue associated with exercise engagement were other top barriers identified by the sample.

### *Exercise needs assessment*

The top five unmet and fulfilled exercise needs identified by nonambulatory people with MS are presented in Table 3. Three of the top five unmet needs were categorized as "exercise facilities needs", one unmet need was categorized as an "education need", and one unmet need was characterized as an "exercise program need". A "*lack of useful exercise information from my neurologist*" was identified as the greatest unmet exercise need (Needs Index = 67.1). Four of the top five fulfilled needs were categorized as "personnel/professional needs", while one fulfilled need was characterized as an "education need". The most fulfilled need was that *"professionals have strong knowledge of exercise"* (Needs Index = 0.5).

## Discussion

This study characterized the perceived benefits of, barriers to, and needs for exercise engagement in a nonambulatory sample of Canadian adults living with MS. Our results indicate that nonambulatory people with MS perceive physical health improvements and personal accomplishment as the greatest benefits of exercise engagement. The current sample identified environmental barriers and beliefs surrounding symptomatic changes as key challenges to exercise. The greatest unmet needs for exercise primarily centered around exercise facilities,

particularly exercise equipment. Further, nonambulatory people with MS expressed satisfaction with exercise professionals, specifically their knowledge regarding exercise. Results from this study can be used to inform the design and implementation of pragmatic exercise programs and supports for nonambulatory people with MS.

### *Benefits of and Barriers to Exercise in Nonambulatory People with MS*

The greatest perceived benefits of exercise identified by the current sample were items related to improvements in physical health and personal accomplishment. A previous investigation of ambulatory people with MS (PDDS = 0 – 6.0) identified similar items as key benefits of exercise engagement (e.g., *exercise gives me a sense of personal accomplishment, exercise increases my muscle strength*) using the EBBS [12]. Further, the EBBS benefit score of the current sample (EBBS benefit score = 85.3) was consistent with scores reported in that previous study (EBBS benefit score = 87.0) [12]. These findings suggest that nonambulatory people with MS, like those with MS who have less disability, are well-aware of potential benefits associated with exercise engagement, and recognize exercise as a valuable strategy for improving physical health outcomes [12].

While most of the benefits identified focused on physical health outcomes, the top-rated exercise benefit reported by the current sample was the '*sense of personal accomplishment'* associated with exercise engagement, which may be fostered through exercise programs and settings that provide opportunities for success and mastery. Mastery experiences provide direct evidence that an individual can successfully complete a task, and can be used to build self-efficacy for exercise [27]. Importantly, high exercise self-efficacy has been associated with long-term exercise engagement in people with MS (mean PDDS = 2.16), and has been identified as a direct

determinant of exercise engagement in nonambulatory people with MS [2,28]. Further, one qualitative study with 35 people with MS identified opportunities to exercise with others of similar ability levels, specialized exercise support, and improving exercise accessibility as potential solutions to address key exercise barriers experienced, and to promote exercise self-efficacy. Collectively, strategies that promote mastery and improve exercise self-efficacy may play a key role in promoting community exercise in non ambulatory people with MS.

While the perceived benefits of exercise were consistent between nonambulatory people with MS and those previously reported in people with MS who have lower disability, there were differences in perceived exercise barriers between these two groups. In the current sample, most top raking exercise barriers were environmental in nature (e.g., *"There are too few places for me to exercise"*). Conversely, people with MS who have lower disability identified fatigue (e.g., *"Exercise tires me"*) as the most prominent barrier to exercise [12]. While the top exercise barriers differed between nonambulatory and ambulatory people with MS in terms of overall ranking, the item scores were comparable between these two samples. For instance, EBBS Item number 6 ("*Exercise tires me"*) was the top ranked exercise barrier in people with MS who have lower disability [12], yet the same item was ranked as the 5$^{th}$ most prominent exercise barrier among nonambulatory people with MS. Despite this difference in ranking, the mean item score in the present sample (2.10) was similar to that reported in the previous sample with lower disability (2.07) [12]. This finding suggests that nonambulatory people with MS do not experience different exercise barriers than those who have lower disability, but rather endure more environmental barriers in addition to common exercise barriers experienced by people with MS overall. This notion is supported by a considerably lower EBBS barrier score (i.e., greater perceived barriers)

in the current sample (EBBS barrier score = 33.1) compared to people with MS who had lower disability (EBBS barrier score = 39) [12].

When examining the greatest perceived exercise barriers, it is evident there is a lack of access and opportunity for nonambulatory people with MS to participate in exercise. This is unsurprising given wheelchair users typically experience reduced societal participation due to accessibility constraints and limited transportation options [29]. Accessibility of exercise facilities remains an issue for those with substantial disability, as these facilities regularly fail to meet basic accessibility guidelines, particularly with regards to equipment accessibility [30,31]. Given the complexity of this issue, multi-level strategies are necessary for increasing opportunities for people with disabilities to access and engage in exercise. Increased advocacy efforts, policy development, and service and resource allocation are all strategies that can be applied to increase opportunities for community exercise for people with disabilities, including nonambulatory people with MS [32].

Telerehabilitation and home-based exercise have been proposed as alternatives to in-person exercise settings that might alleviate some environmental exercise barriers cited by the current sample. One qualitative study involving 20 nonambulatory people with MS reported that the majority of participants expressed interest in telerehabilitation or home-based exercise programming in some capacity [24]. However, despite this interest, participants also cited the desire to exercise in a community-setting, due to social interaction and enjoyment [24]. Furthermore, little is known about the safety and efficacy of home-based exercise for nonambulatory people with MS. While telerehabilitation and home-based exercise offer much needed flexibility and opportunity for nonambulatory people with MS to engage in exercise, future research is needed to establish the feasibility, efficacy, and satisfaction of such programs.

The current sample of nonambulatory people with MS also noted fatigue symptoms as an exercise barrier. Similarly, concerns about fatigue symptoms have been expressed and recognized as an exercise deterrent in people with MS who have lower disability [14]. Previous investigations have reported no significant increase in fatigue symptoms in response to acute exercise in people with MS who had minimal disability (mode PDDS = 1.0) [33], and meta-analyses support the benefits of exercise training for reducing fatigue symptoms in people with mild-to-moderate MS[34,35]. To date, there have been no investigations of the acute symptomatic response to exercise in nonambulatory people with MS, and little is know about the long-term effects of exercise for managing MS symptoms in this population. Such investigations would seemingly provide valuable information for guiding exercise promotion and recommendations for nonambulatory people with MS in clinical and community settings.

***Exercise Needs of Nonambulatory People with MS***

Nonambulatory people with MS identified "*Useful exercise information from my neurologist*" as the foremost unmet exercise need, reinforcing the important role of physicians in facilitating exercise promotion and engagement in nonambulatory people with MS [36–38]. These results are consistent with a previous needs assessment involving 78 people with MS with moderate disability (mean PDDS = 5.0), which also reported a lack of available exercise information as the greatest unmet exercise need [18]. Despite recent support for increased education on exercise in medical school curriculums, there remains a lack of knowledge pertaining to exercise among health care providers [39]. Additionally, health care providers are often unable to discuss exercise information with patients due to time constraints [40]. Increased education and resources for physicians may

be an important component to facilitating exercise engagement in nonambulatory people with MS, especially as physicians are often recognized as a credible source of health information [39,40].

The current nonambulatory sample consistently identified that exercise facilities were failing to meet their exercise needs, specifically related to sufficient and accessible options for exercise. These unmet needs are congruent with the environmental exercise barriers cited by the sample. Future investigations into exercise equipment use in nonambulatory people with MS would be valuable for facilitating exercise engagement for nonambulatory people with MS.

While highlighting unmet exercise needs is valuable, it is also important to acknowledge the exercise needs that nonambulatory people with MS believe are being fulfilled. The current sample conveyed satisfaction with exercise professionals/personnel, expressing that these individuals were knowledgeable about exercise and could promote motivation and accountability. This demonstrates that nonambulatory people with MS recognize exercise professionals as resources that can assist them to achieve their exercise goals, and this can be leveraged in future exercise programming following an asset-based approach. Asset- or strengths-based approaches aim to identify, mobilise, and capitalize on pre-existing resources (i.e., assets) to promote health and have been applied in health promotion efforts in other underserved populations [41]. Asset-based approaches to health promotion are particularly useful in situations where resources are finite [42], and thus represent a valuable approach for promoting community exercise engagement in nonambulatory people with MS.

### *Limitations of the Study*

This study has limitations that should be considered when interpreting the findings. First, responses to this survey were collected during the COVID-19 pandemic, which may have influenced

participants' perceptions about exercise engagement given increased restrictions and lock-down procedures imposed. Another limitation of this study was the self-reported nature of the survey, as such clinical variables such as disability level and disease course were not verified through medical records. The online survey design represents another potential limitation. It is possible that this distribution strategy resulted in a biased sample consisting primarily of individuals with high technological proficiency that were able to access and complete the online survey.

## Conclusion

Nonambulatory people with MS identified physical health improvements and personal accomplishment as the top benefits associated with exercise engagement. These individuals also identified environmental barriers as the most prominent challenges to engaging in exercise. Given these environmental barriers, it is unsurprising that many nonambulatory people with MS reported that exercise facilities failed to accommodate their needs. Collectively, these findings point to the need for increased opportunities for nonambulatory people with MS to access and engage in community exercise, and this may be facilitated through the involvement of knowledgeable exercise professionals.

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**Table 1:** Sociodemographic, clinical, and physical activity and exercise characteristics of the sample. Values are presented as *n* (%) unless specified otherwise.

| | |
|---|---|
| **Sociodemographic Characteristics** | |
| Age, years^ | 60.1 (8.4) |
| Gender | |
| *Female* | 73 (72.3%) |
| *Male* | 28 (27.7%) |
| Living situation | |
| *Living with family* | 72 (71.3%) |
| *Assistive living* | 20 (19.8%) |
| *Living alone* | 9 (8.9%) |
| Annual household income | |
| *<$15,000* | 23 (22.8%) |
| *$15,000-$50,000* | 14 (13.9%) |
| *$50,000 - 100,000* | 37 (36.6%) |
| *>$100,000* | 27 (26.7%) |
| Employment status | |
| *Unable to work due to illness or disability* | 43 (42.6%) |
| *Retired* | 34 (33.7%) |
| *Employed* | 19 (18.8%) |
| *Unemployed* | 5 (4.9%) |
| Community population | |
| *Small population (rural)* | 12 (11.9%) |
| *Medium population (suburban)* | 30 (29.7%) |
| *Large population (urban)* | 59 (58.4%) |
| **Clinical Characteristics** | |
| Disease duration, years^ | 25.6 (9.1) |
| MS type | |
| *Progressive MS* | 94 (93.1%) |
| *Relapsing MS* | 7 (6.9%) |
| PDDS | |
| *7.0 (Wheelchair)* | 77 (76.2%) |
| *6.0 (Bilateral Support)* | 24 (23.8%) |
| Assistive device | |
| *Electric wheelchair/scooter* | 42 (41.6%) |
| *Manual wheelchair* | 35 (34.7%) |
| *Manual and electric wheelchair* | 24 (23.8%) |
| **Physical Activity and Exercise Characteristics** | |
| PASIPD Score^ | 16.5 (14.6) |
| Exercise experience | |
| *Home-based exercise* | 41 (40.6%) |
| *Fitness center (self-guided)* | 41 (40.6%) |
| *Fitness center (personal trainer led)* | 37 (36.6%) |
| *Exercise classes* | 61 (60.4%) |

PDDS, Patient Determined Disease Steps; PASIPD, Physical Activity Scale for Individuals with Physical Disabilities. ^Values are presented as mean (SD).

**Table 2:** Top five perceived benefits and barriers of exercise identified by nonambulatory people with MS.

| Rank | Exercise Benefit | Mean | SD |
|---|---|---|---|
| 1 | *Exercise gives me a sense of personal accomplishment* | 3.50 | 0.56 |
| 2 | *Exercise increases my muscle strength* | 3.38 | 0.53 |
| 3 | *Exercise improves overall body functioning* | 3.33 | 0.58 |
| 4 | *Exercising increases my level of physical fitness* | 3.26 | 0.59 |
| 5 | *Exercise increases my stamina* | 3.24 | 0.51 |
| **Rank** | **Exercise Barrier** | **Mean** | **SD** |
| 1 | *There are too few places for me to exercise.* | 1.56 | 0.76 |
| 2 | *Exercise facilities do not have convenient schedules for me* | 2.00 | 0.65 |
| 3 | *Places for me to exercise are too far away* | 2.07 | 0.82 |
| 4 | *I am fatigued by exercise* | 2.09 | 0.63 |
| 5 | *Exercise tires me* | 2.10 | 0.56 |

**Table 3:** Top five unmet and fulfilled needs identified by nonambulatory people with MS.

| Rank | Unmet Need | Importance | Satisfaction | Needs Index |
|---|---|---|---|---|
| 1 | *Receive useful exercise information from my neurologist* | 85.6 | 18.6 | 67.0 |
| 2 | *Exercise facilities have exercise equipment that can accommodate any impairments I experience* | 90.1 | 27.0 | 63.1 |
| 3 | *Exercise facilities have a variety of different exercise equipment options* | 85.9 | 24.3 | 61.6 |
| 4 | *Exercise facilities have exercise equipment that will not make my MS symptoms worse* | 84.2 | 23.5 | 60.6 |
| 5 | *Exercise programs are tailored to me specifically* | 81.4 | 26.2 | 55.2 |
| **Rank** | **Fulfilled Need** | **Importance** | **Satisfaction** | **Needs Index** |
| 1 | *Professionals have strong knowledge of exercise* | 77.2 | 76.7 | 0.5 |
| 2 | *Professionals are available to ask questions regarding exercise* | 72.8 | 71.8 | 1.0 |
| 3 | *Professional can keep me motivated and on track* | 64.1 | 61.9 | 2.2 |
| 4 | *Professional can adjust my exercise program depending on my needs and preferences* | 69.4 | 64.9 | 4.5 |
| 5 | *My understanding of potential outcomes I can expect by performing exercise* | 51.5 | 46.8 | 4.7 |

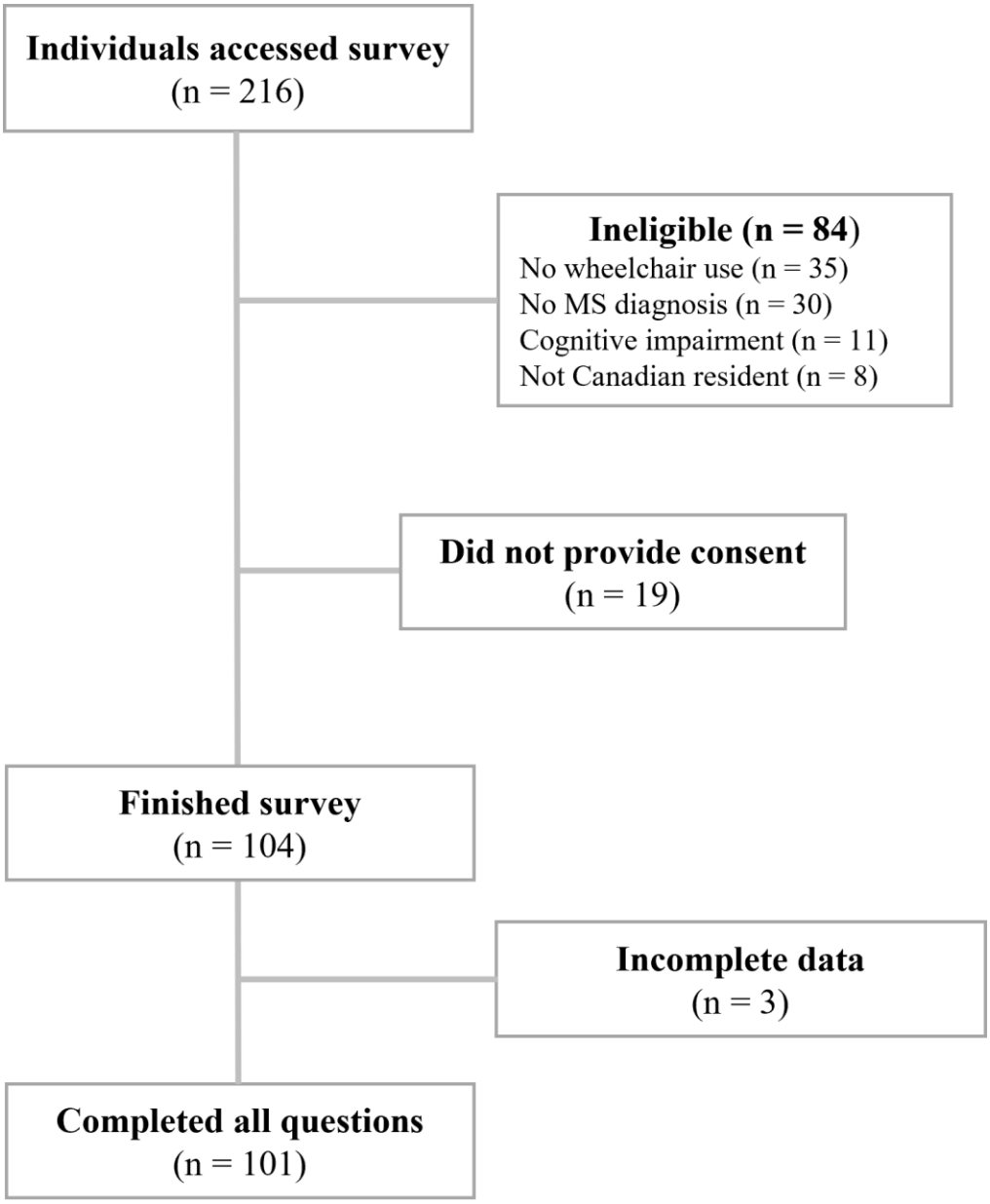


**Figure 1:** Flowchart of participant recruitment.

# Chapter 6 – DISCUSSION

## 6.1 – Dissertation Purpose

Despite having arguably have the greatest need for alternative strategies for disease management, such as exercise training, the exercise literature involving nonambulatory people with MS remains underdeveloped, with the potential benefits of exercise for this population largely unknown.[1] As a result, foundational research involving exercise and nonambulatory people with MS is needed to better understand the role of exercise for this population.

One literature gap involving nonambulatory people with MS has been the lack of examination of the safety of exercise for this population. While previous research has demonstrated the safety of exercise for people with MS with low-to-moderate disability,[2] no comprehensive examinations have been undertaken for nonambulatory people with MS. Therefore, one objective of this dissertation was to evaluate the safety of adapted exercise for nonambulatory people with MS.

As the primary goal of an exercise intervention or training program should be to improve health-related outcomes, an appropriate exercise stimulus for inducing such adaptations is essential. Unfortunately, little is known about the physiological response to exercise in nonambulatory people with MS, with current exercise recommendation being rooted primarily in 'expert-opinion'.[3] As such, this dissertation further aimed to characterize the physiological response of nonambulatory people with MS to three adapted exercise modalities. Together with information on exercise safety and satisfaction, these results can be used to inform expected responses to exercise, and guide the development and design of future exercise trials for this population.

It is also important for any exercise intervention or program to have reliable outcome measures capable of capturing improvements in health- and disease-related outcomes. Many previous exercise trials involving people with MS have used measures of physical fitness or mobility as primary endpoints. However, it may not be possible to utilize these endpoints in the same manner in nonambulatory people with MS. Therefore, patient-reported outcomes that capture 'participation' represent a valuable alternative endpoint. Outcome measures describing 'participation' provide insight into the impact of MS on everyday living and have been identified as outcomes of high importance to people living with MS.[4,5] Despite this, the use of 'participation' outcomes in exercise trial is unclear, and the effect of exercise training on such outcomes remains uncertain. Consequently, another objective of this dissertation was to explore the use of outcome measures that capture 'participation' in MS exercise trials, and the influence of exercise training on 'participation'. Such inquiry can inform outcome selection for exercise trials involving nonambulatory people with MS.

Lastly, another key gap in the exercise literature involving nonambulatory people with MS has been the lack of investigation of perceived benefits of and barriers to exercise. While there have been few, small qualitative investigations exploring exercise benefits and barriers in nonambulatory people with MS,[6,7] large scale quantitative investigations have not been conducted. In contrast, there have been several examinations of exercise benefits and barriers among people with MS with less disability.[8–11] As such, the final objective of this dissertation was to identify perceived exercise benefits, barriers, and needs of nonambulatory people with MS. This information is necessary for the design and implementation of community exercise programs that are pragmatic and beneficial for nonambulatory people with MS.

## 6.2 – Key findings

### 6.2.1 – Safety of exercise in nonambulatory people with MS (Chapter 2)

The second manuscript (Chapter 2) in this dissertation characterizes the safety associated with adapted exercise in nonambulatory people with MS. Overall, participants experienced few adverse events across all submaximal adapted exercise sessions. Few or no adverse events were reported during RS (n=2) and FES (n=0) exercise, with all participants completing the exercise sessions on these modalities. The symptomatic responses associated with RS and FES exercise were also minimal, as no significant increases in pain or fatigue were observed in response to RS or FES exercise. Conversely, adverse events were more frequently experienced during ACE exercise and symptoms of pain and fatigue were also significantly elevated after ACE. Additionally, neurological function and cognitive performance did not change in response to RS or FES exercise. These findings indicate that RS and FES exercise are well-tolerated and represent viable exercise options for nonambulatory people with MS.

### 6.2.2 – Physiological response to exercise in nonambulatory people with MS (Chapter 3)

The third manuscript (Chapter 3) in this dissertation assessed the acute physiological response of nonambulatory people with MS to three adapted exercise modalities (ACE, RS, and FES). Participants were capable of exercising at an intensity that satisfied the American College of Sport Medicine (ACSM)[12] criteria for moderate-to-vigorous physical activity (MVPA) on all adapted modalities. While there were no significant differences between modalities in the majority of cardiovascular outcomes, FES exercise generally elicited a weaker cardiorespiratory response compared to the other modalities. Overall, this suggests that nonambulatory people with MS are

capable of exercising at MVPA and habitual exercise at this intensity would be beneficial for improving health outcomes.

### 6.2.3 – Participation as an outcome of exercise trials in people with MS (Chapter 4)

The fourth chapter within this dissertation (Chapter 4) characterized outcome measures that capture 'participation' in exercise trials involving those with MS and sought to quantify the effect of exercise training on such outcomes in persons with MS. Findings from this review demonstrated considerable variability in how participation has been captured in MS exercise studies, with an emphasis on participation items which describe 'mobility'. Additionally, the Meta-Analysis revealed that exercise training had a moderate, positive effect on outcomes that capture participation, a novel finding regarding the potential benefits of exercise training in MS.

### 6.2.4 – Exercise benefits, barriers, and needs (Chapter 5)

The last manuscript (Chapter 5) within this dissertation depicts findings from a cross-sectional survey involving 101 nonambulatory people with MS. This study demonstrated that nonambulatory people with MS perceive health improvements and personal accomplishments as the greatest benefits associated with exercise engagement. The sample also cited considerable environmental challenges and MS symptoms as prominent barriers to engaging in exercise. With respect to exercise needs, the greatest unmet needs centered around exercise facilities, specifically exercise equipment. Nonambulatory people with MS reported high satisfaction with exercise professionals, noting that they were highly knowledgeable about exercise.

## 6.3 – Synthesis of Dissertation Research and Key Recommendations

It is evident that the current literature pertaining to exercise training and nonambulatory people with MS is underdeveloped relative to exercise research involving people with MS who are ambulatory. The lack of research has resulted in exercise recommendations for this group that are primarily informed by expert opinion. Synthesizing the results from the four chapters within this dissertation and situating them within the context of current research will be important in demonstrating how this dissertation contributes to the field. Figure 1 demonstrates how findings from each dissertation chapter are integrated to impact exercise engagement across the 'exercise continuum' (i.e., exercise initiation to maintenance) for nonambulatory people with MS and provide conclusions/recommendations for guiding exercise participation in nonambulatory people with MS. Collectively, this dissertation proposes key recommendations for engaging in exercise, measuring exercise effects, and addressing prominent barriers hindering community exercise engagement among nonambulatory people with MS.

### 6.3.1 – Evidence-Informed Exercise Prescription

As current exercise recommendations for nonambulatory people with MS are solely informed by expert opinion, findings from this dissertation (Chapters 2 & 3) begin to address critical literature gaps and help inform evidence-based exercise recommendations for this population. Key conclusions and recommendations pertaining to aerobic exercise prescription in nonambulatory people with MS include: (1A) Minor adverse events and transient changes in symptoms can be expected; (2A) The recumbent stepper (RS) modality is safe, well-tolerated and patient-preferred, and therefore, the recommended aerobic modality for nonambulatory people with MS; and (3A) Moderate-to-vigorous intensity exercise is achievable for nonambulatory people with MS and therefore can be prescribed at this intensity for this population. The findings from this dissertation

help to establish a safety profile regarding which adverse events can be expected in response to acute aerobic exercise in nonambulatory people with MS. These conclusions/recommendations will enable clinicians and researchers to be more confident in the safety of exercise for nonambulatory people with MS, and will aid in alleviating patient concerns regarding exercise engagement.[6] Further, the findings from this dissertation will be vital for promoting exercise initiation and engagement among nonambulatory people with MS.

Prior to this investigation, the cardiorespiratory response of nonambulatory people with MS to adapted exercise had not been characterized, and it was uncertain if this population could exercise at a sufficient intensity for improving health outcomes.[3] Current aerobic exercise recommendations for nonambulatory people with MS prescribe an exercise intensity of 70% $HR_{peak}$. Findings from this dissertation confirm that nonambulatory people with MS are capable of exercising at this intensity and higher, as participants exercised at 80%-87% $HR_{peak}$. Future studies should explore the effects of habitual, moderate (64-75% $HR_{peak}$) and vigorous (76-95% $HR_{peak}$) intensity aerobic exercise for understanding the potential long-term benefits of exercise training for nonambulatory people with MS. Within the context of the 'exercise continuum' (Figure 1), these finding are vital for informing evidence-based exercise prescription for this population, contributing to greater promotion of exercise initiation among nonambulatory people with MS.

### 6.3.2 – Appropriate Outcome Measures

The lack of standardization in outcome measures used across exercise trials involving nonambulatory people with MS has been acknowledged.[1] Patient-reported outcomes that capture aspects of 'participation' have been proposed as alternative outcomes of exercise trials with people with MS.[1,13] However, the use of these outcome measures has been scarce in exercise trials

involving nonambulatory people with MS.[1] The findings from this dissertation inform key recommendations regarding the use of participation outcomes for nonambulatory people with MS in an exercise setting: (1B) Participation outcomes should be used across the exercise continuum for tracking exercise effect on daily life; these outcomes are responsive to exercise training and can be applied across disability levels; (2B) Despite widespread use, outcome measures that capture aspects of 'participation' other than 'mobility' have more relevance to this population and should be applied.

As Chapter 4 of this dissertation demonstrated 'participation' outcomes favorably responded to exercise training, future exercise trials or programs involving nonambulatory people with MS should utilize such outcomes as a means of denoting changes in health. Importantly, 'participation' outcome measures represent a valuable endpoint for exercise trials involving nonambulatory people with MS, allowing participants to express their perceived impact of MS on everyday living, providing insight into an individual's functional capacity.[13] Further, meta-regression indicated that improvements in physiological fitness accounted for a significant amount of the variation in the observed effect of exercise training on 'participation'. This suggests an interesting utility of 'participation' outcomes for inferring potential changes in physiological fitness when validated measurements of physiological fitness are not accessible or common practice. This is particularly relevant for trials involving nonambulatory people with MS given the physical limitations and potential lack of access to accessible fitness testing equipment in this population. However, it is important to emphasize that 'participation' outcomes are by no means a substitution for fitness assessment.

While the use of 'participation' outcomes is advantageous among nonambulatory people with MS, not all 'participation' outcomes are relevant for this population. For example, some

'participation' outcome measures are predominantly composed of items capturing aspects of 'mobility' (e.g., Multiple Sclerosis Impact Scale [MSIS-29]), often describing walking/ambulatory ability. Given the high level of physical disability experienced by nonambulatory people with MS, such outcome measures do not adequately capture 'participation' among this population and may potentially misrepresent an individual's level of functioning in everyday life. Conversely, outcome measures that capture a variety of other 'participation' categories (e.g., Impact of Participation and Autonomy Questionnaire [IPA]), including 'self-care', 'major life areas' or 'community, social, and civic life', may better capture 'participation' in nonambulatory people with MS. As such, if 'participation' outcomes are to be used to describe engagement in everyday life in nonambulatory people with MS, it is recommended that outcomes measures capable of capturing aspects of 'participation' most relevant to this population are used.

### 6.3.3 – Increasing Opportunities for Exercise Engagement

Conceptualizing and designing pragmatic exercise programs for nonambulatory people with MS is a challenging task. Considering findings from Chapter 5, the following key conclusions/recommendations can be made with regards to designing and implementing exercise programs for nonambulatory people with MS: (1C) Exercise programs and facilities must consider and address environmental barriers that limit opportunities for exercise for nonambulatory people with MS; (2C) Satisfied exercise needs and perceived benefits of exercise should be leveraged to facilitate exercise initiation and maintenance among nonambulatory people with MS.

The accessibility of fitness centres is an ongoing issue, as fitness facilities often do not meet standard accessibility guidelines.[14,15] As a result, multi-level strategies are needed in order to increase opportunities for exercise engagement for nonambulatory people with MS. Increased

advocacy, adjustments of current policies, and greater resource allocation are all possible options for increasing physical activity and exercise opportunities for nonambulatory people with MS.[16]

The key recommendations from this chapter will be pertinent for supporting exercise engagement across the 'exercise continuum' by facilitating exercise initiation/maintenance among nonambulatory people with MS. Given the findings of this dissertation, it is recommended that exercise facilities and/or programs address the prominent environmental barriers currently hindering exercise engagement among nonambulatory people with MS. Specifically, exercise facilities must procure and provide more adapted exercise modalities for nonambulatory people with MS in order to afford greater opportunities to engage in exercise. It is also recommended that exercise facilities offer variety in adapted exercise options, as this will be vital for accommodating people with MS with different abilities and preferences, thus affording more opportunities for exercise engagement.

Importantly, retrofitting current exercise facilities is not the only viable strategy for addressing environmental barriers hindering exercise engagement, as increased flexibility in how exercise is delivered is also a valuable strategy. Given the reported feasibility and increased prominence of telerehabilitation among those with MS,[17] remote delivery of exercise programs represent a potential strategy for overcoming environmental barriers experienced by nonambulatory people with MS. Therefore, remotely-delivered adapted exercise programs should be offered to provide more opportunities for exercise engagement and facilitate the initiation and maintenance of exercise among nonambulatory people with MS.

While it is undoubtably important to address environmental barriers to exercise, it is also recommended to leverage aspects of community exercise that nonambulatory people with MS are seemingly satisfied with to help facilitate exercise engagement. For example, nonambulatory

people with MS reported high satisfaction with exercise professionals, citing they felt exercise professionals were trustworthy and highly knowledgeable exercise resources. Participants also acknowledged the benefits of exercise engagement and recognized exercise was a valuable tool for promoting improvements in health. This satisfaction with exercise professionals and acknowledgment of exercise benefits represents potential opportunities for an 'asset-based' approach to promoting exercise engagement across the exercise continuum.

## 6.4 – Remaining Literature Gaps and Future Research Directions

### 6.4.1 – Exercise Prescription

There are four core aspects that must be considered when prescribing exercise: *frequency, intensity, time, and type (or modality).* Combined, these four principles are referred to as the FITT principles and are used to guide exercise prescription.[18,19] Findings from this dissertation, specifically Chapters 2 and 3, provide pertinent information regarding exercise *intensity* and *type* for nonambulatory people with MS. However, *frequency* and *time* remain important facets of exercise prescription for nonambulatory people with MS that have yet to be explored.

One qualitative study involving 20 nonambulatory people with MS reported that the majority of participants desired an exercise frequency of 2 – 4 times per week, expressing that they believed this frequency would be sufficient to promote improvements in health outcomes.[7] These people also believed that an exercise time or duration of 15–30 minutes per session was appropriate.[7] Unfortunately, given the lack of studies involving exercise training in nonambulatory people with MS, the necessary exercise frequency and duration needed for improving health outcomes in this population remains unclear.[3] As this dissertation determined that nonambulatory people with MS are capable of engaging in aerobic exercise at an intensity sufficient for improving

health-related fitness, future studies should explore the necessary frequency and duration of exercise for promoting improvements in health- and disease-related outcomes in this population. Such investigations will be essential for allowing researchers and clinicians to make exercise recommendations in accordance with the commonly used FITT principle and represent an important step toward greater evidence-based recommendations for nonambulatory people with MS.

### 6.4.2 – Exercise Type

It is important to note that many of the manuscripts within this dissertation are primarily centered on aerobic exercise. While aerobic exercise is undeniably important, it is also important to acknowledge other types of exercise that may be beneficial for nonambulatory people with MS. For instance, resistance training is a form of exercise training that aims to improve muscular fitness (strength and endurance).[12] Results from a Meta-Analysis of 14 randomized controlled trials (RCT) reported that resistance training improved muscular fitness for people with MS.[20] Current exercise guidelines recommend that people with MS with mild-moderate impairment (EDSS = 0 – 4.5) engage in resistance training 2–3 times per week.[3] However, the resistance training literature involving nonambulatory people with MS is severely limited, with only two studies to date investigating the benefits of resistance training in nonambulatory people with MS, both reporting inconclusive results.[1] As such, evidence-based recommendations for resistance training cannot be made for nonambulatory people with MS at this time.[3] Current guidelines informed by expert opinion-based recommend 2–3 days per week of resistance training for nonambulatory people with MS (EDSS $\geq$ 7.0). Importantly, nonambulatory people with MS have substantially reduced muscular fitness compared to those with MS with less disability, and stand to benefit greatly from

resistance training interventions.[21] Future investigations of the benefits of resistance training for nonambulatory people is needed to understand the role of a comprehensive exercise training program for this population.

Flexibility training is another type of exercise that has not been adequately investigated in nonambulatory people with MS. The purpose of flexibility training is to improve bodily range of motion, reduce spasticity, and enhance posture/balance.[22,23] Flexibility is becoming increasingly recognized as an important component of physical fitness for all people, with increased flexibility being associated with improved health and well-being.[22,23] People with MS stand to benefit from flexibility training, as range of motion and mobility are often compromised due to increased spasticity and sedentary behaviour.[24] Current exercise guidelines for people with MS with lower disability (EDSS = 0 – 4.5) recommend flexibility training 2 – 3 times a week in order to reduce spasticity and increase range of motion.[3] However, due to a lack of evidence on flexibility training and nonambulatory people with MS, evidence-based recommendations can once again not be made for this population. Recommendations primarily based on expert opinion advise daily flexibility exercise for nonambulatory people with MS (EDSS ≥7.0). As such, future investigations should explore the benefits of flexibility training following these guidelines and other prescriptions for nonambulatory people with MS.

### 6.4.3 – Future Exercise Trials and Nonambulatory People with MS

It is important to acknowledge the shortcomings of the few exercise studies which have included nonambulatory people with MS to date. Previous systematic reviews of exercise trials involving nonambulatory people with MS have determined the few studies involving these population have been of "low" or "very low" methodological quality.[1,25] This low quality was attributed to case

study or case report designs, small sample sizes, and detection and/or reporting biases. Further, this review cited little standardization across studies in terms of outcome measures. Simply put, the few exercise training studies that have included nonambulatory people with MS have been of poor methodological quality. As a result, future exercise trials involving nonambulatory people with MS must be adequately powered in order to establish the benefits of exercise training for this population. Further, participation outcomes representing involvement in life situations are of high importance to the lives and functioning of nonambulatory people with MS and warrant evaluation and inclusion in future exercise trials with this population.

Undoubtedly, conducting high quality exercise trials involving nonambulatory people with MS is a complicated and challenging endeavor with numerous practical factors to be considered. For instance, transportation, accessibility of facilities and exercise equipment, personnel support and training, and heterogeneity in disease burden should to be carefully considered.[1] These practical challenges are exacerbated by the lack of foundational exercise research involving this population, making the development and execution of exercise trials in nonambulatory people with MS even more difficult. Fortunately, findings from this dissertation provide a foundation upon which future exercise trials involving nonambulatory people with MS can be built. This dissertation has demonstrated that adapted exercise engagement is safe for nonambulatory people with MS and that this population is capable of engaging in aerobic exercise at an intensity sufficient for improving health-related fitness outcomes. Importantly, these findings provide justification for the development and implementation of high quality, long-term exercise training studies involving nonambulatory people with MS. Moving forward, rigorous exercise trials will be essential for establishing the potential benefits of exercise for nonambulatory people with MS and for informing evidence-based exercise prescription for this population.

### 6.5 – Dissertation Limitations

While the studies within this dissertation address key gaps in current MS and exercise literature, there are limitations of this body of work that must be acknowledged and discussed. One limitation of this dissertation is the relatively small sample of participants, particularly in Chapters 2 and 3. These small sample sizes may limit the applicability of the findings to a larger nonambulatory MS population. Given that these projects targeted a very specific subset of the MS population, recruitment of a larger sample was challenging. This difficulty was further exacerbated by the coronavirus-2019 (COVID-19) pandemic which prematurely halted recruitment for this study. However, despite the relatively small sample size, it is important to acknowledge that these studies were the first investigations of this type involving nonambulatory people with MS. Another potential limitation of note is the format and delivery of the final study (Chapter 5). Given the online format and the self-reported nature of the survey, clinical variables such as disability level and disease course were not confirmed through medical records. While efforts were made to ensure respondents met inclusion criteria, it was not feasible to validate participant characteristics given the study design. It is possible that the online distribution strategy resulted in a biased sample of younger people with high technological proficiency that were able to access and complete the study. However, while some evidence has suggested low technological and computer proficiency among older adults,[26] recent evidence has documented high internet usage and proficiency among people with MS, regardless of age or disability level.[17] Another limitation of this dissertation that warrants recognition is the cross-sectional design of most of the studies. While cross-sectional studies are advantageous and highly feasible due to their relatively low costs and time commitment, the primary limitation of a cross-sectional design is the simultaneous assessment of

both the outcomes and exposure. Without longitudinal data, a true cause-and-effect relationship cannot be established.

### 6.6 – Final Conclusions

The findings from this dissertation meaningfully contribute to the current literature and undoubtedly address prominent gaps in MS and exercise research. Specifically, this dissertation described the safety of adapted exercise in nonambulatory people with MS and demonstrated the potential of these exercise modalities for promoting improvements in health-related fitness outcomes - foundational research that has been unexplored to date. Further, this dissertation examined the utility of outcome measures describing aspects of 'participation'. Such outcomes represent viable endpoints for exercise trials involving nonambulatory people with MS as they provide meaningful insight into an individual's functioning in daily life and can be measured regardless of disability level. Finally, this dissertation highlights the unique exercise barriers and unmet exercise needs that must be considered to increase opportunities for exercise engagement in nonambulatory people with MS. Ultimately, findings from this dissertation will contribute to evidence-based exercise recommendation, the design of future exercise interventions and indicators of intervention success, and provide direction for promoting long-term exercise engagement in nonambulatory people with MS.

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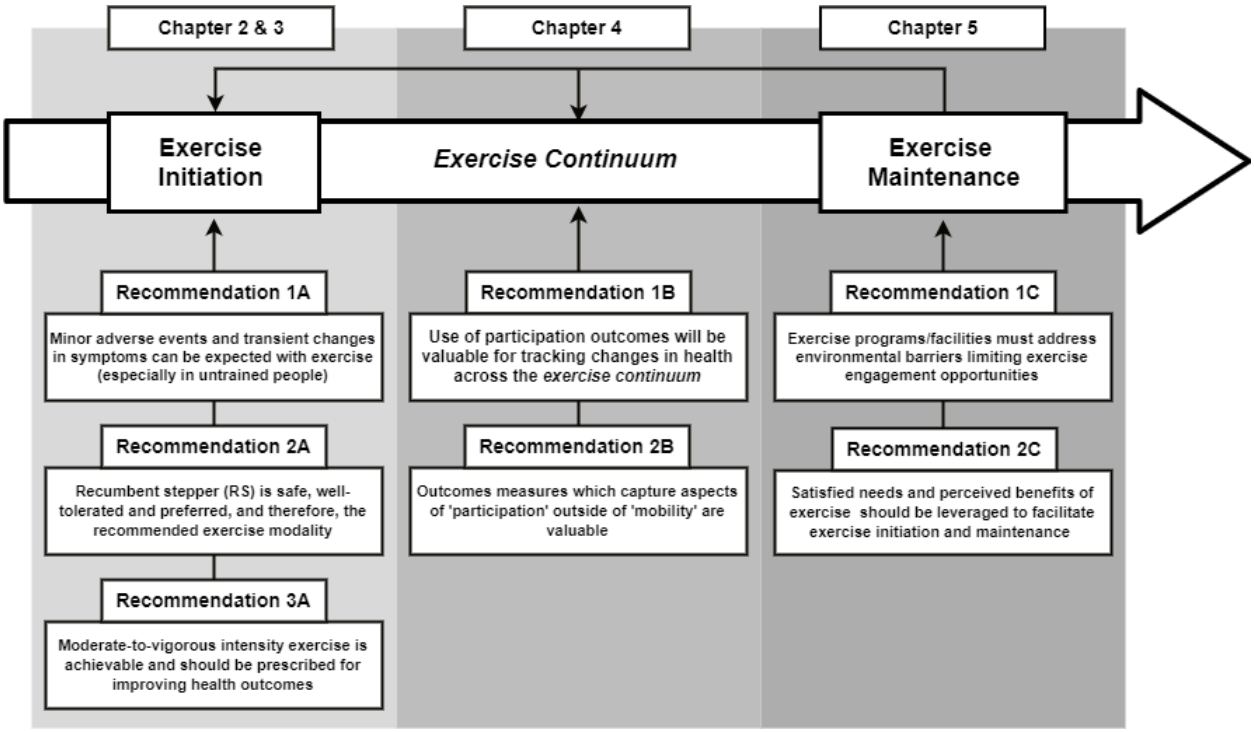


**Figure 1:** Key recommendations from each dissertation chapter presented in relation to the exercise continuum

# APPENDIX A: Chapter 2 and 3 Accessory Documents

## REB Approval Letter

14/06/2021

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

### CERTIFICAT D'APPROBATION ÉTHIQUE | CERTIFICATE OF ETHICS APPROVAL

| | |
|---|---|
| **Numéro du dossier / Ethics File Number** | H-03-19-3436 |
| **Titre du projet / Project Title** | Examination of the Physiological Response Associated with Adapted Exercise Modalities in Nonambulatory People with Multiple Sclerosis |
| **Type de projet / Project Type** | Recherche de professeur / Professor's research project |
| **Statut du projet / Project Status** | Renouvelé / Renewed |
| **Date d'approbation (jj/mm/aaaa) / Approval Date (dd/mm/yyyy)** | 18/06/2019 |
| **Date d'expiration (jj/mm/aaaa) / Expiry Date (dd/mm/yyyy)** | 17/06/2022 |

### Équipe de recherche / Research Team

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**Conditions spéciales ou commentaires / Special conditions or comments**

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14/06/2021

# Université d'Ottawa

Bureau d'éthique et d'intégrité de la recherche

# University of Ottawa

Office of Research Ethics and Integrity

Le Comité d'éthique de la recherche (CÉR) de l'Université d'Ottawa, opérant conformément à l'*Énoncé de politique des Trois conseils* (2014) et toutes autres lois et tous règlements applicables, a examiné et approuvé la demande d'éthique du projet de recherche ci-nommé.

L'approbation est valide pour la durée indiquée plus haut et est sujette aux conditions énumérées dans la section intitulée "Conditions Spéciales ou Commentaires". Le formulaire « Renouvellement ou Fermeture de Projet » doit être complété quatre semaines avant la date d'échéance indiquée ci-haut afin de demander un renouvellement de cette approbation éthique ou afin de fermer le dossier.

Toutes modifications apportées au projet doivent être approuvées par le CÉR avant leur mise en place, sauf si le participant doit être retiré en raison d'un danger immédiat ou s'il s'agit d'un changement ayant trait à des éléments administratifs ou logistiques du projet. Les chercheurs doivent aviser le CÉR dans les plus brefs délais de tout changement pouvant augmenter le niveau de risque aux participants ou pouvant affecter considérablement le déroulement du projet, rapporter tout évènement imprévu ou indésirable et soumettre toute nouvelle information pouvant nuire à la conduite du projet ou à la sécurité des participants.

The University of Ottawa Research Ethics Board, which operates in accordance with the *Tri-Council Policy Statement* (2014) and other applicable laws and regulations, has examined and approved the ethics application for the above-named research project.

Ethics approval is valid for the period indicated above and is subject to the conditions listed in the section entitled "Special Conditions or Comments". The "Renewal/Project Closure" form must be completedfour weeks before the above-referenced expiry date to request a renewal of this ethics approval or closure of the file.

Any changes made to the project must be approved by the REB before being implemented, except when necessary to remove participants from immediate endangerment or when the modification(s) only pertain to administrative or logistical components of the project. Investigators must also promptly alert the REB of any changes that increase the risk to participant(s), any changes that considerably affect the conduct of the project, all unanticipated and harmful events that occur, and new information that may negatively affect the conduct of the project or the safety of the participant(s).

Ethics COORDINATOR
Coordonnateur de l'éthique / Ethics Coordinator
Pour/For **Daniel LAGAREC** Président(e) du/ Chair of the **Comité d'éthique de la recherche en sciences de la santé et sciences / Health Sciences and Sciences Research Ethics Board**

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**Supplementary Table A:** Changes in neurological function, symptoms, cognitive performance, and affect in response to exercise. Values are reported as mean (SD) unless specified otherwise.

| | ACE | | | | RS | | | | FES | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **PRE EXE** | **IMD POST** | **30min POST** | **24hr POST** | **PRE EXE** | **IMD POST** | **30min POST** | **24hr POST** | **PRE EXE** | **IMD POST** | **30min POST** | **24hr POST** |
| **Neurological Function** | | | | | | | | | | | | |
| Visual Score | 2.1 (0.8) | 2.4 (0.7) | 2.1 (0.8) | - | 2.2 (0.7) | 2.3 (0.7) | 2.3 (0.6) | - | 2.2 (0.7) | 2.2 (0.7) | 2.2 (0.7) | - |
| Brainstem Score | 2.7 (0.8) | 2.8 (0.7) | 2.7 (0.8) | - | 2.7 (0.9) | 2.7 (0.8) | 2.7 (0.8) | - | 2.7 (0.8) | 2.6 (0.8) | 2.6 (0.8) | - |
| Cerebellar Score | 2.6 (0.8) | 2.9 (0.7) | 2.8 (0.8) | - | 2.6 (0.9) | 2.7 (0.8) | 2.7 (0.8) | - | 2.6 (0.8) | 2.6 (0.8) | 2.6 (0.8) | - |
| Sensory Score | 2.3 (1.1) | 2.9 (0.8) | 2.6 (0.9) | - | 2.3 (1.1) | 2.6 (0.8) | 2.3 (1.1) | - | 2.3 (1.1) | 2.3 (1.1) | 2.0 (1.0) | - |
| **Symptoms** | | | | | | | | | | | | |
| BPI | 3.8 (1.4) | 6.3 (2.9) | 5.8 (2.9) | 6.4 (1.7) | 3.8 (1.0) | 4.6 (2.2) | 4.3 (2.0) | 4.3 (1.9) | 3.8 (0.9) | 3.5 (0.8) | 3.5 (0.9) | 3.2 (0.5) |
| DFIS | 5.7 (5.2) | 11.3 (8.3) | 9.2 (8.3) | 9.1 (6.6) | 5.5 (4.6) | 7.5 (7.0) | 5.3 (3.2) | 7.0 (5.4) | 5.3 (5.0) | 5.2 (5.0) | 6.0 (5.0) | 4.7 (4.7) |
| **Cognitive performance** | | | | | | | | | | | | |
| SDMT | 46.3 (12.2) | 44.8 (12.7) | 45.4 (12.0) | - | 46.3 (13.0) | 46.1 (12.5) | 48.2 (13.7) | - | 47.4 (12.0) | 48.3 (11.8) | 48.9 (11.8) | - |
| SWCT | 33.2 (10.5) | 35.6 (13.7) | 34.8 (13.3) | - | 34.2 (12.1) | 36.8 (14.8) | 36.5 (14.9) | - | 33.6 (14.7) | 35.3 (15.0) | 37.9 (14.4) | - |
| **Affect** | | | | | | | | | | | | |
| FS | 3.2 (1.6) | 1.9 (1.7) | 2.9 (1.6) | 2.7 (1.7) | 3.3 (1.0) | 3.3 (1.7) | 3.6 (1.7) | 3.7 (1.4) | 3.2 (1.7) | 3.8 (1.1) | 4.0 (1.0) | 4.2 (0.8) |
| EFI | | | | | | | | | | | | |
| *Revitalization* | 3.0 (0.6) | 2.4 (1.1) | 2.9 (0.8) | 3.1 (0.6) | 3.1 (0.6) | 2.7 (1.0) | 3.1 (0.6) | 3.1 (0.6) | 3.1 (0.6) | 3.0 (0.7) | 3.2 (0.6) | 3.3 (0.8) |
| *Tranquility* | 2.0 (0.5) | 2.2 (0.8) | 1.8 (0.5) | 1.9 (0.6) | 2.0 (0.7) | 2.8 (0.8) | 2.5 (0.8) | 2.5 (0.7) | 1.9 (0.7) | 2.5 (0.7) | 2.5 (0.6) | 2.8 (0.6) |
| *PosEng* | 1.9 (0.5) | 2.1 (0.7) | 2.3 (0.7) | 2.2 (0.4) | 1.9 (0.7) | 2.4 (0.7) | 2.4 (0.5) | 2.5 (0.3) | 1.9 (0.7) | 2.4 (0.7) | 2.6(0.3) | 2.6 (0.3) |
| *PhyExh* | 2.6 (1.0) | 3.0 (1.0) | 2.7 (1.0) | 2.8 (1.0) | 2.7 (0.9) | 2.9 (1.0) | 2.6 (0.9) | 2.6 (0.9) | 2.7 (0.9) | 2.9 (0.9) | 2.7 (1.0) | 2.5 (1.0) |

ACE, Arm Cycle Ergometer; RS, Recumbent Stepper; FES, Functional Electrical Stimulation Cycle; BPI, Brief Pain Inventory; DFIS, Daily Fatigue Impact Scale; SDMT, Symbol-Digit Modality Test; SWCT, Stroop Word-Color Test; FS, Feeling Scale; EFI, Exercise-Induced Feeling Inventory; PosEng, Positive Engagement; PhyExh, Physical Exhaustion.

**Supplemental Table B:** Outputs from ANOVA for all variables including Modality effects, time effects, and modality by time interactions.

| | Modality Effect | | | Time Effect | | | Modality *Time Interactions | | |
|---|---|---|---|---|---|---|---|---|---|
| | **F** | **P value** | **$\eta p^2$** | **F** | **P value** | **$\eta p^2$** | **F** | **P value** | **$\eta p^2$** |
| **Neurological Function** | | | | | | | | | |
| Visual Score | 1.2 | 0.33 | .10 | 3.3 | 0.06 | .23 | 3.0 | 0.06 | .21 |
| Brainstem Score | 1.4 | 0.27 | .11 | 0.5 | 0.63 | .04 | 1.4 | 0.26 | .11 |
| Cerebellar Score | 2.0 | 0.16 | .15 | 1.5 | 0.26 | .12 | 1.3 | 0.23 | .10 |
| Sensory Score | **12.0** | **<0.01** *f,g* | **.52** | **7.7** | **<0.01** *a,b* | **.41** | **4.7** | **<0.01** | **.30** |
| **Symptoms** | | | | | | | | | |
| BPI | **10.0** | **<0.01** *f,g* | **.48** | **6.3** | **<0.01** *a* | **.36** | **5.1** | **<0.01** | **.32** |
| DFIS | **6.0** | **0.01** *g* | **.35** | 2.3 | 0.08 | .18 | 2.0 | 0.08 | .15 |
| **Cognitive performance** | | | | | | | | | |
| SDMT | **3.8** | **0.04** *g* | **.26** | 1.6 | 0.23 | .13 | 0.9 | 0.48 | .08 |
| SWCT | 0.5 | 0.53 | .05 | 2.7 | 0.09 | .20 | 0.6 | 0.69 | .05 |
| **Affect** | | | | | | | | | |
| FS | **10.6** | **<0.01** *f,g* | **.49** | **8.3** | **<0.01** *a,d,e* | **.43** | **3.9** | **<0.01** | **.26** |
| EFI | | | | | | | | | |
| *Revitalization* | 2.6 | 0.10 | .19 | **8.2** | **<0.01** *d,e* | **.43** | 0.7 | 0.70 | .60 |
| *Tranquility* | **12.8** | **<0.01** *f,g* | **.54** | 2.4 | 0.08 | .19 | 1.6 | 0.14 | .13 |
| *Positive Engagement* | 2.3 | 0.13 | .17 | **12.9** | **<0.01** *a,b,c* | **.54** | 0.9 | 0.49 | .08 |
| *Physical Exhaustion* | 0.4 | 0.65 | .04 | 1.5 | 0.22 | .12 | 0.6 | 0.74 | .05 |

BPI, Brief Pain Inventory; DFIS, Daily Fatigue Impact Scale; SDMT, Symbol-Digit Modality Test; SWCT, Stroop Word-Color Test; FS, Feeling Scale; EFI, Exercise-Induced Feeling Inventory.

*a* - significant difference between PRE EXE & IMD POST
*b* - significant difference between PRE EXE & 30-min POST
*c* - significant difference between PRE EXE & 24-hr POST
*d* - significant difference between IMD POST & 30-min POST
*e* - significant difference between IMD POST & 24-hr POST
*f* - significant difference between ACE & RS
*g* - significant difference between ACE & FES

# APPENDIX B: Chapter 4 Accessory Documents

**Appendix A:** List of database-specific search terms used for the literature search

| Database | Term 1 | Term 2 | Term 3 |
|---|---|---|---|
| **CINAHL Sport Discuss** | *"Multiple sclerosis"* **OR** *"Disseminated Sclerosis"* | *"Exercise*"* **OR** *"Physical Activit*"* **OR** *"Physical Exercis*"* **OR** *"Acute Exercis*"* OR *"Isometric Exercis*"* **OR** *"Aerobic Exercis*"* **OR** *"Exercise Train*"* **OR** *"Exercise Therap*"* **OR** *"Physical Fitness"* **OR** *"Muscle Stretching Exercise*"* **OR** *"Circuit-Based Exercis*"* **OR** *"Endurance Train*"* **OR** *"High-Intensity Interval Train*"* **OR** *"Plyometric Exercis*"* **OR** *"Resistance Train*"* | *"Activit* Daily Living"* **OR** *"Daily Living Activit*"* **OR** *"Chronic Limitation of Activit*"* **OR** *"Community Particpat*"* **OR** *"Community Involve*"* **OR** *"Public particpat*"* **OR** *"Community Action"* **OR** *"Work Engage*" OR "Work Participat*"* **OR** *"Workplace Engage*"* **OR** *"Employee Participat*"* **OR** *"Employee Engage*"* **OR** *"Functional Independence Measure (FIM)"* **OR** *"Barthel Index of ADL"* **OR** *"Modified Rankin scale"* **OR** *"Frenchay activies Index"* **OR** *"Rivemead ADL Assessment"* **OR** *"Katz Index of Independence in ADL"* **OR** *"Motor Activity Log"* **OR** *"Social participat*"* |
| **EMBASE Ovid MEDLINE CENTRAL SCOPUS** | *"Multiple sclerosis"* | *"Exercise"* **OR** *"Exercise Test"* **OR** *"Isotonic Exercise"* **OR** *"Cardiopulmonary Exercise Test"* **OR** *"Arm Exercise"* **OR** *"Aerobic Exercise"* **OR** *"Aquatic Exercise"* **OR** *"Stretching Exercise"* **OR** *"Static Exercise"* **OR** *"Muscle Exercise"* **OR** *"Isokinetic Exercise"* **OR** *"Dynamic Exercise"* **OR** *"Isometric Exercise"* **OR** *"Anaerobic Exercise"* **OR** *"Treadmill Exercise"* **OR** *"Leg Exercise"* **OR** *"Fitness"* **OR** *"Aerobic Training"* **OR** *"Endurance Training"* **OR** *"High Intensity Interval Training"* **OR** *"Resistance Training"* **OR** *"Plyometrics"* **OR** *"Physical Activity"* **OR** *"Kinesiotherapy"* | *"Daily life activity"* ***OR*** *"Disability"* OR *Community Participation* **OR** *"Work Engagement"* **OR** *"Employment Status"* **OR** *"Permanent Employment"* **OR** *"Employment"* **OR** *"Part-time Employment"* **OR** *"Full-time Employment"* **OR** *"Functional Independence Measure"* **OR** *"Rankin scale"* **OR** *"Barthel Index"* **OR** *"Frenchay Activities index"* **OR** *"Late-Life Function & Disability Instrument"* **OR** *"Social Participation"* **OR** *"Interpersonal Relations"* |

**Appendix B:** Quality assessment of included exercise studies using the TESTEX scale

| | Item | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study [ref]** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **Total** |
| **AEROBIC TRAINING (n=23)** | | | | | | | | | | | | | |
| Backus et al. (2017)[24] | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 3 |
| Baquet et al. 2018[25] | 1 | 1 | 0 | 1 | 1 | 3 | 1 | 2 | 1 | 0 | 1 | 1 | 12 |
| Barclay et al. (2019)[26] | 1 | 1 | 1 | 1 | 1 | 3 | 0 | 2 | 1 | 0 | 1 | 1 | 13 |
| Beer et al. (2008)[27] | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 2 | 1 | 0 | 1 | 1 | 11 |
| Cakt et al. (2010)[28] | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 2 | 1 | 0 | 0 | 0 | 9 |
| Calabrò et al. (2017)[29] | 1 | 1 | 0 | 1 | 1 | 2 | 0 | 2 | 1 | 0 | 0 | 0 | 9 |
| Collett et al. (2011)[30] | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 2 | 1 | 0 | 1 | 1 | 10 |
| Heine et al. (2017)[31] | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 1 | 12 |
| Jackson et al. (2012)[32] | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 2 | 1 | 0 | 0 | 0 | 5 |
| Kargarfard et al. (2012)[33] | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 2 | 1 | 0 | 1 | 1 | 11 |
| Learmonth et al. (2011)[34] | 1 | 0 | 1 | 1 | 1 | 2 | 1 | 2 | 1 | 0 | 0 | 0 | 10 |
| McAuley et al. (2007)[35] | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 2 | 1 | 0 | 0 | 0 | 5 |
| McCullagh et al. (2008)[36] | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 7 |
| Mokhtarzade et al. (2017)[37] | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 2 | 1 | 0 | 1 | 1 | 10 |
| Mostert et al. (2002)[38] | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 2 | 1 | 0 | 0 | 0 | 6 |
| Niwald et al. (2017)[39] | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 1 | 6 |
| Oken et al. (2004)[40] | 1 | 0 | 1 | 1 | 1 | 2 | 0 | 0 | 1 | 0 | 0 | 0 | 7 |
| Petajan et al. (1996)[41] | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 2 | 1 | 0 | 1 | 1 | 10 |
| Pilutti et al. (2011)[42] | 1 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 1 | 0 | 1 | 1 | 6 |
| Pilutti et al. (2019)[43] | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 2 | 1 | 0 | 1 | 1 | 10 |
| Rietberg et al. (2014)[44] | 1 | 1 | 1 | 1 | 1 | 2 | 0 | 2 | 1 | 0 | 0 | 1 | 11 |
| Straudi et al. (2016)[45] | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 2 | 1 | 1 | 1 | 1 | 12 |
| Straudi et al. (2020)[46] | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 2 | 1 | 1 | 1 | 1 | 14 |
| **RESISTANCE TRAINING (n=8)** | | | | | | | | | | | | | |
| Aydin et al. (2014)[47] | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 2 | 1 | 0 | 1 | 0 | 7 |
| Dalgas et al. (2010)[48] | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 2 | 1 | 0 | 1 | 0 | 10 |
| Dodd et al. (2011)[49] | 1 | 1 | 1 | 1 | 1 | 3 | 1 | 2 | 1 | 0 | 0 | 1 | 13 |
| Ertekin et al. (2012)[50] | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 5 |
| Kierkegaard et al. (2016)[51] | 1 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 1 | 0 | 1 | 0 | 6 |
| Kjølhede et al. (2018)[52] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 0 | 0 | 0 | 10 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mutluay et al. (2008)[53] | 1 | 0 | 1 | 1 | 1 | 3 | 0 | 2 | 1 | 0 | 0 | 0 | 10 |
| Taylor et al. (2006)[54] | 1 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 1 | 0 | 1 | 0 | 6 |
| **MIXED TRAINING & OTHER (n=18)** | | | | | | | | | | | | | |
| Bansi et al. (2013)[55] | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 8 |
| Bjarnadottir et al. (2007)[56] | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 2 | 1 | 1 | 1 | 1 | 9 |
| Bulguroglu et al. (2017)[57] | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 2 | 1 | 0 | 1 | 1 | 10 |
| Carter et al. (2013)[58] | 1 | 1 | 1 | 0 | 3 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 12 |
| Carter et al. (2014)[59] | 1 | 1 | 1 | 1 | 1 | 3 | 1 | 2 | 1 | 0 | 0 | 1 | 13 |
| Coote et al. (2017 )[60] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 0 | 0 | 0 | 10 |
| Garrett et al. (2013)[61] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 0 | 0 | 0 | 10 |
| Gobbi et al. (2016)[62] | 1 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 1 | 0 | 0 | 1 | 7 |
| Kahraman et al. (2018)[63] | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 2 | 1 | 0 | 0 | 0 | 5 |
| Kerling et al. (2015)[64] | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 0 | 1 | 0 | 10 |
| Konečný et al. (2010)[65] | 1 | 1 | 1 | 1 | 1 | 3 | 1 | 2 | 1 | 0 | 0 | 1 | 13 |
| Learmonth et al. (2017)[66] | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 2 | 1 | 1 | 1 | 1 | 9 |
| McAuley et al. (2015)[67] | 1 | 1 | 1 | 1 | 1 | 2 | 0 | 2 | 1 | 0 | 0 | 0 | 10 |
| Romberg et al. (2005)[68] | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 2 | 1 | 0 | 0 | 0 | 8 |
| Sabapathy et al. (2011)[69] | 1 | 1 | 0 | 1 | 0 | 2 | 0 | 2 | 1 | 0 | 0 | 0 | 8 |
| Sangelaji et al. (2014)[70] | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 2 | 1 | 0 | 0 | 0 | 8 |
| Straudi et al. (2014)[71] | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 2 | 1 | 1 | 1 | 1 | 14 |
| van der Linden et al. (2014)[72] | 1 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 1 | 0 | 0 | 0 | 5 |

**Appendix C:** Changes in participation outcomes for each study following exercise intervention. Values are reported as means (SD), unless specified otherwise.

| Study, Year | Participation outcome | Exercise group | | Control group | |
|---|---|---|---|---|---|
| | | Pre | Post | Pre | Post |
| **Aerobic exercise (n=13)** | | | | | |
| Baquet et al. (2018)[25] | HAQUAMS | 53.1 (16.9) | 53.7 (17.8) | 51.2 (18.7) | 51.8 (14.7) |
| Barclay et al. (2019)[26] | MSQoL-54 (Physical) | 28.0 (4.0) | 43.0 (4.0) | 34.0 (5.0) | 42.0 (6.0) |
| | MSQoL-54 (Mental) | 52.0 (7.0) | 63.0 (7.0) | 54.0 (9.0) | 65.0 (9.0) |
| | FIM | 98.0 (5.0) | 104.0 (5.0) | 88.0 (6.0) | 98.0 (6.0) |
| Cakt et al. (2010)[28] | SF-36 (Physical function) | 43.3 (16.6) | 64.6 (18.6) * | 43.2 (17.7) | 51.0 (20.5) |
| | SF-36 (Role physical) | 15.9 (23.1) | 50.0 (43.3) * | 30.0 (20.9) | 35.0 (37.1) |
| | SF-36 (Bodily pain) | 60.6 (25.5) | 69.5 (28.7) | 72.0 (28.9) | 76.0 (29.9) |
| | SF-36 (General health) | 50.1 (17.6) | 54.5 (21.5) | 64.8 (13.9) | 68.0 (23.4) |
| | SF-36 (Vitality) | 40.9 (16.2) | 50.0 (27.2) | 53.0 (14.8) | 64.0 (21.6) |
| | SF-36 (Social function) | 62.5 (25.6) | 65.9 (28.0) | 65.0 (1.1) | 70.0 (27.3) |
| | SF-36 (Emotion role) | 33.3 (36.4) | 57.5 (44.9) | 66.6 (47.1) | 86.6 (18.2) |
| | SF-36 (Mental health) | 35.0 (19.6) | 42.2 (22.7) | 38.0 (15.6) | 45.0 (21.5) |
| Heine et al. (2017)[31] | IPA (Autonomy indoor) | 0.7 (0.6) | 0.5 (0.6) | 0.7 (0.6) | 0.7 (0.6) |
| | IPA (Family role) | 1.4 (0.7) | 1.2 (0.8) | 1.6 (0.7) | 1.4 (0.7) |
| | IPA (Autonomy outdoors) | 1.5 (0.7) | 1.4 (0.7) | 1.6 (0.8) | 1.6 (0.8) |
| | IPA (Social relations) | 0.9 (0.5) | 0.9 (0.5) | 0.9 (0.5) | 1.0 (0.6) |
| | IPA (Work/education) | 1.7 (0.9) | 1.7 (0.9) | 2.1 (0.8) | 1.8 (0.7) |
| Kargarfard et al. (2012)[33] | MSQoL-54 (Physical) | 43.9 (6.8) | 65.4 (6.6) ^ | 43.5 (5.8) | 44.2 (4.4) |
| | MSQoL-54 (Mental) | 44.4 (9.3) | 70.2 (5.7) ^ | 42.5 (10.5) | 43.6 (8.9) |
| Learmonth et al. (2011)[34] | LMSQoL | 12.9 (4.9) | 10.9 (3.9) | 14.1 (3.9) | 12.4 (3.1) |
| Mokhtarzade et al (2017)[37] | MSQoL-54 (Physical) | 58.45 (15.0) | 66.3 (11.9) ^ | 56.9 (14.1) | 57.9 (12.6) |
| | MSQoL-54 (Mental) | 50.17 (21.81) | 67.2 (14.2) ^ | 51.92(21.3) | 52.9 (18.3) |
| | MSQoL-54 (Total) | 54.21 (14.63) | 63.8 (12.5) ^ | 52.20(12.9) | 50.9 (11.2) |
| Mostert et al. (2002)[38] | BAECKE - Work | 2.7 (0.7) | 2.6 (0.6) | 2.5 (0.9) | 2.7 (0.9) |
| | BAECKE - Sport | 1.7 (0.7) | 2.0 (0.4) | 1.8 (0.4) | 1.7 (0.4) |
| | BAECKE - Leisure | 2.4 (0.6) | 2.5 (0.8) | 2.3 (0.7) | 2.4 (0.8) |
| Niwald et al. (2017)[39] | WHOQOL-BREF (Physical) | 20.1 (3.6) | 23.1 (2.8) * | 19.5 (2.9) | 21.1 (2.5) * |

| | | | | | |
|---|---|---|---|---|---|
| | WHOQOL-BREF (Psychological) | 18.1 (3.7) | 21.7 (3.1) * | 17.6 (3.2) | 18.2 (1.7) * |
| | WHOQOL-BREF (Social) | 9.8 (2.0) | 10.7 (1.8) | 10.2 (3.1) | 10.5 (1.6) |
| | WHOQOL-BREF (Environment) | 23.8 (4.2) | 26.6 (3.8) * | 24.9 (5.2) | 25.1 (4.0) * |
| Oken et al. (2004)[40] | SF-36 (Physical function) | 58.6 (31.6) | 61.0 (31.6) | 58.1 (19.0) | 58.1 (23.3) |
| | SF-36 (Role physical) | 50.0 (44.0) | 48.8 (39.1) | 40.3 (37.5) | 52.8 (43.6) |
| | SF-36 (Bodily pain) | 71.0 (19.8) | 69.6 (17.3) | 65.1 (26.0) | 68.9 (25.3) |
| | SF-36 (General health) | 60.7 (24.8) | 60.3 (18.4) | 49.9 (19.1) | 55.4 (16.5) |
| | SF-36 (Vitality) | 43.1 (17.7) | 51.2 (16.7) | 39.7 (18.1) | 36.7 (18.1) |
| | SF-36 (Social function) | 72.0 (24.0) | 64.9 (17.9) | 66.0 (27.1) | 70.8 (23.5) |
| | SF-36 (Emotion role) | 72.4 (32.4) | (87.3 (24.7) | 72.2 (43.2) | 72.2 (36.6) |
| | SF-36 (Mental health) | 73.7 (12.9) | 73.5 (14.3) | 75.6 (18.8) | 75.6 (14.3) |
| Petajan et al. (1996)[41] | SIP | 94.4 (29.6) | 55.5 (24.0) | 65.9 (19.0) | 79.4 (22.3) |
| Pilutti et al. (2019)[43] | MSIS-29 (Physical) | 63.1 (21.0) | 59.7 (19.2) | 45.3 (25.1) | 34.1 (13.5) |
| | MSIS-29 (Psychological) | 37.5 (28.6) | 38.9 (36.0) | 25.7 (18.8) | 22.2 (13.8) |
| Rietberg et al. (2014)[44] | FIM | 118.5 (6.8) | 120.0 (7.0) | 122.0 (11.0) | 119.0 (9.0) |
| | MSIS-29 (Physical) | 53.0 (20.0) | 50.0 (22.5) | 43.0 (19.0) | 39.0 (28.0) |
| | MSIS-29 (Psychological) | 18.0 (6.5) | 16.0 (8.8) | 17.0 (6.0) | 18.0 (11.0) |
| | IPA (Autonomy indoor) | 0.4 (0.9) | 0.3 (1.2) | 1.0 (0.9) | 0.9 (1.4) |
| | IPA (Family role) | 1.7 (1.1) | 1.7 (1.3) | 1.4 (1.1) | 1.4 (1.4) |
| | IPA (Autonomy outdoors) | 1.6 (0.8) | 1.8 (1.1) | 1.6 (0.8) | 1.4 (1.1) |
| | IPA (Social relations) | 1.1 (0.8) | 1.2 (0.7) | 1.1 (0.6) | 1.0 (0.9) |
| | IPA (Work/education) | 2.2 (1.5) | 2.0 (0.9) | 1.7 (0.8) | 1.5 (1.0) |
| **Resistance Exercise (n=4)** | | | | | |
| Dalgas et al. (2010)[48] | SF-36 (Physical) | 41.4 (7.0) | 44.9 (7.2) | 42.6 (7.3) | 41.6 (6.8) |
| | SF-36 (Mental) | 54.3 (7.1) | 56.8 (8.0) | 55.0 (8.1) | 53.1 (6.3) |
| Dodd et al. (2011)[49] | WHOQoL-BREF | 3.8 (0.9) | 4.2 (0.9) | 3.9 (1.0) | 4.0 (0.9) |
| Kjølhede et al. (2018)[52] | MSIS-29 (Physical) | 40.5 (2.8) | 37.2 (2.8) | 39.3 (2.9) | 36.6 (2.9) |
| | MSIS-29 (Psychological) | 17.3 (1.2) | 17.0 (1.3) | 20.9 (1.3) | 19.3 (1.3) |
| Mutluay et al. (2008)[53] | MSQoL-54 (Physical) | 51.3 (17.0) | 57.5 (16.0) | 59.7 (14.0) | 58.7 (14.0) |
| | MSQoL-54 (Mental) | 59.1 (17.0) | 63.7 (17.0) | 62.8 (19.0) | 60.7 (19.0) |

| | | | | | |
|---|---|---|---|---|---|
| | Barthel Index | 87.7 (8.8) | 90.9 (7.5) | 90.1 (8.5) | 90.5 (8.5) |
| **Mixed training & other (n=6)** | | | | | |
| Carter et al. (2013)[58] | MSQoL-54 (Physical) | 45.4 (15.7) | 52.6 (11.9) | 47.8 (16.8) | 47.9 (18.5) |
| | MSQoL-54 (Mental) | 60.7 (20.6) | 65.5 (15.7) | 62.3 (20.1) | 58.6 (22.4) |
| | MSQoL-54 (Total) | 69.3 (24.3) | 69.0 (15.4) | 62.3 (20.1) | 61.2 (19.8) |
| | Godin LTEQ | 14.7 (14.9) | 14.7 (14.4) | 13.2 (12.0) | 13.3 (11.8) |
| Carter et al. (2014)[59] | MSQoL-54 (Physical) | 48.8 (21.5) | 59.7 (20.6) | 51.2 (18.8) | 52.6 (11.9) |
| | MSQoL-54 (Mental) | 59.5 (22.5) | 65.5 (20.2) | 62.8 (21.7) | 65.5 (15.7) |
| | MSQoL-54 (Total) | 58.3 (21.8) | 68.1 (20.3) | 62.4 (20.3) | 60.8 (20.0) |
| Learmonth et al. (2017)[66] | Godin LTEQ | 20.4 (15.6) | 29.4 (19.7) | 19.6 (20.8) | 16.9 (19.5) |
| | MSIS-29 (Physical) | 30.9 (10.8) | 32.6 (12.7) | 41.3 (13.7) | 42.0 (17.4) |
| | MSIS-29 (Psychological) | 16.6 (6.9) | 16.4 (7.7) | 19.8 (7.8) | 20.3 (8.7) |
| | LMSQoL | 1.0 (0.6) | 0.92 (0.6) | 1.3 (0.5) | 0.9 (0.6) |
| | LLFDI - Function | 65.1 (8.6) | 64.5 (11.1) | 59.0 (11.1) | 57.4 (11.1) |
| | LLFDI - Disability | 31.6 (3.4) | 32.4 (4.0) | 31.0 (6.7) | 32.4 (4.0) |
| | LLFDI - Limitations | 35.6 (5.3) | 36.5 (5.1) | 31.0 (6.7) | 32.1 (7.1) |
| McAuley et al. (2015)[67] | Godin LTEQ | 8.5 (1.9) | 21.5 (3.0) | 6.85 (1.8) | 12.6 (2.9) |
| | MSIS-29 (Physical) | 44.8 (3.6) | 47.9 (3.7 | 47.7 (3.6) | 42.6 (3.6) |
| | MSIS-29 (Psychological) | 18.9 (1.7) | 19.9 (1.6) | 21.1 (1.6) | 21.0 (1.5) |
| Romberg et al. (2005)[68] | MSQoL-54 (Physical) | 61.7 (18.2) | 63.0 (17.8) | 62.1 (14.7) | 63.3 (16.6) |
| | MSQoL-54 (Mental) | 67.5 (21.7) | 71.2 (20.6) | 68.7 (19.4) | 70.4 (21.3) |
| Straudi et al. (2014)[71] | MSIS-29 (Physical) | 51.7 (20.6) | 41.9 (15.7) | 49.4 (20.1) | 53.1 (19.2) |
| | MSIS-29 (Psychological) | 50.8 (15.6) | 44.4 (11.3) | 51.6 (18.7) | 53.8 (18.1) |

Abbreviations: BAECKE = BAECKE Activity Questionnaire; FIMS = Functional Independence Measure; Godin LTEQ = Godin Leisure-Time Exercise Questionnaire; HAQUAMS = Hamburg Quality of Life Questionnaire Multiple Sclerosis; IPA = Impact of Participation and Autonomy Questionnaire; LLFDI = Late-Life Function and Disability Instrument; LMSQoL = Leeds Multiple Sclerosis Quality of Life scale; MSIS-29 = Multiple Sclerosis Impact Scale; MSQoL-54 = Multiple Sclerosis Quality of Life-54; SF-36 = 36-Item Short Form Survey Instrument; SIP = Sickness Inventory Profile; WHOQOL-BREF = World Health Organization Quality of Life-BREF.

* Significant difference between pre and post value ($p<0.05$)
^ Significant difference between exercise and control condition ($p<0.05$)

# APPENDIX C: Chapter 5 Accessory Documents

## REB Approval Letter

13/03/2021

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

### CERTIFICAT D'APPROBATION ÉTHIQUE | CERTIFICATE OF ETHICS APPROVAL

| | |
|---|---|
| **Numéro du dossier / Ethics File Number** | H-12-20-6324 |
| **Titre du projet / Project Title** | Understanding Needs for Exercise Engagement in Nonambulatory People with Multiple Sclerosis |
| **Type de projet / Project Type** | Thèse de doctorat / Doctoral thesis |
| **Statut du projet / Project Status** | Approuvé / Approved |
| **Date d'approbation (jj/mm/aaaa) / Approval Date (dd/mm/yyyy)** | 13/01/2021 |
| **Date d'expiration (jj/mm/aaaa) / Expiry Date (dd/mm/yyyy)** | 12/01/2022 |

### Équipe de recherche / Research Team

| Chercheur / Researcher | Affiliation | Role |
|---|---|---|
| Thomas EDWARDS | École des sciences de l'activité physique / School of Human Kinetics | Chercheur Principal / Principal Investigator |
| Lara PILUTTI | École interdisciplinaire des sciences de la santé / Interdisciplinary School of Health Sciences | Superviseur / Supervisor |
| Katherine LINDALE | Clinical Exercise Physiology Lab | Autre / Other |

**Conditions spéciales ou commentaires / Special conditions or comments**

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13/03/2021

# Université d'Ottawa

Bureau d'éthique et d'intégrité de la recherche

# University of Ottawa

Office of Research Ethics and Integrity

Le Comité d'éthique de la recherche (CÉR) de l'Université d'Ottawa, opérant conformément à l'*Énoncé de politique des Trois conseils* (2014) et toutes autres lois et tous règlements applicables, a examiné et approuvé la demande d'éthique du projet de recherche ci-nommé.

L'approbation est valide pour la durée indiquée plus haut et est sujette aux conditions énumérées dans la section intitulée "Conditions Spéciales ou Commentaires". Le formulaire « Renouvellement ou Fermeture de Projet » doit être complété quatre semaines avant la date d'échéance indiquée ci-haut afin de demander un renouvellement de cette approbation éthique ou afin de fermer le dossier.

Toutes modifications apportées au projet doivent être approuvées par le CÉR avant leur mise en place, sauf si le participant doit être retiré en raison d'un danger immédiat ou s'il s'agit d'un changement ayant trait à des éléments administratifs ou logistiques du projet. Les chercheurs doivent aviser le CÉR dans les plus brefs délais de tout changement pouvant augmenter le niveau de risque aux participants ou pouvant affecter considérablement le déroulement du projet, rapporter tout évènement imprévu ou indésirable et soumettre toute nouvelle information pouvant nuire à la conduite du projet ou à la sécurité des participants.

The University of Ottawa Research Ethics Board, which operates in accordance with the *Tri-Council Policy Statement* (2014) and other applicable laws and regulations, has examined and approved the ethics application for the above-named research project.

Ethics approval is valid for the period indicated above and is subject to the conditions listed in the section entitled "Special Conditions or Comments". The "Renewal/Project Closure" form must be completedfour weeks before the above-referenced expiry date to request a renewal of this ethics approval or closure of the file.

Any changes made to the project must be approved by the REB before being implemented, except when necessary to remove participants from immediate endangerment or when the modification(s) only pertain to administrative or logistical components of the project. Investigators must also promptly alert the REB of any changes that increase the risk to participant(s), any changes that considerably affect the conduct of the project, all unanticipated and harmful events that occur, and new information that may negatively affect the conduct of the project or the safety of the participant(s).

Kim THOMPSON
Responsable d'éthique en recherche / Protocol Officer
Pour/For **Daniel LAGAREC** Président(e) du/ Chair of the **Comité d'éthique de la recherche en sciences de la santé et sciences / Health Sciences and Sciences Research Ethics Board**

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