# BARRIERS TO RECRUITMENT AND PARTICIPATION IN PHYSICAL REHABILITATION RESEARCH: A MIXED METHODS STUDY AMONG PEOPLE WITH MULTIPLE SCLEROSIS.

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## ABSTRACT

**Background:** Quality medical treatment requires research that applies to clinical practice. Unfortunately, research participants do not represent the population seeking treatment, with Multiple Sclerosis (MS) rehabilitation research excluding those who have had a recent relapse and those with physical disability; two groups who often seek rehabilitation. There is likely a subset of people with MS who are being excluded from rehabilitation research.

**Purpose:** To categorize those who are not willing to participate in MS rehabilitation research, and to identify facilitators and barriers to participation.

**Methods:** We analyzed registry data collected during an MS clinic visit and a physical performance assessment. Participants had the option of consenting to one, both, or neither of these visits. Those who did not agree to the physical assessment were termed 'non-participators', and regression determined predictors of this decision. Interviews explored barriers to participation described by 'non-participators', and a patient engagement session with 'participators' considered their views on reported barriers.

**Results:** There were 109 participators and 27 non-participators. Non-participators scored lower in cognition, and were more likely to live in an urban area. Those without cognitive impairment were 3.45 times more likely to participate in rehabilitation research.

Interviews (n=8) revealed four themes: (1) fear and uncertainty regarding testing, (2) negative perceptions of research, (3) frustrations with healthcare, and (4) physical impairment as a barrier to participation. Patient engagement event (n=7) revealed three themes: (1) frustrations with healthcare, (2) perceiving participation as beneficial, and (3) interest in holistic treatment.

**Conclusion:** About 19% of the sample were non-participators. Cognitive impairment predicted rehabilitation research non-participation. Fear and uncertainty, physical barriers and negative perceptions of research and healthcare influenced decisions among non-participators, while participators in physical rehabilitation research prioritized the overall benefits of research for themselves and to the community. For rehabilitation research to be applicable to the patients as intended, researchers must identify and overcome barriers and engage patients in the research process.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| BMI | Body Mass Index |
| EDSS | Expanded Disability Status Scale |
| MRI | Magnetic Resonance Imaging |
| MS | Multiple Sclerosis |

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# Chapter 1: Overview and Introduction

## 1.1 GENERAL OVERVIEW

Evidence-based health care integrates current best evidence, clinical experience, and patient values when making decisions to ensure that patients receive the very best care possible (Sackett, Richardson, Rosenberg, & Haynes, 2000). As such, effective treatment is only possible if the research informing the treatment is of the highest possible quality. For this research to adequately benefit patients, it must be applicable and generalizable to the group being studied and to clinical practice (Freemantle & Hessel, 2009). Unfortunately, those who choose to participate in clinical research do not entirely represent the population seeking treatment. For example, even after fulfilling inclusion and exclusion criteria, women, people with little formal education, people having low socioeconomic status, minorities, and the elderly tend to be underrepresented in samples used for clinical research (Ford et al., 2008; Hennekens & Buring, 1998; Killien et al., 2000; Larson, 1994). In many cases, groups excluded from research, either intentionally or unintentionally, are exactly those who could benefit from it the most, as the excluded groups have more health problems, lower mobility, and an increased mortality risk (Kelfve, Thorslund, & Lennartsson, 2013). Barriers to research participation have not been thoroughly investigated, despite the fact that barrier identification and potential subsequent elimination would greatly improve the quality of all types of clinical research, and therefore, medical treatment.

Defined as an immune-mediated disorder, Multiple Sclerosis (MS) affects the body's central nervous system, often leading to severe physical or cognitive symptoms in young adults (Ghasemi, Razavi, & Nikzad, 2017). Typically diagnosed during an individual's 30s, MS impacts people during child rearing and family development, which are some of the most

productive and important times of their lives (Gilmour, Ramage-Morin, & Wong, 2018). As a result, those living with MS experience drastically lower quality of life and higher psychological stress than those without the disease (Barin et al., 2018; McCabe & McKern, 2002; Nortvedt, Riise, Myhr, & Nyland, 1999).

MS has no known cure, and even current treatments aimed at alleviating symptoms and slowing disease progression are only partially effective (Yamout & Alroughani, 2018). Fortunately, there is increasing promise for more holistic treatments such as physical rehabilitation (Motl & Pilutti, 2012), yet the field faces a number of challenges. Recruitment for this type of research is incredibly challenging (Carter et al., 2015), likely because of the extremely low rates of exercise participation among people with MS, even those with mild levels of impairment (Chaves, Kelly, Moore, Stefanelli, & Ploughman, 2019). Additionally, the limited body of existing research in MS falls short by typically excluding people with MS who have experienced a relapse or a recent decline in function (Learmonth & Motl, 2016) despite these being the individuals who seek physical rehabilitation services (Finlayson, Plow, & Cho, 2010). Identifying and removing barriers to participation in physical rehabilitation research would help strengthen the generalizability of research findings not only for the MS population but for rehabilitation patients in general. Despite the importance of addressing the issue of non-participation, it is challenging to identify the characteristics of people who do not participate in research, precisely because they have not consented to do so.

This research uses data collected in a unique longitudinal registry that provides deep clinical phenotyping of people with MS who are referred from a tertiary MS clinic. Participants in the study can complete some or all of the three study profiles (clinical, immunological, and physical rehabilitation). In the clinical profile, participants receive a neurological exam which

includes completion of a cognitive screening tool, the Montreal Cognitive Assessment and a questionnaire scoring mood, the Hospital Anxiety and Depression Scale (Freitas et al., 2018; Snaith, 2003). The immunological profile involves having blood samples drawn and takes place at the same time as the clinical profile. The physical rehabilitation profile involves attending a session in a rehabilitation laboratory to complete further cognitive and physical testing, including a graded exercise test. This research specifically examines those participants who refuse to take part in the physical rehabilitation component. With this information, we are able to examine the characteristics of people who decline the rehabilitation portion of the study visit.

While we can potentially characterize non-participators quantitatively, engaging with and interviewing non-participators helps place context around quantitative findings and potentially reveal opinions of research and perceived barriers to participation. A mixed-methods research approach which combines quantitative and qualitative methodologies permits a more in-depth discovery of the multiple facets of a health issue or condition (Newland, Thomas, Riley, Flick, & Fearing, 2012). As such, we determined that a mixed-methods approach would be optimal for the current project.

This thesis is prepared in manuscript format with three chapters. Chapter one provides an overview of evidence-based medicine, clinical research and MS, followed by an explanation of the tools used and rationale of the current study. Chapter two is a manuscript examining barriers that prevent individuals with MS from participating in rehabilitation research, written in format for publication in Health Expectations Journal. Therefore, there is some inevitable overlap in the content between Chapter 1 and 2 in order for Chapter 2 to stand alone as a potential manuscript for publication. Lastly, Chapter Three includes an expanded discussion on barriers to research for those living with MS, with implications for research in individuals with other neurological

diseases. Chapter Three concludes with suggestions for future directions in improving recruitment methods in clinical research in populations with chronic disease and discusses limitations of this study.

## 1.2 EVIDENCE-BASED MEDICINE

Accepted as the gold standard within medical practice (Gupta, Wander, & Gupta, 2016), evidence-based medicine is the conscientious, explicit, judicious, and reasonable use of modern, high quality clinical research best evidence in making decisions about the care of individual patients (Masic, Miokovic, & Muhamedagic, 2008). Coined in 1991 by Gordon Guyatt (Guyatt, 1991), this now colloquial term was defined after Guyatt noted that traditionally, clinicians were taught to look to authority to resolve issues of patient management. He proposed that a better approach involved critically appraising research directly relevant to a clinical problem and applying the results of the best studies to the clinical problem at hand. Despite this modern nomenclature, evidence-based medicine is in fact not a novel paradigm.

If fact, years of previous work by many others, such as Suzanne and Robert Fletcher, laid the foundation for an evidence-based approach to medical treatment. Now recognized as pioneers in the evidence-based movement, Drs. Suzanne and Robert Fletcher reported in the 1960s that biomedical science often lacked translational application to clinical medicine. Working to remedy this shortcoming of research, the couple trained through the clinical scholars' program funded by the Carnegie Foundation and were taught to consolidate work in the once separate entities of public health and medicine (Sur & Dahm, 2011), going on to outline strategies to better evaluate the evidence on which clinical decisions are based in their 1982 book *Clinical Epidemiology: The Essentials* (Fletcher, Fletcher, & Wagner, 1982), a publication that

became a foundational text in the field. The body of literature surrounding evidence-based medicine has grown immensely since its inception, yet the core notion has not changed since the aforementioned early work of Drs. Suzanne and Robert Fletcher: to base medical practice on the highest quality research available.

The challenging nature of determining the quality and credibility of, or "critically appraising" (Al-Jundi & Sakka, 2017), clinical research has led to the development of a number of strategies to facilitate this process. The popular "Critical Appraisal Skills Programme", developed in 1993 by Dr. Amanda Burls (Singh, 2013) is one of the several strategies designed to aid in the assessment of the many facets of a study which must be considered during the appraisal process, such as study design, outcome variable selection and measurement, statistical analyses, and sampling methodology, all of which impact the overall quality of the appraised work (Al-Jundi & Sakka, 2017). Many critical appraisal tools include assessment of the sampling strategy and generalizability of the investigated work (Critical Appraisal Skills Programme, 2018). This raises an important consideration, as an evidence-based approach to medicine indicates that in order for research to adequately benefit patients, it must be applicable and generalizable to the group being studied and to clinical practice (Freemantle & Hessel, 2009).

### 1.3 SAMPLING IN CLINCAL RESARCH

In clinical research, we are often interested in a certain population, generally a group of people who share a common characteristic or condition. This population of interest could be as specific as volunteers at our laboratory, or as broad as MS patients worldwide, a group too large to logically include in most studies. In such cases, clinical researchers resort to selecting and including a "sample population" in the study, that is, a subset of the population which represents

the target population as much as possible (Elfil & Negida, 2017). A multitude of sample selection strategies exist, and have been broadly categorized into probability and non-probability sampling methods (Elfil & Negida, 2017), the former of which typically yields a more representative sample, as all subjects in the target population have equal chances of being selected (Shorten & Moorley, 2014). The aforementioned sampling methods are illustrated in Figure 1.1.

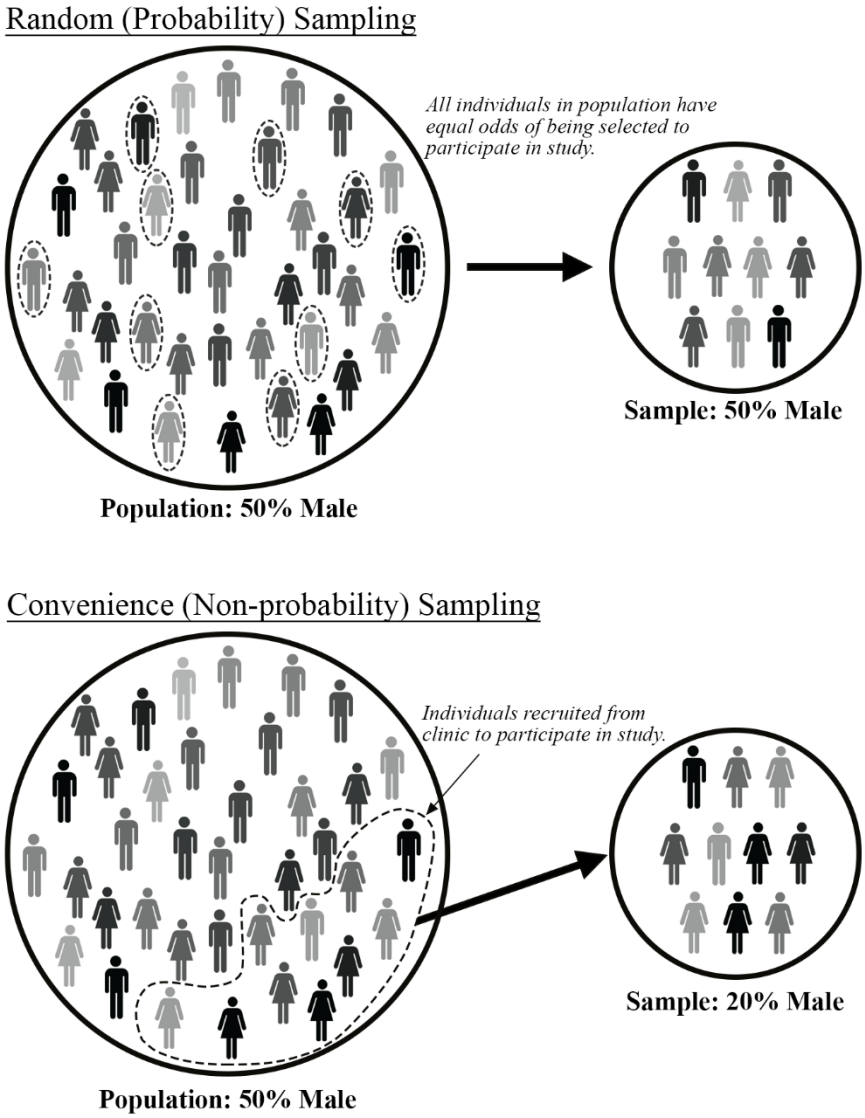


Figure 1.1: Comparing Random and Convenience Sampling

*The above figure illustrates random and convenience sampling methods. In both examples, the population of interest contains equal proportions of males and females. However, the bottom example did not yield a representative sample due to the use of convenience sampling. Original image.*

While clearly a superior sampling methodology, in actual practice, the expensive and time consuming nature of probability sampling makes it far too laborious a task for most research projects. In most cases, researchers opt for non-probability convenience sampling methods, which allow subject enrollment as availability and accessibility allow (Elfil & Negida, 2017; Emerson, 2015). For example, if we wished to perform a study on individuals from Newfoundland and Labrador with MS, our convenience sample would be confined to a population that is accessible to the team, likely meaning patients of the hospital in which our laboratory is located. According to convenience sampling methods, all patients who visit this hospital during the recruitment period, meet the eligibility criteria, and consent to participate would be included in this study. This example illustrates the potential for convenience sampling to yield an unrepresentative sample, as individuals in the population do not have equal chances of being selected for the sample. In fact, sampling method is the main methodological issue that influences the generalizability of clinical research, explaining why it is well-recognized that people who choose to participate in research typically do not entirely represent the population to be treated (Elfil & Negida, 2017). For example, even after fulfilling inclusion and exclusion criteria, women (Killien et al., 2000) and those who have less formal education and who are of a lower socioeconomic status (Hennekens & Buring, 1998) tend to be underrepresented in samples used for clinical research, a trend that is likely found in a variety of areas of research.

Investigators from an array of backgrounds have provided some insight into groups who have been underrepresented in past studies. In 2007, Dr. Jean Ford and colleagues (Ford et al., 2008) summarized much of the literature published between 1966 and 2005 which addressed barriers to enrollment in cancer treatment or prevention trials. This large systematic review revealed that African-American men, Latinos/Hispanics, Asian and Pacific Islanders, American

Indians/Alaska Natives, adolescents, adults 65 years of age and older, individuals who resided in rural areas, and individuals of low socioeconomic status were noticeably underrepresented in national cancer trials. As a result of poor sampling strategies, an abundance of cancer trials have provided findings which cannot be generalized to the population seeking cancer treatment (Ford et al., 2008), a phenomenon which is not exclusive to cancer research.

Individuals who are over the age of 77 have also historically been excluded from a variety of research studies; even research specifically addressing this "oldest old" population, have used samples in which women, those who have fewer years of formal education, and those who are institutionalized have been underrepresented (Kelfve et al., 2013). According to a 1994 descriptive review of over 700 approved research protocols, the use of unrepresentative samples is not unique to research involving individuals over 77 years of age (Larson, 1994). Larson et al. reported that the elderly, people with lower socioeconomic status, and ethnic minorities were purposively excluded from protocols without justification, implying that sampling issues are not limited to research involving a specific population. Unfortunately, in many cases, groups underrepresented in these research samples are exactly those who need it the most, as the excluded groups have more health problems, lower mobility, and an increased mortality risk (Kelfve et al., 2013).

Ramifications of poor sampling methodologies have become clear in stroke research, where groups underrepresented in stroke prevention and treatment clinical trials, specifically older individuals and ethnic minorities, have experienced a rapidly increasing incidence of stroke events (Howard & Goff, 2012). The exclusion of certain groups from research across a number of areas is yet to be explained, but personal, social, environmental, or health-related barriers to research participation undeniably contribute to these exclusions. According to Haley et al (Haley

et al., 2017), clinical research coordinators who recruited for neurological clinical trials reported that greater disease severity, poor literacy, and insufficient family support were major barriers to recruitment to clinical trials. Trials involving participants with neurological conditions such as MS have long struggled with recruitment (Carter et al., 2015), making MS a severely under-researched condition, despite its prevalence and impact on the quality of life of those living with it (Barin et al., 2018; Berrigan et al., 2016; McCabe & McKern, 2002; Nortvedt et al., 1999). Like other neurological conditions, barriers to research participation in MS have not been thoroughly considered despite the possibility that, like many other fields, research in MS has largely used samples which do not represent the population seeking treatment. The identification and subsequent elimination of barriers to research participation in MS and other neurological conditions are crucial steps in the expansion of this body of research, and will greatly improve the caliber of research which informs the medical treatment of those living with these conditions.

## 1.4 MULTIPLE SCLEROSIS

### *1.4.1 Epidemiology of MS*

Over 2.2 million people worldwide lived with MS as of 2016, a value that increased 10.4% from just 16 years prior, putting global MS prevalence at an estimated 30.1 cases per 100 000 people (Wallin et al., 2019). While increasing globally, the rate of change in MS prevalence varies by location, reaching as high as an 81.9% increase in Canadian MS cases over the same 16-year period (Wallin et al., 2019). Similarly, MS prevalence varies remarkably between geographical regions, ranging from 127 or more cases of MS per 100 000 age-standardized population in North America and northern European countries to approximately three cases of MS per 100 000 age-standardized population in eastern and central sub-Saharan Africa,

corroborating the longstanding observation of decreased MS prevalence in countries near the equator (Sharpe, 1986). Clearly, population differences have a great impact on MS prevalence.

In addition to varying prevalence based on geography, MS prevalence also varies between sexes. MS affects five women for every two men worldwide (Ghasemi et al., 2017), a trend also seen in Canada, with domestic prevalence estimates of 418 cases per 100 000 women and 159 cases per 100 000 men, respectively (Gilmour et al., 2018). These prevalence values also indicate that Canadian MS prevalence is higher than previously expected with over 290 cases per 100 000 population according to Statistics Canada, a much higher prevalence than observed in most other countries (Beck, Metz, Svenson, & Patten, 2005; Evans et al., 2013; Pugliatti et al., 2006). Nationally, an estimated 93 500 Canadians report a diagnosis of MS, making it the sixth most common neurological condition in the country (Statistics Canada, 2012).

Unlike those with other, more common, neurological conditions, individuals with MS tend to live until quite an old age. A 60-year longitudinal population study (Lunde, Assmus, Myhr, Bo, & Grytten, 2017) of 1388 individuals with MS in Norway revealed that people with MS experienced a median life expectancy of 74.7 years, compared to 81.8 years for the general population (Lunde et al., 2017). An earlier mortality analysis of Norwegian MS patients attributed only about half of the deaths to MS, with comorbid conditions such as cardiovascular disease, cancer, and infection responsible for 32.3% of deaths, combined (Smestad, Sandvik, & Celius, 2009). The causal relationship between MS and these comorbid conditions is not clear, as many of the comorbid conditions associated with MS such as hypertension, hyperlipidemia and chronic lung disease share a number of common risk factors with MS (Marrie, 2016).

Due to the complex nature of the disease, MS risk factors vary from being genetic, environmental, and even lifestyle in nature (Olsson, Barcellos, & Alfredsson, 2017; Ramagopalan, Dobson, Meier, & Giovannoni, 2010). MS displays generally low risks of familial inheritance, with first-degree relatives of people with MS displaying only a two-percent risk of developing the condition, and in cases where one monozygotic twin is diagnosed with MS, the other twin has a 17.26% chance of developing MS (Westerlind et al., 2014). Genetic inheritance of MS is attributed to a single region of the chromosome, specifically the human leukocyte antigen class II region of the HLA-DR2 haplotype on chromosome 6p21 (Miretti et al., 2005). With the relatively low genetic risk of MS development, a number of other risk factors must be considered in order to better understand, diagnose, and predict disease onset.

Environmental risk factors for MS include Epstein–Barr virus infection, history of smoking, and vitamin D deficiency (Yamout & Alroughani, 2018). Globally, 90% of the general population has been infected with Epstein-Barr virus (Cohen, 2000), a virus in which those infected present as either asymptomatic or with mild symptoms similar to those that commonly accompany other mild illnesses (Dowd, Palermo, Brite, McDade, & Aiello, 2013). Interestingly, over 99% of those living with MS have been infected with the Epstein-Barr virus (Ascherio & Munger, 2007), with MS risk increasing with the virus antibody concentration found in the system (Sundstrom et al., 2004). Additionally, a clear temporal relationship between Epstein-Barr-virus infection and onset of MS suggests the presence of a causal relationship between the two, with virus infection leading to disease onset (Sundstrom et al., 2004). Still, the widespread nature of the virus makes its vaccination and prevention quite a challenging target for MS prevention, leaving researchers to consider other risk factors and prevention strategies.

As the leading cause of preventable disease worldwide, it is not surprising that tobacco smoking has been linked to MS diagnosis, in addition to its established relationship with other diseases such as bacterial meningitis, rheumatoid arthritis, Crohn's disease, systemic lupus erythematosus, and cancer (Hedstrom, Hillert, Olsson, & Alfredsson, 2013; Piao et al., 2009). A Swedish study including over 7800 cases and 9000 controls found a distinct dose response association between cumulative dose of smoking and MS risk, suggesting a causal relationship between the two (Hedstrom et al., 2013). Present regardless of age at initial tobacco exposure, the effect of smoking on MS risk also persists for a number of years following smoking cessation, emphasizing the danger of tobacco use (Hedstrom et al., 2013). By synthesizing data from 36 articles which consider smoking-related risk of MS, a 2017 systematic review (Degelman & Herman, 2017) concluded that smoking led to a 50% increase in MS risk with a clear dose-response relationship, corroborating the previously proposed notion of a causal relationship. This evidence establishes smoking as a clear risk factor for MS, supporting the importance of the efforts of countries such as Canada, which have invested in public health strategies aimed at smoking cessation and prevention (Government of Canada, 2020).

Finally, stemming from the observance of decreased rates of MS close to the equator, many have proposed that vitamin D and sun exposure might act as another risk factor to MS (Acheson, Bachrach, & Wright, 1960). The connection between the consumption of foods high in vitamin D (fatty fish) and decreased MS prevalence in Norway suggests an antidote against the higher prevalence of MS in areas such as Canada and Scandinavia with less sun exposure (Kampman & Brustad, 2008). Ultraviolet-B light, found in sunlight, promotes vitamin D production in the human body (Nair & Maseeh, 2012), however, the exact nature of the relationship between exposure to sunlight, vitamin D, and risk of MS is not thoroughly

understood. One registry-based study which analyzed blood samples of over seven million United States military members found that higher serum concentrations of vitamin D was associated with reduced risk of MS by approximately 62% (Munger, Levin, Hollis, Howard, & Ascherio, 2006). Similarly, a decreased risk of MS has been attributed to increased cod liver oil supplementation (Cortese et al., 2015), vitamin D supplementation (Munger et al., 2004), and fatty fish consumption (Baarnhielm, Olsson, & Alfredsson, 2014), providing further evidence for the relationship between vitamin D and MS risk. Overall, it seems that increased vitamin D consumption contributes to a moderate decrease in the risk of MS development.

Knowing the risk factors and global trends associated with MS have potential to decrease the number of people suffering as a result of the disease and might provide researchers with some helpful insight into the complex pathophysiology of MS. Worldwide disease patterns often form the basis of many hypotheses of basic and clinical research, as researchers wish to understand the underlying mechanisms behind the identified trends. As such, future epidemiological research remains crucial. Technological advances surrounding health record access and analysis contribute to the constant improvement of this field, allowing for more thorough analytics and the inclusion of higher quality data.

### *1.4.2 Pathophysiology*

Defined as an immune-mediated disorder, MS affects the body's central nervous system, often leading to severe physical or cognitive symptoms in young adults (Ghasemi et al., 2017). Within the central nervous system, cells called oligodendrocytes produce a membrane known as myelin, which surrounds the axons of neurons and promotes fast and efficient nerve conduction (Stadelmann, Timmler, Barrantes-Freer, & Simons, 2019). Among individuals with MS, focused

zones of inflammation within the central nervous system caused by T-lymphocyte and macrophage infiltrations and oligodendrocyte death are responsible for damage of the myelin sheath, known as demyelination (Dendrou, Fugger, & Friese, 2015; Loma & Heyman, 2011). The demyelination and subsequent degeneration caused by MS (often called plaques or lesions) characterize the pathology of the disease, generally occurring in the white matter of the brain and spinal cord (Dendrou et al., 2015).

While present at all stages of MS, inflammation is most pronounced in acute and early phases of the disease. Minimal brain and spinal damage occurs early in the disease course, with any lesions presenting as highly focused and defined (Chard et al., 2002). These early lesions show invading peripheral immune cells and leakage of the blood–brain barrier (Dendrou et al., 2015). As the disease progresses, inflammatory T cell and B cell infiltration, microglia and astrocyte activation, and diffuse myelin reduction and axonal injury become increasingly evident, resulting in a more pronounced atrophy of the grey and white matter (Popescu & Lucchinetti, 2012). With disease progression also comes a gradual decrease in inflammation, while microglia and macrophages remain in a chronic state of activation throughout the entire disease course (Fischer et al., 2012; Frischer et al., 2015).

### *1.4.3 Types of MS*

The extreme heterogeneity of MS means that disease presentation can vary extensively from one patient to the next. Observed patterns in the clinical presentation and disease activity of individuals with MS have facilitated the development of a framework for the classification of MS presentation (Lublin et al., 2014). This framework provides clear and consistent patient group definitions for natural history and demographic studies, allowing for increased

homogeneity in clinical trials, and clarifying communications regarding MS among clinicians (Lublin & Reingold, 1996). Current MS phenotypic classifications include relapsing-remitting MS, clinically isolated syndrome, radiologically isolated syndrome, primary-progressive MS, and secondary-progressive MS (Katz Sand, 2015).

#### *1.4.3.1 Relapsing-Remitting MS*

The vast majority of patients with MS initially follow a relapsing-remitting course, defined by acute relapses from which they completely or mostly recover, with periods of relative clinical stability in between (Katz Sand, 2015). In general, a relapse refers to an acute inflammatory demyelinating event which lasts for at least 24 hours in the absence of fever or infection (Polman et al., 2011). Diagnosis of relapsing-remitting MS requires patients to present with symptoms suggestive of demyelinating lesions and imaging results consistent with MS (Katz Sand, 2015). In total, about 85% of those with MS are initially diagnosed with the relapsing-remitting type (Nazareth et al., 2018), where relapses occur once every two years, on average (Burton, O'Connor, Hohol, & Beyene, 2009). Within 10 years following diagnosis, up to 50% of those with relapsing-remitting MS develop a progressive form of the disease, with the proportion increasing to 90% within the 25 years following diagnosis (Weinshenker et al., 1989).

According to a survey completed by 5311 individuals with MS (Nazareth et al., 2018), the most common symptoms of a relapse were fatigue, numbness, tingling, problems with walking and balance, weakness, cognitive dysfunction, muscle spasms, pain, loss of coordination, depression, and sensitivity to heat. In the majority of cases, symptoms subsided within a month, yet symptoms can persist for over two months in more than 10% of cases (Nazareth et al., 2018). Like the disease itself, MS relapse heterogeneity means that symptom

severity differs between patients and relapses, from mild to extremely debilitating in severity (Nazareth et al., 2018).

#### *1.4.3.2 Clinically Isolated Syndrome*

Added to the revised MS phenotypic classifications in 2014 (Lublin et al., 2014), the classification of Clinically Isolated Syndrome is recognized as the first clinical presentation of a disease that shows characteristics of inflammatory demyelination that could be MS, but has yet to fulfill criteria of dissemination in time (Miller, Barkhof, Montalban, Thompson, & Filippi, 2005). In 85% of young adults who develop MS, onset occurs with a Clinically Isolated Syndrome (Efendi, 2015), indicating that individuals diagnosed with this classification of MS have a high likelihood of going on to meet criteria for relapsing-remitting MS in the future (Kuhle et al., 2015). Research including those diagnosed with Clinically Isolated Syndrome, has potential to provide some insight into some of the early signs and mechanisms which preface a diagnosis of MS (Efendi, 2015). With the discovery of disease modifying therapies (Discussed in section 1.4.7), an increasing number of practitioners have expressed interest in beginning MS treatment at Clinically Isolated Syndrome diagnoses in an effort to prevent further damage and disease progression as early as possible (Efendi, 2015).

#### *1.4.3.3 Radiologically Isolated Syndrome*

With the widespread use of magnetic resonance imaging (MRI) for the assessment of conditions such as headache, trauma, and other conditions, abnormalities suggestive of MS have been noted in patients who have not previously experienced clinical symptoms of the disease. Beginning in 2009, these patients have been classified as having Radiologically Isolated

Syndrome (Katz Sand, 2015). To fit this classification, discovered abnormalities must be incidental, meaning there must be no history of neurological symptoms suggestive of a demyelinating event, and the lesions must not account for functional impairment. The lesions must not be better explained by a substance or toxic exposure or another disease process with a specific exclusion for those with extensive white matter disease not involving the corpus callosum. A 2014 study found that 34% of patients diagnosed with Radiologically Isolated Syndrome developed a clinical event consistent with MS within 5 years of diagnosis (Okuda et al., 2014), making this classification, like Clinically Isolated Syndrome, an important diagnosis to consider.

#### *1.4.3.4 Primary Progressive MS*

Patients with progressive decline in neurological function for a least one year from the time of disease onset are diagnosed as having primary progressive MS (Katz Sand, 2015). An estimated 10-15% of those living with MS are diagnosed with this form of the disease (Cottrell et al., 1999). Those diagnosed with primary progressive MS experience a gradual increase in disability, with a median time between seven and 14 years until patients reach an Expanded Disability Status Scale (EDSS; Explained in section 1.5.1) score of six or more, defined as requiring a walking aid to walk less than 100 meters (Signori et al., 2018). However, it is important to note that some patients who are diagnosed with a mild form of primary progressive MS do not reach this disability level even 20 years following diagnosis (Signori et al., 2018).

In 2014, the North American Research Committee on Multiple Sclerosis described a profile of individuals with primary progressive MS based on data from 632 participants with primary progressive MS in their registry project (Salter, Thomas, Tyry, Cutter, & Marrie, 2018).

In this large sample of individuals with primary progressive MS, the mean age of diagnosis was 44.3, slightly older than the age of diagnosis for those in the registry with relapsing-remitting MS (38.2 years) and secondary progressive MS (40.0 years) (Salter et al., 2018). Primary progressive MS also differs from the other types of MS in the ratio of females to males that are affected by the disease, with reports of an equal prevalence between men and women (Ebers, 2004).

#### *1.4.3.5 Secondary Progressive MS*

Patients who experience gradual disease progression following an initial relapsing course fit the classification of secondary-progressive progressive MS (Katz Sand, 2015). Typically, gradual decline in neurologic functioning, often predominantly involving areas of the central nervous system previously involved during the relapsing-remitting course, characterizes this classification (Katz Sand, 2015). This point of transition to a progressive form of the disease can be difficult to define and is often recognized only in retrospect, at times coming years after subtle hints of progression first appear (Katz Sand, Krieger, Farrell, & Miller, 2014). Disability progression occurs at an accelerated rate for those with secondary progressive MS, with, in one study, 50% of the sample requiring a walking aid to walk less than 100 meters (EDSS of six or greater) in just four years, compared to it taking ten years to reach this proportion in those with primary progressive MS.

### *1.4.4 Diagnosis*

The McDonald criteria, most recently updated in 2017, defines the criteria for the diagnosis of MS (Thompson et al., 2018). Diagnosis of the disease requires a multifaceted approach, often including a combination of clinical symptom observation, imaging, and

laboratory testing, due to the extreme variance in disease presentation (Thompson et al., 2018). For example, many individuals with the relapsing-remitting form of the disease often appear asymptomatic between relapses, providing a situation where imaging and laboratory testing would be imperative for a diagnosis (Nazareth et al., 2018). Comparatively, in more severe cases of MS, clinical observation alone is often sufficient for diagnosis, provided the individual has had separate episodes of neurological symptoms characteristic of MS (Thompson et al., 2018).

No single reliable biomarker has been identified for MS. Still, MRI acts as an invaluable diagnostic tool which provides supportive data and often facilitates the diagnosis of MS by imaging the brain and spinal cord to check for areas of demyelination (Kaunzner & Gauthier, 2017). Approximately 50–90% of patients with MS have spinal cord lesions which are detectable using MRI, making this imaging modality sufficient for diagnosis in these cases, provided other diagnostic criteria are met (Kaunzner & Gauthier, 2017). Specifically, T2-weighted and fluid-attenuated inversion recovery MRI are used to detect high signal lesions, which are indicative of plaques of demyelination (Deangelis & Miller, 2014). This imaging approach can identify both old and new lesions, allowing for the demonstration of dissemination in time to be seen on a single scan (Deangelis & Miller, 2014).

The McDonald criteria emphasizes the importance of "dissemination in time" (suggestions that damage has occurred more than once) and "dissemination in space" (suggestions of damage in more than one place in the nervous system) when it comes to observations of biomarkers and clinical signs suggestive of disease presence (Thompson et al., 2018). Put more clearly, this means that observations indicative of MS must exist both in multiple areas of the nervous system and must be detectable at multiple points in time to meet the criteria for diagnosis. Depending on the presentation and diagnostic results, patients who do

not meet the space and time criteria are often diagnosed with clinically isolated syndrome or radiologically isolated syndrome and subsequently monitored in anticipation of an event which would lead to diagnosis of MS (Thompson et al., 2018)

### *1.4.5 Symptomology*

A wide variety of symptoms accompany MS, such as physical disability, cognitive impairment, sensory deficits, and even mental health issues (Goldenberg, 2012; Kilkkinen et al., 2007). In many cases, the first symptoms of MS include sensory disturbances such as numbness and tingling in the limbs (Goldenberg, 2012). As the disease progresses, these initially mild sensory disturbances often manifest as unilateral numbness affecting one leg that spreads to involve the other leg and rises to the pelvis, abdomen, or thorax (Goldenberg, 2012). These sensory disturbances can sometimes resolve, but unfortunately also have potential to develop into chronic neuropathic pain.

At some point during the course of the disease, at least 75% of MS patients report experiencing fatigue, making it the most commonly reported symptom of people with MS (Braley & Chervin, 2010). Defined as "a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual or desired activity", the specific type of fatigue experienced by those with MS goes far beyond a typical feeling of tiredness that one might expect (Braley & Chervin, 2010). Many have deemed fatigue the greatest contributor to a decreased quality of life among people with MS, recognizing it as the most debilitating symptom, ahead of pain and physical disability (Krupp, Alvarez, LaRocca, & Scheinberg, 1988; Smith & Arnett, 2005). While the cause of fatigue in MS remains poorly understood, some

propose that immune system dysfunction and central nervous system damage are responsible (Braley & Chervin, 2010).

In addition to fatigue, the mental health struggles which commonly accompany MS have also been recognized as contributors to the decreased quality of life experienced by those with the disease (Wood et al., 2013). Using a representative population-based cohort of 203 individuals in Australia with MS, Wood et al. (2013) found that anxiety (44.5%), depression (18.5%), and fatigue (53.7%) were extremely common among those in their sample, with rates higher than those found in an Australian sample of individuals without MS (Kilkkinen et al., 2007). Using a Norwegian sample of people with MS, another study (Beiske et al., 2008) found that prevalence of symptoms of depression and anxiety were two to three times higher in people with MS than in the general population, corroborating trends observed by Wood et al. (2013). These works illustrated the importance of considering co-morbid conditions and symptoms that commonly come with MS, observing a relationship between depression and a decreased quality of life, and an accelerated disease progression as a result of obesity and other comorbid conditions (Wood et al., 2013). The psychological toll of MS emphasizes the importance of a holistic approach to treating and understanding MS, and begins to identify the many barriers and struggles faced by people with MS face every day.

The barriers and struggles faced by those with MS are not limited to decreased mental health and fatigue, with many patients reporting limitations associated with physical impairments as well. According to the German MS registry (Stuke et al., 2009), spasticity and ataxia are also incredibly common symptoms, with prevalence rates of 59.1% and 46.8%, respectively. In the same sample, 56.6% of participants experienced bladder dysfunction, 21.7% reported sexual dysfunction, and 20.9% reported constipation, emphasizing the widespread nature of the physical

symptoms that often accompany MS (Stuke et al., 2009). A high prevalence of these physical symptoms have been shown in other samples (Azimi et al., 2019; Lin et al., 2019; Rizzo, Hadjimichael, Preiningerova, & Vollmer, 2004), with a prevalence of ataxia as high as 80% (Wilkins, 2017). Prevalence of all symptoms increase with disease progression, including prevalence associated with less common symptoms such as problems with controlling eye movement, speech problems, and difficulty swallowing, which occurred in 19.4%, 14.6%, and 7.8% of the sample, respectively (Stuke et al., 2009).

Finally, impairments in cognitive functioning associated with MS have been well documented for almost 100 years, with incredible variance between measures of prevalence reported by the early works (Cottrell & Wilson, 1926; Jambor, 1969). More recently, estimates of the prevalence of cognitive impairment among people with MS ranged from 36-70% (Amato, Zipoli, & Portaccio, 2006; Grzegorski & Losy, 2017; Stuke et al., 2009). About 30% of those with early onset MS (diagnosed before age 25) present with cognitive impairment, and novel research involving this population suggests that cognitive impairment predicts long-term disease progression, with more impairment predicting an increase in disability (Carotenuto et al., 2019). The widespread and debilitating nature of cognitive impairment and the other symptoms which accompany MS expectedly have a large impact on the lives of those with the condition.

### *1.4.6 Impact of MS*

In Canada, 82% of those living with MS reported being diagnosed between the ages of 20 and 49, with an average age of diagnosis of 37 (Gilmour et al., 2018). The average age at which Canadian mothers give birth to their first child is 29.2 years (Provencher, Milan, Hallman, & D'Aoust, 2018), meaning that MS diagnosis comes at a critical point in their lives where they are

raising and establishing a family. Upon MS diagnosis, increased disability, depression and anxiety symptoms, fatigue, and physical comorbidity are associated with decreased quality of life (Berrigan et al., 2016). This comes as no surprise, as other research has consistently shown that MS patients experience lower quality of life than control subjects without MS (McCabe & McKern, 2002; Nortvedt et al., 1999).

A Swiss research group (Barin et al., 2018) recognized that MS can severely decrease quality of life and impose high levels of psychological stress and financial strain on affected persons, by using a dataset including 855 participants with MS to consider the symptoms which act as the greatest predictors of increased burden of MS. The group found that gait problems, balance problems, fatigue, and depression had the greatest impact on the quality of life of individuals living with relapsing-remitting MS. Results were different for those living with progressive forms of the disease, where spasticity, paralysis, bowel problems, weakness, and pain were the most significant predictors of increased disease burden. Clearly, no single aspect of MS is responsible for the immense burden it places on those who live with the condition.

### *1.4.7 Treatment of MS*

Despite best efforts, researchers have yet to discover a cure for MS. As such, the current strategy to best treat those with MS involves the prescription of disease-modifying therapies with the hope of reducing relapse rates and delaying disease progression. Current approaches to disease-modifying therapies include the use of injectable and oral pharmaceuticals, as well as more experimental approaches such as bone marrow transplants and stem cell therapies (Gholamzad et al., 2019). Despite these options, there is still no optimal treatment for MS.

Beginning in the 1990s, some of the first disease-modifying drugs, such as Copaxone and interferon beta, were injectable drugs that were approved for clinical use following multiple phase III clinical trials proving their efficacy for the treatment of MS (Ali, Nicholas, & Muraro, 2013; Boster, Ford, Neudorfer, & Gilgun-Sherki, 2015). Both drugs exhibit similar immunomodulatory effects and reduce relapsing-remitting MS relapse rate by about 30% (Lugaresi et al., 2013). Despite promising evidence of a slowed disease progression as a result of the drugs, side effects such flu-like symptoms, elevated liver enzymes, and injection-site reactions limit their use for many people with MS (Gholamzad et al., 2019).

Two decades after the approval of Copaxone and interferon beta, humanized monoclonal antibodies, specifically Alemtuzumab and Daclizumab, showed similar promise in decreasing the relapse rate and slowing the progression of relapsing-remitting MS (Coles et al., 2012), yet the risk of secondary autoimmunity and decreased liver function have limited their use as a first-line therapy (Baldassari & Rose, 2017; Torkildsen, Myhr, & Bo, 2016). Recently, a number of other monoclonal antibodies have shown great promise for treating those with relapsing-remitting MS who do not respond to first and second-line therapies (Berenguer-Ruiz et al., 2016; Kappos et al., 2011), yet trials remain in preliminary stages and further research is required to bring them to regular practice.

Clearly, pharmaceutical interventions which once showed promise for the treatment of MS almost always come with an abundance of extremely debilitating side effects. In hindsight, this trend could also be found with mitoxantrone injections and oral medications such as teriflunomide, two drugs which passed clinical trial testing after displaying either potential for improving symptomatology in patients with relapsing-remitting MS and secondary progressive MS (mitoxantrone) or decreasing disease progression and number of central nervous system

lesions (teriflunomide) (Hartung et al., 2002; Millefiorini et al., 1997; O'Connor et al., 2011). Unfortunately, some of those treated with mitoxantrone developed complications such as acute leukemia (Tanasescu, Debouverie, Pittion, Anxionnat, & Vespignani, 2004), and teriflunomide treatment resulted in alanine aminotransferase increase, diarrhea, headache, nausea, and thinning hair (Comi et al., 2016). Despite their differing mechanisms of action and routes of administration, like many pharmaceutical approaches to treating MS, clinical use of mitoxantrone and teriflunomide has decreased due to physicians opting for safer and more tolerable treatment options.

The side effects which accompany traditional disease-modifying therapies have motivated researchers and clinicians across a multitude fields to explore novel treatment options including stem cell therapy and autologous bone marrow transplants (Gulin, 2015; Radaelli et al., 2014). Stem cell therapy has become an incredibly popular topic in the media, with claims of efficacy in treating a variety of conditions such as spinal cord injury, diabetes, fertility diseases, and even periodontal disease (Zakrzewski, Dobrzynski, Szymonowicz, & Rybak, 2019). Unsurprisingly, some have begun to test the efficacy of stem cell therapy in treating MS. While research is still limited, early testing suggests that stem cell therapy might improve MS-related physical impairment and regulate immune function (Karussis et al., 2010). Research is ongoing in this area, with a large phase II clinical trial, the MEsenchymal Stem cell therapy for CAnadian MS patients (MESCAMS) study, led by researchers in Ottawa and Winnipeg (Gulin, 2015).

Finally, in extreme cases of MS where patients do not respond to all treatment options, transplantation of autologous bone marrow has shown potential to improve the quality of life of those living with MS in phase I (Radaelli et al., 2014) and phase II (Mancardi et al., 2015) trials. Despite these preliminary results, like many other treatment options, bone marrow transplants

come with an abundance of risks and side effects, and still lacks sufficient evidence to support their use. Taken together, it is clear that across all treatment options, there is no ideal treatment for MS. With this is mind, it is important to consider lifestyle interventions that have potential to improve the quality of life of people with MS.

### *1.4.8 Benefits of Exercise for People with MS*

The side effects and variable efficacy associated with disease-modifying pharmaceutical approaches to MS treatment have resulted in an increased interest in research investigating the effects of modifiable lifestyle factors on MS prognosis (Hadgkiss et al., 2013). In particular, the number of clinical trials investigating the effects of exercise on MS has more than doubled in the past decade, demonstrating the growth of the field (The Cochrane Library, 2020). Proving the value of this work, recent research suggests that exercise has the capacity to help many individuals who live with MS, showing beneficial effects on muscular strength, aerobic capacity ambulatory performance, fatigue, gait, balance, and quality of life in patients with MS (summarized in Figure 1.2) (Motl & Pilutti, 2012). Research considering the benefits that people with MS might experience from changes in modifiable lifestyle factors such as physical activity is of utmost importance and can provide insights which can greatly improve the quality of life experienced by this population.

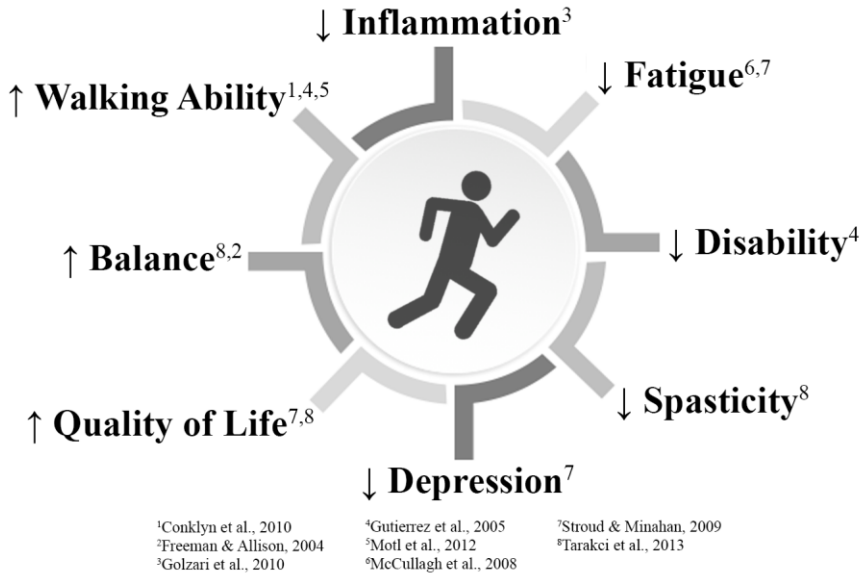


Figure 1.2: Potential Benefits of Exercise for People with Multiple Sclerosis

*Figure 1.2 provides a general summary of the proposed benefits of physical activity for people with MS. Original image.*

Understood as the underlying cause of demyelination in MS (Dendrou et al., 2015; Loma & Heyman, 2011), inflammation provides an obvious target to intervene and influence the course of the disease. Fortunately, exercise has the capacity to lower levels of inflammation in people with MS, according to a small randomized control trial involving 20 people with relapsing-remitting MS (Golzari, Shabkhiz, Soudi, Kordi, & Hashemi, 2010). Following an eight-week aerobic and resistance training program, statistically significant decreases in systemic levels of proinflammatory cytokines IFN-γ and IL-17, but not of the anti-inflammatory cytokine IL-4, were observed in study participants but non-exercise controls. Unfortunately, no firm conclusions can be made, since another trial (Schulz et al., 2004) reported no changes in levels of the proinflammatory cytokine IL-6 following an 8-week aerobic exercise intervention of slightly lower frequency involving 15 people with MS. Despite a lack of concordance, these studies prove the safety of exercise trials in populations with MS, allowing future studies to further consider effects of exercise on inflammation in hopes of developing conclusive results.

With the widespread prevalence of fatigue in people with MS, other trials have tested the effectiveness of exercise in improving fatigue levels. Results have been mixed, with one small pilot randomized control study (McCullagh, Fitzgerald, Murphy, & Cooke, 2008) involving 24 people reporting a maintained reduction in fatigue for 12 weeks following an exercise intervention. Fatigue was also addressed in an Australian cross-sectional questionnaire study (Stroud & Minahan, 2009) involving 121 participants with MS. Study participants who exercised regularly reported favorable fatigue, depression, and quality of life scores when compared to those who did not. Due to the cross-sectional nature of survey research, it important to note that it is impossible to determine whether exercise participation was responsible for the results, or that those who are less affected by MS tend to be able to be more physically active. While

promising, these studies contrast with results from another randomized control trial (Mostert & Kesselring, 2002) in which participants who engaged in regular exercise multiple times per week reported no difference in fatigue compared to a control group. However, the lack of observable differences between groups might be explained by the use of regular physiotherapy as a control condition. Overall, exercise remains a safe intervention, and shows some promise in improving fatigue in people with MS.

Other studies related to exercise in MS have considered its effects on overall quality of life. A 2013 randomized control trial (Tarakci, Yeldan, Huseyinsinoglu, Zenginler, & Eraksoy, 2013) included 99 ambulatory individuals with MS and showed promising results for exercise following a 12-week group exercise program, with participants showing improvements in quality of life, balance, functional timed test scores, spasticity, and fatigue (Tarakci et al., 2013). A 2004 pilot study (Freeman & Allison, 2004) corroborated the idea that physical activity can improve balance, reporting significantly improved balance scores which were attributed to a 10-week stretching and core stability program. With these observed differences in balance, it comes as no surprise that exercise training has also been proven to improve the gait and walking ability of individuals with MS in a number of small pilot studies (Conklyn et al., 2010; Gutierrez et al., 2005; Motl et al., 2012). Using home-based walking programs with auditory stimulation as an intervention, Conklyn et al. (2010) and Gutierrez et al. (2005) found that exercise was responsible for significant improvements lower-extremity strength, self-reported disability and gait. Similarly, Motl et al. (2012) discovered a clear relationship between an eight-week program which included aerobic, resistance, and balance activities and improvements in various measures of participants' walking ability.

The aforementioned research demonstrates the potential for exercise to greatly improve the lives of those living with MS. With the majority of research in this field reporting significant benefits, and all reporting no negative consequences, it should be recommended that people with MS engage in regular physical activity. The Multiple Sclerosis Society of Canada shares this sentiment, and has published a set of physical activity recommendations for people living with MS (Multiple Sclerosis Society of Canada, 2020). Despite this knowledge and the established guidelines, exercise participation among people with MS remains very low (Chaves et al., 2019).

### *1.4.9 Exercise Participation in MS*

For many years, it was believed that exercise exacerbated symptoms of MS and should therefore be avoided (Dalgas, Stenager, & Ingemann-Hansen, 2008; Petajan & White, 1999). Fortunately, this paradigm has changed, with many MS organizations recommending that people with MS regularly participate in physical activity (Multiple Sclerosis Society of Canada, 2020; National Multiple Sclerosis Society, 2020). Despite these recommendations, exercise participation remains extremely low among people with MS, even those with mild levels of impairment (Chaves et al., 2019). This comes as no surprise, as many of the symptoms that come with MS act as significant barriers to engaging in physical activity, with disability and fatigue cited as the greatest barriers to exercise participation. (Learmonth & Motl, 2016; Ploughman et al., 2015). In one study (Kohn, Coleman, Michael White, Sidovar, & Sobieraj, 2014), those with moderate and severe mobility impairment had 65% and 90% reduced odds of meeting recommended levels of physical activity, respectively, corroborating the association between increased disability levels and decreased physical activity.

### *1.4.10 Status of Research in MS*

Despite an enormous increase volume of research in the field of MS over the last three decades, this body of research has grown at a much slower rate than that of research involving many other conditions. Comparing the body of MS literature to that of the most common neurological condition in Canada, stroke (Statistics Canada, 2012), provides a better understanding of the relative growth in the relatively new field of MS research. A visual comparison of the number of articles published in each of these fields (Figure 1.3) clearly demonstrates the significantly accelerated growth of the field of stroke compared to that of MS. To date, no studies have addressed the complicated reasoning for the relatively slow progress in MS research.

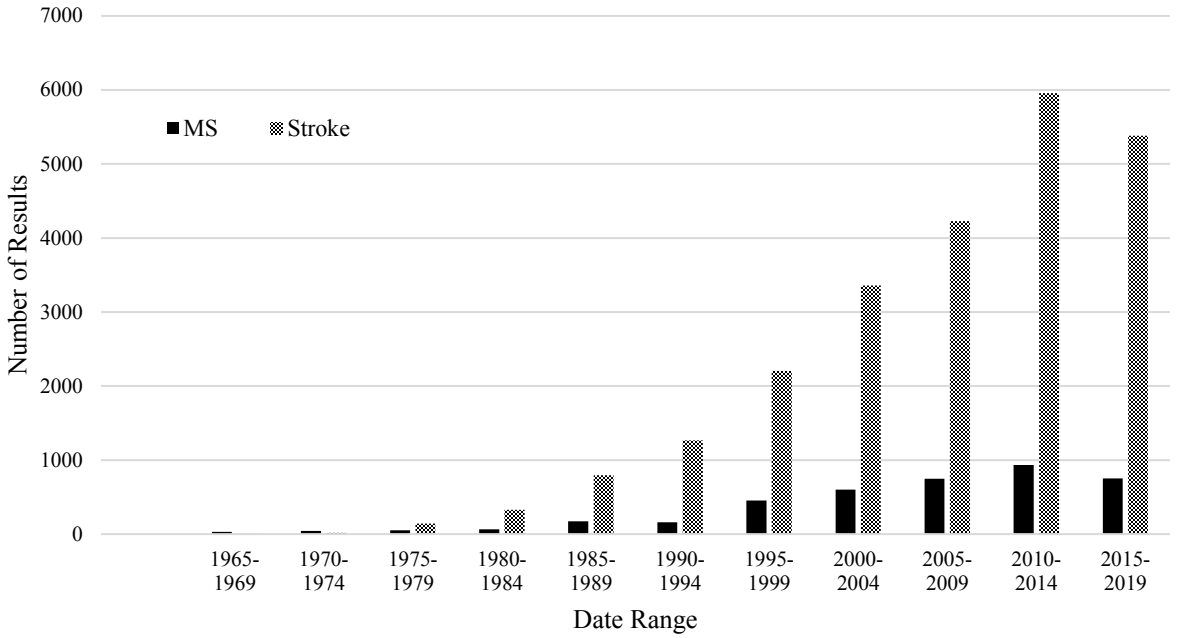


Figure 1.3: PubMed Clinical Trial Results for MS and Stroke

*These counts were obtained by searching "Multiple Sclerosis" or "Stroke" on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) and filtering results to include only clinical trials within the date range. Raw number of search results were recorded and presented in the figure. Original figure.*

Many of those living with MS report dissatisfaction with conventional healthcare, likely due to a lack of research to inform quality practice. As a result, more than half of those living with MS seek complimentary or alternative medical treatment (Nayak, Matheis, Schoenberger, & Shiflett, 2003). In some cases, people with MS have sought unproven and invasive procedures, such as the controversial "liberation procedure", as a desperate attempt to alleviate some of the struggles that accompany MS (Ploughman, Harris, et al., 2014). Interest in this sort of non-pharmacological treatment has grown rapidly, resulting in an insurgence of research surrounding holistic and alternative treatments for MS.

In particular, an increasing number of articles have been reporting the value of rehabilitation in MS (Burks, Bigley, & Hill, 2009). According to the World Health Organization, rehabilitation can be defined as "a set of measures that assist individuals who experience, or are likely to experience, disability to achieve and maintain optimal functioning in interaction with their environments", and focuses on using a team approach to improve a person's functional ability (World Health Organization, 2011). Research on rehabilitation in this population suggests that it can greatly benefit those living with MS, yet individuals with MS refrain from seeking such rehabilitation treatment, even if it is available free of charge (Helland, Holmoy, & Gulbrandsen, 2015). This suggests the presence of a barrier preventing people with MS from taking advantage of rehabilitation services.

#### *1.4.11 Barriers to Research Participation in MS*

Investigators from many disciplines of clinical research report difficulties with participant recruitment, causing many trials to fail in achieving the desired sample size within the study's originally planned timeline or budget (McDonald et al., 2006). Similar frustrations related to

recruitment are apparent in MS-specific trials, with only 6.4% of eligible participants responding to an invitation to participate in one study, and less than half of them actually agreeing to participate (Carter et al., 2015; Helland et al., 2015). As a result, it seems that samples used in MS research might fail to represent the target population, as MS-specific research typically excludes people with MS who have experienced a relapse or a recent decline in function (Learmonth & Motl, 2016). To make matters worse, those excluded are precisely those who seek physical rehabilitation services, meaning that much of the research informing rehabilitation might not apply to those being treated (Finlayson et al., 2010). Evidently, there are barriers which prevent certain groups within the MS population from participating in research. Identification of these barriers is of utmost importance, as their resolution would greatly improve the generalizability and accessibility of future research in this field.

While barriers to participation in MS rehabilitation research have not been comprehensively investigated, one qualitative study (Helland et al., 2015) consolidated data from five focus groups which discussed motivational factors and barriers related to participants' willingness to stay in a specialized rehabilitation institution. Helland et al. (2015) found that patient beliefs surrounding rehabilitation, frustrations with healthcare, personal identity, and personal or financial and time constraints acted as significant barriers to participation in the rehabilitation program. For example, many patients felt let down by the healthcare system, as they were not aware of available services, and what rehabilitation specifically entailed. Other participants in the study wanted to avoid confronting their condition, instead wishing to live "as normally as possible, as if the disease were never there". Participants also reported that financial, family, and work constraints prevented their participation, as many feel that the benefits of rehabilitation do not justify the time commitment. These subjective barriers provide some

insight, but the inclusion of objective comparisons between those who are and are not willing to participate in rehabilitation research is imperative in the pursuit of exhaustively identifying and addressing barriers to participation.

## 1.5 METHODOLOGY RATIONALE

The current study employs a mixed methods design, which combines quantitative and qualitative investigative approaches. By using this strategy, researchers can often capitalize on the advantages of both research methodologies while offsetting the drawbacks of each (Doyle, Brady, & Byrne, 2016). Within the current study, a mixed-methods approach allowed for triangulation of findings, where multiple methodological approaches are used to ensure conclusion corroboration, and expansion, where qualitative investigation can provide more insight into quantitative findings (Doyle et al., 2016; Harrell & Bradley, 2009). For example, qualitative interviews can provide context and explanation of quantitative analysis of test results, while focus groups can provide a space for participants to reflect on findings and comment on the accuracy of study conclusions. Overall, while requiring a very different technique and approach, both quantitative and qualitative investigative approaches offer many benefits to research studies.

### *1.5.1 Rationale for Quantitative Investigation*

Quantitative research utilizes a systematic and empirical approach to investigate observable phenomena by employing mathematical models, theories, and hypotheses (Given, 2008). As such, this approach allows for the controlled and objective testing of a research hypothesis, with standardized steps to reduce bias when collecting and analyzing data, making

the validity and reliability of findings a major advantage of this approach (Carr, 1994; Given, 2008). The tightly controlled nature of this approach also brings some weaknesses, such as lacking the ability to measure human behaviour in natural settings, and the inability to investigate some topics which are difficult to quantify in numbers, such as patient symptoms and subjective well-being (Au et al., 2005; Given, 2008). Overall, these weaknesses must be taken into account when designing studies and interpreting results, while making an effort to utilize techniques which minimize the impact of the shortcomings of this approach.

### *1.5.2 Rationale for Qualitative Investigation*

Qualitative research explores the human elements of a given topic and often provides insight into many of the "why" questions that arise during a research project (Given, 2008). Unlike quantitative research, which uses a simplified, reductionist view of a variable to measure and count the occurrence of states or events, qualitative methods take a holistic perspective which preserves the complexities of human behaviour (Black, 1994). This subsequently allows researchers to deeply probe and obtain rich descriptive data about social phenomena (Given, 2008) by employing various qualitative methodologies such as interviews and focus groups, which are the most popular (Gill, Stewart, Treasure, & Chadwick, 2008). As such, the current study included the use of semi-structured interviews and a focus group within the study design, to provide some qualitative insight into the investigated phenomena.

#### *1.5.2.1 Use of Semi-Structured Interviews*

Interviews allow for the collection of information from individuals about their own beliefs, practices, and opinions, making them the most common method of data collection in

qualitative research (Harrell & Bradley, 2009). The current study used semi-structured interview methods and followed an interview guide (Appendix D). The questions and topics within the guide help provided structure, yet the researcher retained the freedom to decide the order of questions and to use subsequent probing questions to ensure that interview responses completely and thoroughly explored the issues covered (Harrell & Bradley, 2009). For instance, the researcher can probe by asking for answer clarification, which stimulates the interview and can uncover new data. The use of interviews can provide valuable insight into the experiences and opinions of participants in the current study.

#### *1.5.2.2 Engaging Patients and their Perspectives*

According to the Canadian Institutes of Health Research (2014), patient engagement refers to "meaningful and active collaboration in governance, priority setting, conducting research and knowledge translation", and has the ability to engage people who bring the collective voice of specific, affected communities. Recognized as the next evolution in healthcare delivery (Manafo, Petermann, Mason-Lai, & Vandall-Walker, 2018), the rising popularity of patient engagement reflects a growing realization of the benefits that including patients in research can bring, including improved participant-research relationships, the discovery of new perspectives on findings and research methodology, improved patient enrollment and decreased study attrition (Edwards, Wyatt, Logan, & Britten, 2011; Oliver et al., 2004; Swartz et al., 2004). Knowledge of these benefits has led many researchers in the field of MS to incorporate methods of patient engagement into their research, with the 21st Century Steering Group in MS (Rieckmann et al., 2015) publishing guidelines to establishing patient engagement in MS. In concordance with past research in other fields, these guidelines emphasize

the importance of patient engagement in chronic illnesses such as MS, where treatment involves a multifaceted approach and patients are faced with decisions related to treatment, interventions, and available services.

As with much of the MS-based literature, the body of work around patient engagement in MS remains quite limited. Again, groups of experts have compiled information from related fields to suggest some of the implications of incorporating patient engagement into MS research. Yeandle et al. (2018) outline a plethora of potential benefits of patient engagement is MS research such as improved outcomes, reduced healthcare utilization, and improved service quality. The group also mentioned that people with MS should have some say in the complex course of treatment that they are prescribed for the disease. Clearly, patient engagement has become a valuable tool for MS research and treatment, and has potential to benefit both researchers and patients.

## 1.6 MEASUREMENT TOOLS

Many of the patient symptoms and opinions which are of interest to researchers are incredibly nuanced and intangible, making them notoriously difficult to reliably quantify and report. With this in mind, researchers commonly use a number of measurement tools which can provide more objective measures of abstract concepts such as disability and cognition. Tools used to measure study variables are decided based on their ability to answer a research question with acceptable levels of validity and reliability (Bastos, Duquia, Gonzalez-Chica, Mesa, & Bonamigo, 2014). Validity and reliability refer to an instrument's ability to evaluate the specific intended phenomena, and to consistently generate the same results after being applied repeatedly to the same group of subjects, respectively (Bastos et al., 2014). The current study includes data

collection instruments which were designed to measure disability, disease impact, mental health status, and cognition. Before the inclusion of these instruments in current analysis, it is important to consider their validity and reliability when used in people with MS.

### *1.6.1 Disability*

The current study assessed disability using the Expanded Disability Status Scale (EDSS). Developed in 1983 to rate neurologic impairment in MS, the EDSS rates patient disability status on a scale ranges from zero to ten, in increments of 0.5, with 0.0 to 3.5 indicating good functional status with no assistance required, 4.0 to 5.5 indicating decreased walking ability, 6.0-9.5 indicating increased need of assistance for daily living, and 10 indicating death due to MS (Kurtzke, 1983). Scores are determined by assessing the functional status of bodily functions such as voluntary movement, coordination, organ function, sensory processing, bowel and bladder function, visual acuity, and others (Kurtzke, 1983). The EDSS has been widely used since 1983 with very few alterations, and remains the most widely used instrument in clinical trials assessing the effectiveness of therapeutic interventions (Cinar & Yorgun, 2018; Meyer-Moock, Feng, Maeurer, Dippel, & Kohlmann, 2014).

According to a systematic literature review and validity evaluation of the EDSS, the scale provides a perfectly acceptable tool to score physical disability in people with MS (Meyer-Moock et al., 2014), with some limitations to consider. The scale sacrifices some objectivity, as it incorporates the subjective judgement of a neurologist while scoring patient impairment (Meyer-Moock et al., 2014). Likely due to the subjective nature of scoring, EDSS scores sometimes show low inter- and intra-rater reliability, and a substantial degree of inter-examiner variability (Amato & Portaccio, 2007; Meyer-Moock et al., 2014). Despite its limitations, EDSS

remains the gold standard for tracking disability progression in people with MS (Bermel, Waldman, & Mowry, 2014).

### *1.6.2 Perceived Impact of MS*

The current project used the Multiple Sclerosis Impact Scale (Appendix A) to measure the perceived, subjective impact of MS on participants. The Multiple Sclerosis Impact Scale measures the physical and psychological impact of MS from the patients' perspective by asking the amount which MS impacts the patient's ability to do tasks such as carry objects or do physically demanding tasks, or the amount that patients have been bothered by occurrences such as problems with balance, difficulty using hands, or feeling low in confidence (Hobart, Lamping, Fitzpatrick, Riazi, & Thompson, 2001). Initial tests by the creators report that it provided acceptable, reliable, and valid results in the original test population (Hobart et al., 2001). Subsequently, an assessment of the psychometric properties of the Multiple Sclerosis Impact Scale in community and hospital settings revealed that it provides an adequately reliable and sensitive self-report measure to use in future research (McGuigan & Hutchinson, 2004), corroborating past evidence reporting its reliability and validity for use in hospital and community samples (Riazi, Hobart, Lamping, Fitzpatrick, & Thompson, 2002).

### *1.6.3 Mental Health*

Results of the Hospital Anxiety and Depression scale (Appendix B), developed by Zigmond and Snaith in 1983, provided a measure of symptoms associated with anxiety and depression in this study (Zigmond & Snaith, 1983). The hospital anxiety and depression scale includes seven questions related to both anxiety and depression, asking participants to report the

degree to which they experience worrying thoughts, can still enjoy things they used to enjoy, or feel restless (Zigmond & Snaith, 1983). In MS, this has been proven to be a valid self-reported screening instrument for depression and anxiety (Honarmand & Feinstein, 2009). The Hospital Anxiety and Depression scale is also a reliable and valid instrument for screening clinically relevant anxiety and depression symptoms in other conditions such as cancer, epilepsy, stroke, and autism (Ayis, Ayerbe, Ashworth, & C, 2018; Uljarevic et al., 2018; Villoria & Lara, 2018; Wiglusz, Landowski, Michalak, & Cubala, 2016).

### *1.6.4 Cognitive Ability*

Within the registry data used for this study, administration of the Montreal Cognitive Assessment (Appendix C) provided measures of cognitive function. The Montreal Cognitive Assessment is a one-page, 30-point test that assesses short-term memory, visuospatial abilities, executive function, attention, concentration, working memory, language, and orientation to time and place (Nasreddine et al., 2005). This assessment acts as a valid and reliable instrument for assessing global cognitive function in individuals with Parkinson's disease (Kletzel, Hernandez, Miskiel, Mallinson, & Pape, 2017), mild cognitive impairment (Kaya et al., 2014), dementia (Kaya et al., 2014), Huntington's disease (Videnovic et al., 2010), and also in elderly individuals (Lu et al., 2011). In the field of MS, the Montreal Cognitive Assessment has been deemed a useful and sensitive instrument to identify MS-related cognitive impairment (Freitas et al., 2018) (Konstantopoulos & Vogazianos, 2019), even in patients with mild functional disability measured using EDSS (Dagenais et al., 2013).

## 1.7 OBJECTIVE OF THESIS

The purpose of the current project is to address the generalizability of rehabilitation-based MS research by comparing characteristics of individuals who were and were not willing to participate in the physical rehabilitation portion of a study. Additionally, we aimed to identify barriers that prevented individuals with MS from participating in rehabilitation-based research with the goal of facilitating future recruitment of research subjects.

## 1.8 CO-AUTHORSHIP STATEMENT

This research was conducted under the supervision of Dr. Michelle Ploughman, who provided guidance and insight during each phase of the project. The current project analyzed data initially collected for the Health Research Innovation Team in Multiple Sclerosis registry, a collaborative project by Drs. Michelle Ploughman, Craig Moore, and Mark Stefanelli. Ryan Pretty completed the literature review and wrote all sections of the thesis. Additionally, Ryan independently performed all quantitative data analysis and qualitative investigation, collaborating on the qualitative data analysis where required. Qualitative analysis requires collaboration, and Caitlin Newell helped with transcript analysis at this point. Dr. Michelle Ploughman, Arthur Chaves, Marie Curtis, Caitlin Newell, Hailey Wiseman, Elizabeth Wallack, and Alice Chen have helped with data collection for the registry project from which we extracted data. Drs. Michelle Ploughman, Craig Moore and Holly Etchegary initially provided insight into the logistics of designing the current project, and provided feedback on the thesis.

Barriers to recruitment and participation in multiple sclerosis physical rehabilitation research: A mixed methods study.

Ryan Pretty, Arthur Chaves, Caitlin Newell, Craig S. Moore, Mark Stefanelli, Michelle Ploughman

## Chapter 2: Manuscript

### 2.1 Introduction

Modern medical practice integrates current best evidence, clinical experience and patient values while making decisions to ensure that patients receive the very best care possible, an approach known as evidence-based medicine (Sackett et al., 2000). As such, the quality of patient care reflects the quality of the research informing the treatment, highlighting the importance of performing high-caliber research which directly applies to the person seeking treatment (Freemantle & Hessel, 2009). Unfortunately, research often involves samples which do not entirely represent the population to be treated, creating issues in the generalizability of results. For example, even after fulfilling inclusion and exclusion criteria, women, people with little formal education, people having low socioeconomic status, minorities, and the elderly tend to be underrepresented in samples used for clinical research (Ford et al., 2008; Hennekens & Buring, 1998; Killien et al., 2000; Larson, 1994). In many cases, those who are excluded from research, either intentionally or unintentionally, are exactly those who could benefit from it the most, as the excluded groups tend to have more health problems, lower mobility, and an increased mortality risk (Kelfve et al., 2013). Research investigating the barriers to research remains limited. Nevertheless, their identification and potential subsequent elimination would greatly improve the quality of all types of clinical research, and therefore, medical treatment.

Participants must consent to participate in research, leaving no data available describing a potential participant who has not been contacted, who does not volunteer, or refuses to participate. This data gap places the research community in a conundrum in that “it doesn’t know what it doesn’t know”. The characteristics and circumstances of study ‘non-participants’ are essentially inaccessible to researchers and to evidence-based practice in general. Some studies

gather enough descriptive information from non-participants that the reader can surmise whether there was systematic or unintentional exclusion of certain groups. For example, MS-specific rehabilitation research typically excludes people with MS who have experienced a relapse or a recent decline in function (Learmonth & Motl, 2016), despite these being the individuals who seek physical rehabilitation services (Finlayson et al., 2010). While limited, even existing quantitative literature in this field does not outline the characteristics of people who refuse to participate, important information in order identify and remove barriers to rehabilitation research participation. Qualitative research may offer insight into the lived experience of research participation and non-participation. By exploring the lived experiences and perspectives of people who consider participating in rehabilitation research, researchers can gain insight on factors influencing participation such as potential participants' attitude, knowledge and perceived barriers that may otherwise be inaccessible. For example, using qualitative interviews, one study (Helland et al., 2015) revealed that negative opinions surrounding rehabilitation, frustrations with healthcare, and financial, family, and work constraints acted as barriers to participation in a rehabilitation program; many participants expressed that the possible benefits of rehabilitation did not justify the time commitment. Additionally, while not specifically in the field of MS, greater disease severity and poor literacy have been reported as barriers to recruitment for neurological clinical trials (Haley et al., 2017). Utilizing mixed methods that include quantitative and qualitative inquiry and patient engagement may help uncover "who are we missing and why?" in terms of rehabilitation research.

Defined as an immune-mediated disorder, MS affects the body's central nervous system, often leading to gradual and unpredictable symptomology including physical disability, fatigue, cognitive impairment, sensory disturbances, mental health issues, and bladder, bowel and sexual

dysfunction (Beiske et al., 2008; Braley & Chervin, 2010; Ghasemi et al., 2017; Goldenberg, 2012; Kilkkinen et al., 2007; Stuke et al., 2009; Wood et al., 2013). Typically diagnosed between the ages of 16 and 40, MS impacts people during some of the most productive times of their lives (Gilmour et al., 2018). Largely due to the timing and severity of the symptomatology that comes with MS, those with the disease report a drastically lower quality of life and higher psychological stress compared to those without MS (Barin et al., 2018; McCabe & McKern, 2002; Nortvedt et al., 1999).

MS has no known cure, and even current treatments aimed at alleviating symptoms and slowing disease progression are only partially effective (Yamout & Alroughani, 2018). Fortunately, complimentary treatments such as exercise and physical rehabilitation show increasing promise for helping those with MS (Motl & Pilutti, 2012), yet this new field faces a number of challenges. First, recruitment for this type of research is challenging (Carter et al., 2015), likely because participation in exercise is known to be extremely low among people with MS, even those with mild levels of impairment (Chaves et al., 2019). Additionally, the limited body of existing research in MS typically excludes people with MS who have experienced a relapse or a recent decline in function (Learmonth & Motl, 2016) despite these being the individuals who seek physical rehabilitation services (Finlayson et al., 2010). Determining the factors that influence participation in MS rehabilitation research and addressing these factors may ultimately improve both the quality and accessibility of MS research. To date, there has been no research exploring the reasons why certain patients, especially those who would typically avail of rehabilitation services, would become research non-participants.

Our team operates a unique longitudinal research registry that provides annual deep clinical phenotyping of people with MS using a battery of tests which includes three

components: 1. clinical assessment by a neurologist, 2. blood samples obtained during the clinical visit for neuroimmune profile and 3. physical profile completed in a rehabilitation research laboratory that is scheduled in follow-up. Subjects are approached to participate in the registry during their MS clinic visit and have the option of consenting to some, none, or all components of the registry. By providing these options, the registry holds at least clinical data on those who do not consent to participate in the physical rehabilitation profile. With this information, we are able to characterize non-participators to potentially identify factors that could explain why they may have refused to participate in rehabilitation research.

In this study, the overarching aim was to identify factors contributing to refusal to participate in the physical rehabilitation research component of a longitudinal registry among persons with MS. Using three methodological approaches, the objectives of the study were to: 1. Determine predictors of non-participation from clinical data (quantitative aspect), 2. Explore barriers to participation using qualitative interviews among non-participators and 3. Engage the members of the patient advisory committee (who were also rehabilitation research 'participators') to obtain perspectives on the themes derived from qualitative interviews. Based on previous results from exercise research in MS, we hypothesized that people with higher levels of disability, depression and fatigue would be less likely to participate in rehabilitation research (Ploughman, 2017; Ploughman et al., 2015)**.** We also anticipated that because the rehabilitation research assessment required a separate visit, geography and transportation could be barriers.

## 2.2 Materials and Methods

The MS longitudinal registry project was approved by the Health Research Ethics Board (HREB#2015.103). Secondary use of the data (HREB#2018.067) and permission for qualitative research (HREB#2018.212) was approved by the same board.

### *2.2.1 Registry Participants*

The current study utilized data collected between 2015 and 2018 as part of a longitudinal registry of people with MS in the province of Newfoundland and Labrador, Canada. This registry combines clinical, neuroimmune, physical and psychological profiles to create rich, detailed longitudinal profiles of individuals with MS. An MS neurologist collected clinical and cognitive profile data, and for those individuals who provided written consent, a physical profile assessment was scheduled in a rehabilitation research laboratory supervised by a neuroscientist/physiotherapist. The physical rehabilitation research visit included upper limb measurement, walking tests, a graded maximal exercise text, and non-invasive measurement of central nervous system function using Transcranial Magnetic Stimulation. Participants were provided detailed descriptions of all three aspects of the registry (clinical, neuroimmune, rehabilitation) and could consent to any combination of components. Therefore, the registry includes people with MS who participate in the clinical visit and the rehabilitation research visit (herein referred to as "participators") and people who specifically refused the physical rehabilitation research testing; for the purposes of this analysis, these individuals were designated as "non-participators".

### *2.2.2 Qualitative Interview Participants*

"Non-participators" identified in the registry were contacted randomly by a member of the research team and invited to participate in a short telephone or in-person interview. If the participant expressed interest, the researcher scheduled an interview in the time and format preferred by the individual. Participants were recruited until no new information was being gleaned, known as the point of data saturation (Saunders et al., 2018)

### *2.2.3 Patient Engagement Participants*

Individuals who previously volunteered as patient engagement advisors to the research team were contacted until eight individuals agreed to attend a focus group session. This group size was chosen because it aligned with previous recommendations of typical focus group size ranging between five and eight participants (Krueger & Casey, 2014). These consultants had participated in all aspects of the longitudinal registry project including the physical rehabilitation profile. They were chosen because they could potentially provide a different viewpoint than non-participators, creating data triangulation in order to validate previous results while adding a new perspective (Carter, Bryant-Lukosius, DiCenso, Blythe, & Neville, 2014). Seven individuals attended the patient engagement focus group, all of whom were already included in the registry project.

### *2.2.4 Quantitative Methodology*

#### *2.2.4.1 Predictor Variables*

Demographic variables collected by a neurologist during the clinic visit included age, sex, height, weight, postal code, type of MS, and years with symptoms of MS. As established by

the World Health Organization (World Health Organization, 1995), height and weight values were used to calculate Body Mass Index (BMI). Participant's postal code provided geographical location as either urban (1) or rural (0), according to the Canada Post postal code classification.

The current study assessed disability using the Expanded Disability Status Scale (EDSS), the gold standard for tracking disability progression in people with MS (Bermel et al., 2014). Developed in 1983 to rate neurologic impairment in MS, the EDSS rates patient disability status on a scale ranges from zero to ten, in increments of 0.5, with 0.0 to 3.5 indicating good functional status with no assistance required, 4.0 to 5.5 indicating decreased walking ability, 6.0-9.5 indicating increased need of assistance for daily living, and 10 indicating death due to MS (Kurtzke, 1983). The EDSS has been deemed an acceptable tool to score physical disability in people with MS (Bermel et al., 2014)

In terms of symptom severity, participants rated the impact of fatigue, pain and heat sensitivity by placing a mark on a 100mm line from 0, no symptom impact, to 100, severe symptom impact. The use of a visual analogue scale to rate MS symptoms has been validated among people with MS (Ploughman, Austin, Stefanelli, & Godwin, 2010; Ploughman, Beaulieu, et al., 2014).

The Multiple Sclerosis Impact Scale (Appendix A) provided insight into the perceived impact of MS on participants. This scale measures the physical and psychological impact of MS from the patients' perspective, and provides acceptable, reliable, and valid results in both hospital and community settings (Hobart et al., 2001; McGuigan & Hutchinson, 2004; Riazi et al., 2002). Multiple Sclerosis Impact Scale scores range from 29-145, with 20 questions addressing the physical impact of MS (range of 20-100), and nine addressing the psychological impact of MS (range of 9-45) (Hobart et al., 2001). This scale asks participants to rate the degree to which they

have been bothered by physical impacts such as stiffness and spasms in their limbs, and psychological effects such as feelings of depression or anxiety.

Results of the Hospital Anxiety and Depression scale (Appendix B), developed by Zigmond and Snaith in 1983, provided the measures of anxiety and depression included in this study (Zigmond & Snaith, 1983). The Hospital Anxiety and Depression scale includes seven questions related to both anxiety and depression, asking participants questions such as the degree to which they experience worrying thoughts, can still enjoy things they used to enjoy, or feel restless (Zigmond & Snaith, 1983). In MS, this tool has been proven to be a valid self-reported screening instrument for depression and anxiety (Honarmand & Feinstein, 2009), and provides a reliable and valid instrument for screening clinically relevant anxiety and depression symptoms in other conditions such as cancer, epilepsy, stroke, and autism (Ayis et al., 2018; Uljarevic et al., 2018; Villoria & Lara, 2018; Wiglusz et al., 2016). This scale includes anxiety and depression subscales, which use a four point (0–3) response category yielding a possible score range of zero to 21 for each subscale (Snaith, 2003), with subscale scores of 11 or greater suggesting the likely presence of anxiety or depression (Snaith, 2003). Statistical analysis revealed clear skewness in Hospital Anxiety and Depression Scale scores, leading to the recording of anxiety and depression subscale totals into a binary variable, with subscale scores of 11 or greater being labelled as likely anxiety or depression (Snaith, 2003).

Within the registry data used for this study, administration of the Montreal Cognitive Assessment (Appendix C) provided measures of cognitive function. This assessment tool is a one-page, 30-point test that assesses various areas of cognition such as short-term memory, visuospatial abilities, and orientation to time and place (Nasreddine et al., 2005). In the field of MS, the Montreal Cognitive Assessment (MOCA) has been deemed a useful and sensitive

instrument to identify MS-related cognitive impairment (Freitas et al., 2018; Konstantopoulos & Vogazianos, 2019), even in patients with mild functional disability (Dagenais et al., 2013). MOCA scores can range from zero to 30, with scores of 26 or above indicating a very low likelihood of the participant having mild cognitive impairment (Nasreddine et al., 2005).

#### *2.2.4.2 Outcome Variable*

The outcome of participation in the physical profile was simply categorized based on whether or not the participant gave consent to participate in the physical rehabilitation research testing portion of the study (yes/no).

#### *2.2.4.3 Data Analysis*

Participant characteristics of the entire sample were described using either mean and standard deviation (descriptive statistics) or a percentage (frequencies). To compare the characteristics between participator and non-participator groups, we used mean and standard deviations for continuous variables (ANOVA) and percentages for categorical variables (chi-square test comparisons). Prior to ANOVA mean comparisons, normality of distribution was checked for all variables using Kolmogorov-Smirnov and Shapiro-Wilk's tests, and variance homogeneity between groups was assessed using Levene's Test for Equality of Variances. In the case of EDSS, skewed data led to the use of a non-parametric comparison, the Mann–Whitney U test.

To determine the variables which predicted participation in the physical rehabilitation research component of the project, a simple binary logistic regression was conducted for each predictor variable (demographic, disability, symptom severity, mood and cognition) with the

outcome of participation (yes/no) in the physical profile. Before proceeding to be included in the regression, all continuous variables were assessed for normality using acceptable limits of ±2 for skewness and kurtosis based on previous research (Gravetter, Wallnau, & Forzano, 2018). Variables that failed the test of normality were recoded into categorical variables, with recoded variables retained based on higher $R^2$ values when compared to the original variables using a simple logistic regression. At this stage, BMI was recoded into four categories: 1. underweight (15 to 19.9), 2. normal (20 to 24.9), 3. overweight (25 to 29.9), and 4. obese (30 or greater) (World Health Organization, 1995), and Montreal Cognitive Assessment scores were recoded into a binary variable, with scores of 25 and below indicating the probable presence of mild cognitive impairment, based on previously determined cutoff scores (Nasreddine et al., 2005).

Next, we assessed the significance of each explanatory variable, and predictors which were significant at the $p<0.01$ level proceeded to the final multivariate logistic regression. An assessment of correlation coefficients and variance inflation factor determined that there was a low likelihood of multicollinearity between regression variables. IBM SPSS Statistics Version 24 was used for all data analysis.

### *2.2.5 Qualitative Methodology*

#### *2.2.5.1 Qualitative Interviews*

A male graduate student researcher (RP) who had been working in the field of MS for four years at the time of data collection and was outside of the participants' circle of care conducted the interviews. These interviews were one hour long, and the researchers used a semi-structured interview guide to direct conversation, and probe accordingly (Appendix D). Participants' were prompted to discuss their experiences living with MS, focusing on their

current symptoms, their views on how health behaviours such as exercise impacted MS, and their opinions of research and the health care system. The questions and topics within the guide helped provide structure, yet the researcher retained the freedom to decide the order of questions and to use subsequent probes to ensure that interview responses completely and thoroughly explored the issues covered (Harrell & Bradley, 2009). Participant demographic information was extracted from the database.

#### *2.2.5.2 Interview Analysis*

Interviews were audio recorded and transcribed verbatim with identifying information removed and names substituted with pseudonyms. The interviews were analyzed using the framework method (Gale, Heath, Cameron, Rashid, & Redwood, 2013), in which the following steps were employed: (1) transcription, (2) familiarization with interview, (3) coding, (4) developing a working analytical framework, (5) applying the analytical framework, (6) charting data into the framework matrix, and (7) interpreting the data. Content familiarization involved two researchers (RP, CN) re-reading the transcripts and engaging in reflexive dialogue to ensure depth and richness of the interviews. The two investigators then separately coded the transcripts, and independently grouped their own codes into subthemes and themes. The researchers then collaborated to identify similarities and differences, re-classify ambiguous codes and create a framework of inter-related themes. This framework includes constructivist assumptions, such as the understanding that people construct their own knowledge. Finally, the researchers returned to the original transcripts and selected salient quotes that represented the subtheme or theme, ensuring that quotes originated broadly from the participants and that all opinions were considered.

#### *2.2.5.3 Patient Engagement*

The same male researcher who performed the interviews led the patient engagement event, with support from a female research assistant with training in social science. Following introductions at the engagement session, the researcher led a brief (25-minute) presentation summarizing the rationale, methods and some preliminary findings of the quantitative and qualitative aspects of the study. Specifically, the researcher described all aspects of the registry project, outlined how research informs health care, and explained the issue of barriers to research participation and our unique position to address these barriers. Participants were repeatedly encouraged to express any questions or comments during the presentation to ensure a thorough understanding of the project. Following the structured presentation, participants reflected on each of the findings, expressing their experiences with the outlined barriers to participation. Both researchers regularly probed with short questions to receive clarification or to stimulate discussion. To provide participants with an opportunity for anonymous comments, all participants were provided with a feedback form allowing for additional comments and questions. The engagement session lasted for 60 minutes, including the presentation and discussion portion.

#### *2.2.4.3 Patient Engagement Analysis*

The event was audio recorded, transcribed verbatim, and independently analyzed by two researchers (RP, CN) who followed the aforementioned framework method (Gale et al., 2013). The transcripts were coded, and codes were placed into emerging themes. The researchers

collaborated to identify similarities and differences and re-classified ambiguous codes. During analysis, it is important to consider the guided nature of this interaction, as participants were encouraged to discuss results of the study and the opinions of "non-participators" discovered during interviews.

## 2.3 Results

### *2.3.1 Registry Sample Characteristics*

The age of the participants in the registry (n=136) ranged from 20 to 70 years with a mean age of 48.3 years (SD=11.18), reflecting the vast age range of people with MS (Table 2.1) (Gilmour et al., 2018). The ratio of females to males (2.58:1) was similar to that reported previously (Gilmour et al., 2018). On average, participants experienced symptoms of MS for more than a decade; however, there was substantial variability with 10.5% of participants being recently diagnosed (within 5 years), and 21.1% of participants diagnosed more than 30 years before. The majority were living with the relapsing-remitting form of the disease. There were equal amounts of people living in rural and urban areas. (Table 2.1).

In terms of overall health and symptoms, on average, participants' BMI fell in the overweight category (Table 2.1), and median EDSS score of participants was 2.00 (range 0.0 – 6.5), indicating that most participants in the registry had minimal disability as defined by the MS neurologist (Kurtzke, 1983). Based on the Multiple Sclerosis Impact Scale, average physical impact was 38.78 (SD=15.26), indicating a relatively low impact based on the possible range of 20 to 100.

With respect to mood and cognitive health, prevalence of symptoms suggestive of depression and anxiety were low in comparison to expected prevalence rates based on other research (Table 2.1) (Beiske et al., 2008; Wood et al., 2013). In addition, the mean score for the psychological impact of MS based on the Multiple Sclerosis Impact Scale was 18.65 (SD=7.76), based on a possible range of 9-25, indicating a moderate perceived impact. MOCA results indicate that 38.76% of participants scored below 26, which suggests mild cognitive impairment (Hobart et al., 2001). This puts the sample of cognitive impairment prevalence at the lower end

of the expected range of 36-70% (Amato et al., 2006; Grzegorski & Losy, 2017; Stuke et al., 2009).

Table 2.1

*Participant Characteristics*

| **Characteristic** | **Overall** (n=136)<br>Mean±SD *(Range),*<br>Median *(Range), or* n (%) |
|---|---|
| Physical Profile Participation *% participators* | 80.10% |
| Age | 48.29±11.18 *(20-70)* |
| Years Since First Symptoms of MS | 17.87±10.42 (*2-54*) |
| Sex *female/male* | 98/38 |
| Location *urban/rural* | 76/60 |
| Type of MS | |
| Relapsing-Remitting | 114 (83.8%) |
| Primary Progressive | 2 (1.5%) |
| Secondary Progressive | 7 (5.1%) |
| BMI | 27.72±6.39 *(16.75-60.22)* |
| Underweight | 3 (2.2%) |
| Normal | 48 (35.3%) |
| Overweight | 40 (31.01%) |
| Obese | 38 (29.46%) |
| Fatigue *0 (low) to 100 (high)* | 39.52±31.80 *(0-100)* |
| Pain *0 (low) to 100 (high)* | 22.68±27.78 *(0-100)* |
| Heat Sensitivity *0 (low) to 100 (high)* | 28.95±32.61 *(0-100)* |
| Physical Impact of MS *20 (low) to 100 (high)* | 38.78±15.26 *(19-88)* |
| Psychological Impact of MS *9 (low) to 45 (high)* | 18.65±7.76 *(8-43)* |
| EDSS *0 (low) to 10 (high)* | 2.00 *(0-6.5)* |
| Depression *% with suggestive symptoms* | 4.24% |
| Anxiety *% with suggestive symptoms* | 15.25% |
| MOCA *% with scores below normal* | 38.76% |

### *2.3.2 Comparing Participators and Non-Participators*

Of the 136 participants included in the sample, 109 (80.15%) gave consent to participate in the physical profile and 27 (19.85%) did not. Groups did not significantly differ in any demographic variables aside from geographic location, BMI and type of MS, with a greater proportion of individuals with secondary progressive MS in the non-participator group than the participator group. As hypothesized, non-participators were more often living in a urban region. Additionally, the participator group contained more overweight and fewer underweight individuals (according to BMI) than the non-participator group. All comparisons are summarized in Table 2.2.

Average Montreal Cognitive Assessment (MOCA) score was significantly higher in the participator group. Using SPSS, a test of normality of MOCA determined that scores were skewed. As such, scores were recoded into a binary variable of simply having a score suggestive of mild cognitive impairment, with a score of 25 or less indicating likely presence of mild cognitive impairment (Nasreddine et al., 2005). Following recode, a significant difference between groups remained, with a greater proportion of non-participators having cognitive assessment scores suggestive of mild cognitive impairment.

Table 2.2

*Comparing Participators and Non-Participators*

| **Characteristic** | **Participators** *Mean±SD, %, or Mean Rank (Range)* | **Non-participators** *Mean±SD, %, or Mean Rank (Range* | *F, $\chi^2$, or U; p* |
|---|---|---|---|
| Number | 109 | 27 | |
| Age | 47.88±11.39 | 49.93±10.37 | 0.72; 0.40 |
| Years Since First Symptoms of MS | 17.08±10.53 | 20.83±9.64 | 2.49; 0.12 |
| Gender *% female* | 69.72% | 81.48% | 1.49; 0.22 |
| Geographic Location *% urban* | 59.63% | 37.04% | **4.47; 0.035** |
| Type of MS | | | |
| Relapsing-Remitting | 95.90% | 84.00% | 3.40; 0.062 |
| Primary Progressive | 2.04% | 0% | 0.52; 0.47 |
| Secondary Progressive | 3.06% | 16.00% | **6.21; 0.013** |
| BMI | 27.74±5.58 | 27.71±9.57 | 0.00; 0.99 |
| Underweight | 0.93% | 9.10% | **5.34; 0.021** |
| Normal | 34.58% | 50.00% | 1.86; 0.17 |
| Overweight | 35.51% | 9.10% | **5.96; 0.015** |
| Obese | 28.97% | 31.82% | 0.071; 0.79 |
| Fatigue *0 (low) to 100 (high)* | 40.56±31.52 | 34.15±33.51 | 0.68; 0.41 |
| Pain *0 (low) to 100 (high)* | 22.48±27.01 | 23.70±32.28 | 0.03; 0.86 |
| Heat Sensitivity *0 (low) to 100 (high)* | 29.12±33.28 | 28.10±29.64 | 0.02; 0.90 |
| Physical Impact *20 (low) to 100 (high)* | 37.29±16.05 | 36.50±10.84 | 0.60; 0.44 |
| Psychological Impact *9 (low) to 45 (high)* | 18.89±7.69 | 17.55±8.15 | 0.54; 0.46 |
| EDSS | 63.38 | 74.85 | 1047.50; 0.17 |
| Depression *% with suggestive symptoms* | 3.13% | 9.09% | 1.57; 0.21 |
| Anxiety *% with suggestive symptoms* | 12.50% | 27.27% | 3.02; 0.082 |
| MOCA *% with scores below normal* | 33.64% | 63.64% | **6.92; 0.009** |

### *2.3.3 Identifying Predictors of Non-Participation in Physical Rehabilitation Research*

In order to identify which of the variables predicted participation or non-participation, each were subjected to binary logistic regression with participation (yes/no) as the binary outcome. Assessment of continuous variables for normality using acceptable limits of ±2 for skewness and kurtosis (Gravetter et al., 2018) led to the recoding of BMI scores into categorical variables for further analysis. This univariate logistic regression step showed that geographic location (urban versus rural), type of MS, absence of mild cognitive impairment, anxiety, disability level, and BMI were all predictive of the outcome at the $p<0.10$ level. At this step, predictor variables age, years with MS, depression, fatigue, pain, heat sensitivity, physical impact of MS, psychological impact of MS, and gender were deemed not predictive of the outcome and were excluded from the final model. Aforementioned predictive variables were included in the final model for stepwise logistic regression. Once analyzed using stepwise logistic regression, absence of mild cognitive impairment remained the only variable to significantly predict physical profile participation ($B=0.23$, $p = 0.024$; Table 2.3).

Table 2.3

*Binary Logistic Regression Analysis of Predictors of Participation*

| **Characteristic** | **B** | **Sig.** | **Odds Ratio** | **95% CI** *[LL, UL]* |
|---|---|---|---|---|
| Constant | -6.54 | 0.032 | 0.001 | |
| MOCA | 0.23 | 0.024 | 1.26 | [1.03, 1.54] |
| EDSS | 0.41 | 0.64 | 1.51 | [0.27, 8.49] |
| Location | -0.26 | 0.69 | 0.77 | [0.21, 2.76] |
| Anxiety | 1.33 | 0.043 | 3.79 | [1.04, 13.82] |
| BMI | 0.047 | 0.37 | 1.05 | [0.95, 1.16] |

*2.3.4 Interview Participant Characteristics*

Table 2.4

*Interview Participant Characteristics*

| **Name** | **Gender** | **Age** | **Type of MS** | **EDSS** *0 (low) to 10 (high)* |
|---|---|---|---|---|
| Laura | Female | 61 | RRMS | 6.0 |
| Lori | Female | 54 | RRMS | 0.0 |
| Gail | Female | 51 | RRMS | 0.0 |
| Alice | Female | 21 | RRMS | 2.0 |
| Rachel | Female | 57 | RRMS | 2.0 |
| Dana | Female | 50 | RRMS | 1.0 |
| Candace | Female | 56 | SPMS | 6.0 |
| Tamara | Female | 33 | RRMS | 1.0 |

*RRMS = Relapsing Remitting MS; SPMS = Secondary Progressive MS*

*2.3.5 Interview Results*

Eight females were interviewed. Six participated in telephone interviews, while two opted for in-person interviews. Interview length ranged from 25 to 45 minutes. Following independent coding of interview text by two investigators, one coder presented eight codes, while another presented ten, with six codes in common. Following discussion regarding the differing codes, researchers agreed on nine codes in total, which could be grouped into four overarching themes. The researchers re-coded all interviews based on the new framework to ensure consensus on transcript coding and interpretation.

*Theme 1: Fear and uncertainty regarding exercise and physical rehabilitation research.*

Codes categorized under the theme "Fear and uncertainty" appeared in all interview transcripts. This broad theme was subdivided into three subthemes, based on the types of reports that led to fear and uncertainty surrounding participation in physical rehabilitation research.

*Subtheme 1a: Incongruence between what the research nurse explained during the consent process and participant's recollection of what was being asked of them* occurred in seven of eight interviews.

*I'm pretty sure [the research nurse] mentioned heat and steam (…) As soon as she said that, I went oh my god, no... I am not deliberately making myself sick for a research study. Like, that ain't going to happen. (Candace age 56, EDSS 6.0)*

Participants expressed that it was unclear to them what the research appointment consisted of and what was expected of them. Participants reported feeling overwhelmed with information and tests during the visit with their neurologist; as such, adding more decision-making regarding rehabilitation research felt like an additional burden.

*I don't remember. As far as I know, I didn't hear anything about that. There was some mention of another part, but I didn't totally understand it. The only exercise-related thing that comes up is the physio that I do, and my walking tests and things. (Alice, age 21, EDSS 2.0)*

*I might have been told about it, but don't know what it involves. (Gail, age 51, EDSS 0.0)*

*Subtheme 1b: Concern that they would not be able to withstand the physical testing or it could make them feel sick.* Participants described concerns that physical exertion would cause worsening of symptoms. For example, Rachel (age 57), who had been living with symptoms of MS for 22 years, expressed that she did not understand the components of the physical profile, only recalling that it involved "something about running or walking". Rachel then said:

*I'm not going to come in there and make myself worse. I'll talk to you on the phone. (Rachel, age 57, EDSS 2.0)*

Tamara, who had been living with symptoms of MS for six years, echoed this sentiment:

*At the time, I wasn't feeling great as it was, and I thought exercise would just make me feel worse. (Tamara, age 33, EDSS 1.0)*

For others such as Alice, past experiences with exercise were associated with unpleasant symptoms:

*I find that when I exercise, I get really sluggish and it feels like my muscles are melting. If I'm relaxing, I feel great, but when I'm actually active it really isn't fun, and I couldn't put myself through that just for research. (Alice, age 21, EDSS 2.0)*

*There's no way… no way… that anybody who has symptoms of MS could do that physical thing, in my personal opinion. (…) I think that [the researcher] was looking for a very healthy person with MS. (Candace, age 56, EDSS 6.0)*

*Walking is getting harder for me. I use my walker everywhere I go. (…) There's no way I'd be able to do the [fitness] test. Impossible. (Laura, age 61, EDSS 6.0)*

*Subtheme 1c: Incongruence between maintaining a healthy lifestyle and participation in health research.*

Despite being unwilling to participate in the rehabilitation-based component of the registry, many interviewees acknowledged the benefits of a healthy lifestyle and recounted changes they had made in their own lives to incorporate practices that they perceived as healthy.

*I eat fish, no meat, no dairy, no egg yolks, and very low fat. I only eat very minimal olive oil, and I take omega 3 flax seed oil every day. I do mindfulness meditation for 20 or 30 minutes every day, and I exercise. I do a high dose of vitamin D…. In my own mind, it at least gives me a little bit of power. (Lori, age 54, EDSS 0.0)*

In spite of chronic fatigue and dizziness, Gail reported being physically active.

*Well, you have to stay active. I go to water aerobics twice a week and in the summer I walk pretty well every day. I'm cautious about walking outside because I don't want to fall. I really do think that's the biggest thing: to stay active. (Gail, age 51, EDSS 0.0)*

Lori and Gail were not the only interviewees to express their interest in staying physically active. Others, such as Tamara (age 33, EDSS 1.0) and Rachel (age 51, EDSS 2.0) reported taking a more moderate approach, and make sure to take a walk every day.

*Theme 2: Disillusionment with and negative perceptions of MS research overall.*

Six transcripts included multiple codes describing that participants would be unwilling to participate in future studies due to their past negative experiences with MS research.

*Subtheme 2a: Negative perceptions of research.* Some participants felt that they had lost faith in MS research and researchers, citing previous instances in which they considered the

studies to be poorly organized. In several cases, respondents felt that researchers had failed to recognize the study volunteer's time and effort.

*When I was first diagnosed, I said yes to everything and was happy to help. Now, I'm kind of over it all. Got tired of [the researchers] rescheduling my appointments, and when I did go it felt like I was just doing paperwork. (Laura, age 61, EDSS 6.0)*

Candace had participated in a number of studies, and expressed dissatisfaction with many aspects of these in great detail, she concluded:

*"Every study that I've signed up for, MS-related, (...) goes on too long, it's like there's no interest, it's pro forma, we're just filling out paperwork. (...) The people who were doing it didn't care, so why should I care? So that really turned me. (Candace, age 56, EDSS 6.0)*

For Rachel, her negative feelings towards research come from experiencing the side effects of an experimental drug:

*I was put on a drug in one study and had a really bad reaction to it. Ever since that, I haven't been interested in being in [research]. (Rachel, Age 57, EDSS 2.0)*

*Subtheme 2b: Research which tests drugs for MS having greater appeal and potentially competing with physical rehabilitation research.* Several interviewees described limiting their research participation to drug trials which they felt could provide greater personal benefit to them

than other types of research. Alice, who previously expressed her disinterest in engaging in physical activity for research, stressed the importance of pharmaceutical research, stating that she would be willing to try a new pharmaceutical treatment:

*I know that research is super important because right now there's no cure. I think taking steps that will get us to a better place with medication is the most important. Right now, I find it all very overwhelming. I'd be willing to try a new drug, but that's about it. (Alice, age 21, EDSS 2.0)*

Based on past negative experiences with injectable drugs and the cost of pharmaceutical treatment, Dana also mentioned her interest in drug research:

*Taking needles was awful. I'd like to see research on the drug side of it. I don't take any right now. I stopped them because I just can't afford it. If I have another attack, I'll see how it goes. (Dana, age 50, EDSS 1.0)*

*Unless it's a drug study, as in, you got a new drug for me to try. (Candace, age 56, EDSS 6.0)*

*Theme 3: Disappointment and frustrations with MS-related healthcare.*

Although the discussions focused mainly on research, participants reported unanimous disappointment with the MS-related care that they had received.

*I wish we had a better team. I was just reading about the new MS center in [large center], and was wondering how I could get there. I have a friend who lives in [European city], and she said that the difference is night and day. My wish is that we had a good team the worked together, and was accessible*

*when we need them. My family doctor read the neurologists notes back to me recently, and it sounded as if he was writing about somebody who didn't have anything wrong with them. It feels like [the neurologist] barely does any testing. It just isn't good enough. (Lori, age 54, EDSS 0.0)*

*To be quite honest, I'm not happy with the way things happen in [location] with my MS. When I had my [relapse], I phoned and I phoned and I phoned because I needed to see [my neurologist] then, while I was in this mess. That happened in April and I didn't get to see him until December of last year. So, it was quite disappointing. I was very frustrated. (Rachel, age 57, EDSS 2.0)*

*Theme 4: MS-related fatigue and mobility problems create barriers to participation in research.*

All eight participants identified that they felt limited by MS symptoms making it more challenging to participate in research, exercise, or activities of daily living. In particular, six of the eight participants discussed fatigue as a factor preventing their participation in physical rehabilitation research and making future plans.

*Sometimes I'll have two or three good days, but then I have a third or fourth day where I am just too tired to do and can't do much of anything. (...) I can't plan ahead very far. I even tell people that I can't promise anything anymore. I say "I'll try". (Gail, age 51, EDSS 0.0)*

*Getting anywhere is twice as hard as it used to be, and it makes me extremely fatigued. My routine is to get up around five and get dinner ready (...) If I wait too long, my walking goes downhill and I can't get anything done. Then the fatigue comes and I go and have an afternoon nap. (Rachel, age 57, EDSS 2.0)*

*[MS] really affects me more than I realize sometimes, because there are days where I get up and can't leave my house because I can't function or move properly, where I feel frozen. (...) I wish more people realized that [MS] is kind of invisible. Especially my [professors] (...) it still seems like they don't understand; I really have to sit down with them and explain what's going on. (Alice, age 21, EDSS 2.0)*

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*2.3.6 Patient Engagement Event Participants*

Table 2.5

*Patient Engagement Event Participant Characteristics*

| **Characteristic** | **Overall** (n=7)<br>*Mean±SD,*<br>*Median (Range), or Count* |
|---|---|
| Age | 46.00±8.83 |
| Gender *female/male* | 6/1 |
| Type of MS | 100% RRMS |
| EDSS *0 (low) to 10 (high)* | 2.5 *(0-6.0)* |

*2.3.5 Patient Engagement Event Results*

To begin the patient engagement session, the investigator discussed findings from the aforementioned quantitative and qualitative aspects of the project. These included (1) cognitive impairment as a barrier to exercise participation, (2) significant differences between "participators" and "non-participators", and (3) prominent themes that emerged during interviews with non-participator group members. Participants were encouraged to interject and comment as they saw fit, which they frequently did. After the study findings were presented, the investigator asked, "what are your thoughts regarding these findings?". Much discussion took place and the investigator provided occasional probes such as asking whether participants agreed or disagreed with the presented barriers and opinions.

The patient engagement session led to the formation of three distinct themes. Both verbal and non-verbal communications suggested apparent unanimous agreement among participants in the focus group. Due to the nature of the discourse, quotes could not be attributed to individuals.

*Theme 1: Endorsing disappointment with healthcare.*

Members of the patient engagement focus group agreed with many of the sentiments expressed in the previous qualitative interviews regarding dissatisfaction with their MS-related healthcare.

*When I try to tell [my neurologist] about my struggles with diet and my gut problems, they only tell me how great it is that I'm losing weight. I'm really not healthy, and my doctor just doesn't have the time to help.*

Other participants corroborated this sentiment:

*I've run into that a lot, too. I've had doctors outright deny that diet affects the disease. There is no question in my mind that diet is a huge part of it.*

*We're not told by doctors that exercise and diet can help our life. Now, when a researcher asks me to do an exercise test, I sometimes wonder why I'm being asked to do that if my doctor told me that exercise wouldn't necessarily help.*

*I think there are a lot of people who are jaded when it comes to their MS treatment. All it takes is for something with the healthcare system to not work or your doctor not being able to see you for a long time. It's really frustrating.*

*Theme 2: Research participation as personally beneficial and an altruistic contribution to the MS community.*

Despite their overall agreement with comments made by the non-participator interviewees regarding shortcomings in their MS-related healthcare, members of the patient engagement focus group viewed research as a way to improve care for MS. One participant put this quite clearly.

*I'm more altruistic. I am able to help. I'm able to do it to help people, so I'll gladly do that. If it was my child who had something wrong with him, I'd want you to be part of it to help him.*

*For people with MS, participating in research is what we must do to find a cure. This is the best way to help.*

*Participation gives us a chance to learn and ask questions. I have learned a lot.*

*Theme 3: "There has been enough done with drugs": Seeking knowledge and opportunities to improve health*

An interest in pharmaceutical research became a popular theme among non-participators, but members of the patient engagement focus group did not echo this sentiment. Instead, participators all discussed actively seeking more information on diet and lifestyle changes that could make them feel better, stressing that research on this sort of holistic approach is the most important.

*There has been enough done with drugs. Studies concerned with exercise, healthy living, things like that are the most important right no.*

*I had enough of asking my doctor for help, so I went ahead and started seeing a personal trainer at the gym. I'm their first MS patient, but thanks to exercise, I am not the same person I was a year ago. It has helped immensely.*

## 2.4 Discussion

We undertook this three-phase mixed-methods study to uncover factors contributing to refusal to participate in the physical rehabilitation research component of an MS longitudinal registry (n=136). First, about 20% did not consent to the physical testing; regression analysis

revealed that persons having cognitive impairment were 24% less likely to consent. Factors such as MS severity, age and living location were not predictive. During the second phase, we interviewed persons with MS who had refused to attend the physical testing session. They expressed frustration with their MS-related care which negatively impacted their views on research. Furthermore, they felt fearful about engaging in an exercise test and their recollections of what they were asked to do during the consent process months before did not entirely align with what would actually take place. Interviewees felt that fatigue and mobility problems made it challenging to plan to attend a future appointment. Finally, by engaging with members of the patient advisory committee (who were also rehabilitation research 'participators'), we learned that despite having frustration with MS-related care, they prioritized participation in research mainly for altruistic reasons. Their comments suggested that they were seeking ways to improve their MS and their overall health, including lifestyle modifications so physical rehabilitation research was of interest to them.

### *2.4.1 Cognitive Impairment as the only Predictor of Non-Participation*

For the first time, we have been able to characterize and engage with individuals who were not willing to participate in rehabilitation-based research. Following thorough quantitative analysis, presence of mild cognitive impairment remained the only significant predictor of participation in the rehabilitation-based portion of the study. This presents a previously undocumented finding, and is the first time that it has been suggested that samples of people with MS who participate in rehabilitation research have higher levels of cognitive ability than those who do not. Similar findings have been reported in geriatric research, where cognitively impaired geriatric patients (Taylor, DeMers, Vig, & Borson, 2012) were frequently excluded

with or without justification from general research, causing those with this impairment to be severely underrepresented in the literature

The fact that cognitive impairment influences research participation is understandable when considering that perceived personal relevance of the research is an established barrier to research participation (Attwood et al., 2016) and that cognitive impairment acts as a barrier to exercise participation in this population (Riemann-Lorenz et al., 2019). Many patients who experience cognitive decline show great deficits in decisional capacity to consent to research and often cannot grasp the ultimate benefits that their participation might yield (Gilbert, Bosquet, Thomas-Anterion, Bonnefoy, & Le Saux, 2017). This has been made apparent in the stroke population, as surrogate consent is often used in patients with a compromised cognitive status (Mendyk et al., 2015). While efforts have been made to address issues with ethical informed consent among cognitively compromised individuals (Gilbert et al., 2017; Mendyk et al., 2015), unfortunately health care providers often incorrectly assess patient reading level or comprehension of the consent process (Montalvo & Larson, 2014).

### *2.4.2 Fear and uncertainty regarding exercise and physical rehabilitation research.*

Three distinct subthemes contributed to the overall theme of fear and uncertainty regarding associated with physical activity or research involving exercise, including an incongruence between actual study components and participant recollection of these components. Additionally, many expressed worries that the physical component of the study would either be too difficult, or would lead to an exacerbation in symptoms. These two subthemes are not unique to this study, as fear of symptom exacerbation has been a well-established barrier to exercise participation among people with MS (Halabchi, Alizadeh,

Sahraian, & Abolhasani, 2017). The rationale behind this aversion to physical testing has not been thoroughly investigated, and the interviews in the current study provided little additional insight. Interestingly, this aversion to physical exercise and testing was not expressed by members of the focus group involving "participators", suggesting that it is unique to "non-participators", and acts as a barrier to participation.

The fear and uncertainty expressed by interviewees regarding participating in physical rehabilitation research could have been linked to difficulty understanding what was being expected of them. Our findings suggested that there was a mismatch between interview participants' recall of what was being asked of them and what was actually outlined in the consent form. This difficulty with recall could be related to cognitive impairment. In addition to impairing participants' decisional capacity for consent and ability to understand the benefits of research, cognitive impairment, which occurs in 36-70% of people with MS (Amato et al., 2006; Grzegorski & Losy, 2017; Stuke et al., 2009), also causes deficits in comprehension and memory in this population (Jongen, Ter Horst, & Brands, 2012). Our analysis of registry data suggests that almost 64% of "non-participators" had mild cognitive impairment, an impairment which could have contributed to the reported uncertainty and misunderstanding among interviewees from this group.

### *2.4.3 Frustrations with Healthcare and Research are a Barrier to Participation*

Many interviewees reported negative past experiences with research and healthcare, and the engagement session revealed that "participators" also express dissatisfaction with their MS-related care. This finding illustrates the importance of implementing a patient-centered approach to research, where the needs of patients inform research studies, involving patients at each step

along the way (Sharma, 2015). While many of those involved in the study cited frustrations with local services such as long wait times for appointments and lack of services as causes of their dissatisfaction, it is important to consider that many of those with MS feel helpless as a result of living with a disease with no known cure (Shnek et al., 1997). Importantly, these negative perceptions of the person's health services likely contributed to their reluctance to engage in physical rehabilitation research. Researchers attempting to recruit subjects must be cognizant of the inter-relationships between the two.

### *2.4.4 Physical Impairment as a Barrier to Participation*

Many interviewees reported that fatigue and mobility create barriers to participation both in research and in activities of daily living. Physical impairment is a well-known barrier to exercise in people with MS (Riemann-Lorenz et al., 2019), and it is therefore conceivable that this barrier would carry over to rehabilitative research participation. This presents a case of research potentially not benefitting those who need it most, as people with MS who have experienced a relapse or a recent decline in function are more likely to seek physical rehabilitation services (Finlayson et al., 2010). For individuals with MS, exercise training has beneficial effects on muscular strength, aerobic capacity, ambulatory performance, fatigue, gait, balance and quality of life (Motl & Pilutti, 2012). Breaking down this barrier to research participation has not been thoroughly considered in the field of MS, or even in many of the related fields. While some studies have tested ways to improve physical activity participation and adherence among people with MS (Backus, 2016; McAuley et al., 2007), methods to remove the barrier of physical disability have not been assessed.

### *2.4.5 Altruism as Motivation for Research Participation*

Participants of the engagement session expressed that their interest in research participation came from an understanding of the benefits of research for people living with MS. Participators valued research to such an extent that they were willing to take time to participate even while feeling dissatisfied with their overall medical care. This mindset surrounding research appears across many fields of research, and often comes from a sense of connection to science, society, or an organization (Carrera, Brown, Brody, & Morello-Frosch, 2018). Interestingly, this altruistic mindset has been associated with improved well-being for people with MS (Schwartz, Quaranto, Healy, Benedict, & Vollmer, 2013)

### *2.4.6 Limitations*

Our study is not without limitations. First, the prevalence of depression within our sample is a much lower prevalence of depression than would be expected in a typical sample of individuals with MS. It is possible that this is a result of an issue with our mental health assessment procedure, and will be addressed in subsequent research. Additionally, the sample size for the current study (n=136) is somewhat lower than desired to allow the full predictive power of the analyses. MS is an extremely heterogeneous disease with multiple subtypes and to adequately consider differences between subtypes would require a larger sample. Finally, we had a small pool of participants eligible for an interview (n=27), and as a result, were unsuccessful in recruiting any males for an interview. While the quantitative portion of the current project did not reveal any sex differences, it is important to acknowledge that interview data only provides insight from the female perspective.

## 2.5 Conclusion

We report that cognitive impairment is a barrier to rehabilitation research in MS. Additionally, those not willing to participate in the rehabilitation component of a study cite fear and uncertainty, physical impificantairment, and frustrations with research and healthcare as deterrents.

Future projects should attempt to address these barriers and make studies more accessible by taking steps to make consent and study information easier to comprehend for individuals with cognitive impairment, and should pay special attention to research accessibility and the participant-researcher relationship.

The current study has great implications for the entire body of MS-related rehabilitation-based research literature, as it suggests that certain people with MS are under-represented. Additionally, we now know that cognitive impairment is a significant barrier which prevents people with MS from participating in rehabilitation-based research. It is important that there is greater effort made for future studies in MS to be more accessible and representative of the entire population, addressing the reported barriers of cognitive and physical impairment. In this study, we also provide evidence for the value and feasibility of incorporating a multi-methods approach to research in MS. Future researchers should consider incorporating this methodological approach.

# Chapter 3: Discussion

The body of rehabilitation-based literature in MS is quite limited due to the plethora of barriers to participation that exist in this field, and even existing literature lacks generalizability to the group being treated. The primary purpose of this study was to assess the generalizability of samples used in rehabilitation-based MS research and to identify barriers that prevent individuals with MS from participating in rehabilitation-based research to facilitate future research recruitment.

We hypothesized that people with higher levels of disability, depression and fatigue would be less likely to participate in rehabilitation research (Ploughman, 2017; Ploughman et al., 2015)**.** We also anticipated that because the rehabilitation research assessment required a separate visit, geography and transportation could be barriers.

## 3.1 Discussion of Results

### *3.1.1 Cognitive impairment predicts participation in rehabilitation research*

Throughout our investigation, lack of mild cognitive impairment was associated with participation in the physical profile of our registry. Each stage of this mixed-methods project offered further evidence to support this claim. Initially, controlling for all other variables, cognition was the only significant predictor of participation in the rehabilitation-based component of our registry project within our quantitative analysis. The fact that those in the non-participator group did not seem to understand the study components further corroborates the idea that this could be because of cognitive impairment experienced by this group.

This is a previously undocumented finding, and the first time that it has been suggested that samples of people with MS who participate in rehabilitation research have higher levels of

cognitive ability than those who do not. A number of studies have reported results that can make sense of how cognitive impairment can influence research participation. For example, many patients who experience cognitive decline show great deficits in decisional capacity to consent to research and often cannot grasp the ultimate benefits that their participation might yield (Gilbert et al., 2017). A 2012 systematic review by Taylor et al. of 434 articles (Taylor et al., 2012) found that cognitively impaired geriatric patients were frequently excluded with or without justification from general research, causing those with this impairment to be severely underrepresented in the literature. Like our sample of people with MS, it appears that geriatric samples used in research might also underrepresent those with cognitive impairment.

This is precisely a case of research potentially not benefitting those who need it most. While we have established that MS patients experience lower quality of life than healthy controls (McCabe & McKern, 2002; Nortvedt et al., 1999), some research (Fernandez, Baumstarck-Barrau, Simeoni, Auquier, & MusiQo, 2011) suggests that cognitive impairment predicts lower quality of life in this population. Fernandez et al. enrolled 1992 patients from 15 countries in their multicenter, cross-sectional observational study. Using multivariate analysis, the group found that cognitive impairment was one of the significant predictors of decreased quality of life. With substantial evidence that exercise and physical rehabilitation (Motl & Pilutti, 2012; Tarakci et al., 2013) benefits quality of life in those with MS, those with cognitive impairment are those who could benefit most from this type of research and intervention.

This barrier to research participation must be addressed to benefit those with cognitive impairment, and to improve participation in all MS research. It is even unethical to include individuals in research projects if there is a chance that they do not understand all components of the project. Fortunately, there are some established methodologies which have been implemented

across a variety of fields to make research participation more accessible for those with cognitive impairment. In 2015, Fields and Calvert (Fields & Calvert, 2015) performed a review which outlined best practices to providing informed consent for people with cognitive impairment. Initially, the group emphasizes that an assessment of cognitive capacity must be performed prior to consent to determine a participant's ability to adequately understand all aspects of the research. This initial recommendation might not be sufficient, as health care providers often incorrectly assess patient reading level or comprehension of the consent process (Montalvo & Larson, 2014). Taking this and the fact that 43-70% of those living with MS experience cognitive impairment (Grzegorski & Losy, 2017) into account, it appears that the most ethical way to obtain consent, in the case of MS, would be to implement consent methodologies which are designed for those with cognitive impairment to ensure that everyone receives proper consent.

Making the informed consent process more accessible isn't a far-fetched idea. In fact, some simple alterations to the consent process can make this facet of research participation much more accessible. The aforementioned review by Fields and Calvert (2015) makes suggestions regarding two areas in which the consent process should be modified.

First, the group states that for the purposes of ethical informed consent, having a legal proxy make the decision regarding consent is often the easiest and most reliable method to provide ethical informed consent. For the purposes of the current study, we were more concerned with engaging and benefitting those who had cognitive impairment. As such, a second type of modification suggested by Fields and Calvert can benefit researchers who want to make consent more accessible for those who have cognitive impairment. The group suggests making alterations to the presentation of study information such as drastically lowering the reading level

of study and consent materials, and incorporating multiple ways of presenting information and information summaries to increase understanding of treatment information.

### *3.1.2 Physical impairment is a barrier to participation in rehabilitation research*

We report that physical impairment is a barrier to participation in rehabilitation research for people with MS. Following analysis of our semi-structured interviews, it became clear that some mention of being limited by MS-related physical impairment was made by all of those interviewed. Commonly, it was perceived by interviewees that their impairment limited their ability to participate in research, exercise, or activities of daily living despite the fact that in many cases, their EDSS scores were quite low and indicative of very mild MS.

Disability is already an obvious and well-known barrier to exercise in people with MS (Riemann-Lorenz et al., 2019), and it is therefore conceivable that this barrier would carry over to rehabilitative research participation. This reported barrier and difference between groups means that currently studied samples of people with MS who have been recruited for exercise-based research are likely less disabled, and therefore may not be representative of the population as a whole.

Like the previously mentioned barrier of cognitive impairment, the reported barrier of disability is again a case of research potentially not benefitting those who need it most. In fact, people with MS who have experienced a relapse or a recent decline in function are more likely to seek physical rehabilitation services (Finlayson et al., 2010). For individuals with MS, exercise training has beneficial effects on muscular strength, aerobic capacity, ambulatory performance, fatigue, gait, balance and quality of life (Motl & Pilutti, 2012). This is particularly important for those with higher levels of disability, as, like cognition, individuals with MS who are more

disabled tend to experience a lower quality of life, as determined by Fernandez et al in the previously described study (Fernandez et al., 2011).

Breaking down this barrier to research participation has not been thoroughly considered in the field of MS, or even in many of the related fields. While some studies have tested ways to improve physical activity participation and adherence among people with MS (Backus, 2016; McAuley et al., 2007), methods to remove the barrier of physical disability have not been assessed.

### *3.1.3 Frustrations with research and healthcare*

Frustration with the overall healthcare system was mentioned at some point by all of the interviewees. For many of the participants, healthcare and research were a single entity, and therefore negative opinions surrounding healthcare were also extended to research by proxy, despite no actual past experience with research. This is not surprising, as the fact that MS is a disease with no known cure (Yamout & Alroughani, 2018) causes many individuals with MS to feel helpless (Shnek et al., 1997) when it comes to living with the condition. A 2016 qualitative study including 16 individuals (Attwood et al., 2016) who did not agree to participate in a primary care-based physical activity trial reported a similar theme. A number of the individuals in this study reported frustrations with the staff at the clinic, as well as difficulty obtaining and scheduling appointments with their physician. Unfortunately, this is a difficult barrier to address, as researchers do not have control over the care that our participants receive. Instead, implementing educational sessions which outline the importance of research have potential to address this barrier. Our interviews revealed that many of the individuals in the non-participator group felt that healthcare and research are connected in all aspects, even sometimes blaming

researchers for some of their care-related frustrations. Mistrust of research is not a novel theme. In fact, it was noted by Holzer et al. (Holzer, Ellis, & Merritt, 2014) as one of the three shortfalls of the US public's regard for medical research. Incorporation of patient engagement into research has potential to improve the researcher-patient relationship (Johansson, 2014), making it an obvious place to begin in an effort to break down the barrier of healthcare frustrations.

### *3.1.4 Importance of Patient Engagement*

Patient engagement was one of the multiple investigation methodologies used in the current project, proving its feasibility for use in MS-related research. In the case of the current project, we engaged with participators, asking for their reflection on preliminary results from the quantitative analysis and interviews with non-participators. By engaging with research advisors who were also physical rehabilitation research participators, we were able to determine whether opinions of non-participators were shared with those in the participator group. The use of this methodology allowed us to determine that while both groups expressed great disappointment with their medical treatment, those in the participator group viewed research participation as a way to improve their outcomes. This suggested to us that the main difference in philosophy between participators and non-participators comes down their individual perception of whether research participation can benefit those living with MS.

### *3.1.5 We must exercise caution when generalizing findings to the whole population.*

In research, using representative samples if of utmost importance if we wish to use our findings to make generalizations about the population as a whole (Elfil & Negida, 2017). Unfortunately, this project has revealed that there are a number of significant differences

between those who were and were not willing to participate in the physical profile portion of our registry. This means that there is a subset of individuals with MS who have been unintentionally excluded from our research. Many researchers are not as fortunate as we are; they often do not know anything about those who do not participate in their studies, and have no way of engaging with these individuals. Based on our findings, it seems plausible that many samples used in other studies in this field have also excluded similar groups from studies. These unintentionally unrepresentative samples mean that a large amount of the current findings in MS are not generalizable to all of those living with the condition.

*3.1.6 Participators and non-participators significantly differed in place of residence.*

As hypothesized, a larger proportion of participators were from an urban area. A simple explanation for this is that our research facility is located in an urban area, making it easier for those who live in close proximity to participate. This finding is not surprising, as other studies have established that those living in rural areas and ethnic minorities are less likely to participate in health research (Tanner, Kim, Friedman, Foster, & Bergeron, 2015).

It is important to note that, in Canada, those living in rural areas tend to have a poorer health status compared to those living in urban areas (Pong, Desmeules, & Lagace, 2009). Specifically, according to Statistics Canada data (Mitura & Bollman, 2003), self-rated health of Canadians declines from the most urban regions of the nation to the most rural and remote parts. This can potentially be attributed to personal health risk factors being significantly higher in small town regions, rural regions and northern regions of Canada. These differences in health status were potentially undetectable in our data and could potentially explain our significant difference.

To address this difference, future research should determine whether the significant difference in proportion of individuals from an urban area between participators and non-participators is a result of proximity to research site or another factor that is present in a rural population. To achieve this, researchers can place some emphasis on incorporating some sort of cluster sampling technique ensure representative samples of those living in rural areas.

*3.1.7 Some established barriers to research participation were not observed in the current study.*

We hypothesized that depression and fatigue would act as barriers to participation in rehabilitation-based research, yet these differences were not present in our study.

In our sample, the Hospital Anxiety and Depression Scale was used to determine self-reported levels symptoms suggestive of anxiety and depression. Our data suggest that 4.24% of our sample had symptoms which suggest the presence of depression, while overall, the prevalence of depression in MS is approximately 30.5% (Boeschoten et al., 2017). Unfortunately, this indicates an issue with the use of the Hospital Anxiety and Depression Scale in this specific population, and does not allow us to draw any conclusions based on this data.

In MS, fatigue is typically measured using complex scales such as the Chalder Fatigue Scale, Krupp's Fatigue Severity Scale, or the Modified Fatigue Impact Scale. In the registry used for the current project, fatigue was assessed using a simple visual analogue scale which resulted in a very large variance in reported fatigue. It is possible that our tool for fatigue measurement was not sensitive enough to adequately detect differences in fatigue levels between groups.

3.2 Limitations

There are a number of limitations to the current study which could have impacted our results and conclusions. First, a number of participants had to be excluded from analysis due to incomplete data collection. Some of the tests and questionnaires for the registry are to be completed by a neurologist during a regular clinical visit. As such, there is often not enough time during an appointment to collect all data, leading to missing data. Second, the magnitude and duration of the registry project mean that inevitably, a number of individuals are responsible for data collection. This variance in study staff makes many of the outcomes subject to issues with inter-rater reliability. The sample size with complete data (n=136) seems large relative to much of the research in this field, yet is quite low for thorough analysis using data collected as part of a general MS registry. MS is an extremely heterogeneous disease with multiple subtypes, and to adequately perform analysis which takes the subtypes of MS into consideration, a larger sample size is required. Additionally, this sample was obtained in Newfoundland and Labrador, a province that is quite genetically isolated, as a result of developing from a founder population (Rahman et al., 2003). This homogenous population makes for racially homogenous samples of predominately Caucasian individuals of European descent, limiting generalizability of studies using these samples.

Furthermore, we could only successfully contact a small number of "non-participators", making convenience sampling the only viable option for choosing interview participants. As a result, we were unsuccessful in recruiting any males for an interview, leading to an interview sample which was not entirely representative of the population of people with MS. Additionally, in the introduction, we report that a factors such as socioeconomic status and race have been identified as barriers to research participation. Unfortunately, our dataset includes no information related to these fields, and therefore we could not include these factors in our analysis.

Finally, our results report much a much lower prevalence of depression than would be expected in a typical sample of individuals with MS. While depression is an important predictor to consider when it comes to research participation, this inaccurate value makes it impossible for us to perform any reliable statistical analyses involving depression scores.

### 3.3 Future Research

The current study provides the first thorough consideration of some of the barriers to participation in rehabilitation-based MS research. While discovering these barriers is a great achievement, we now realize that there is much work to do in addressing our outlined barriers. Specifically, we reveal that cognitive impairment and increased disability levels act as barriers to participating in rehabilitation-based research. Future studies should assess ways to improve the accessibility of rehabilitation research for those with cognitive and physical impairments, a field that has not been considered. We reveal that the sample of people with MS in the rehabilitation-based portion of the registry project does not represent the MS population as a whole, a unique consideration in this field. Future projects should implement methodologies which allow researchers to engage with individuals who are not willing to participate in a project, allowing researchers to determine if they are unintentionally excluding certain subgroups of individuals from research and thus diminishing the generalizability of their findings.

The current study used three methodological approaches to come to its conclusions. Quantitative analysis, interviews and patient engagement have rarely been combined within one research project. Each of these methodologies have their own strengths and weaknesses. By incorporating all three, we were able to thoroughly examine the phenomena in this study. Much of the literature in the field of MS relies on a single quantitative or qualitative investigation

method. Future studies should consider employing a mixed-method strategy allow for more thorough investigation.

### 3.4 Conclusions

We are the first to employ a mixed-method investigative strategy to examine barriers to participation in rehabilitation-based research, and reveal that cognitive impairment and physical impairment are common barriers to participation in this type of research for people with MS. We also reveal that many of the samples used in this type of research are likely not representative of the larger population, suggesting that many researchers should exercise caution when making generalizations about the larger population. Our discovered barriers stress that we must urgently work to improve accessibility of rehabilitation-based research in MS, as to no longer exclude those with cognitive and physical impairment.

We also prove that implementing mixed-methods within a registry project is feasible and quite worthwhile. Future researchers should consider incorporating this methodological approach into their own work.

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Appendix A: Multiple Sclerosis Impact Scale (MSIS-29)

- The following questions ask for your views about the impact of MS on your day-to-day life during the past two weeks.
- For each statement, please circle the one number that best describes your situation.
- Please answer all questions

| In the past two weeks, how much has your MS limited your ability to... | | Not at all | A little | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|---|---|
| 1. | Do physically demanding tasks? | 1 | 2 | 3 | 4 | 5 |
| 2. | Grip things tightly (e.g. turning on taps)? | 1 | 2 | 3 | 4 | 5 |
| 3. | Carry things? | 1 | 2 | 3 | 4 | 5 |

| In the past two weeks, how much have you been bothered by... | | Not at all | A little | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|---|---|
| 4. | Problems with your balance? | 1 | 2 | 3 | 4 | 5 |
| 5. | Difficulties moving about indoors? | 1 | 2 | 3 | 4 | 5 |
| 6. | Being clumsy? | 1 | 2 | 3 | 4 | 5 |
| 7. | Stiffness? | 1 | 2 | 3 | 4 | 5 |
| 8. | Heavy arms and/or legs? | 1 | 2 | 3 | 4 | 5 |
| 9. | Tremor of your arms or legs? | 1 | 2 | 3 | 4 | 5 |
| 10. | Spasms in your limbs? | 1 | 2 | 3 | 4 | 5 |
| 11. | Your body not doing what you want it to do? | 1 | 2 | 3 | 4 | 5 |
| 12. | Having to depend on others to do things for you? | 1 | 2 | 3 | 4 | 5 |

| In the past two weeks, how much have you been bothered by... | | Not at all | A little | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|---|---|
| 13. | Limitations in your social and leisure activities at home? | 1 | 2 | 3 | 4 | 5 |
| 14. | Being stuck at home more than you would like to be? | 1 | 2 | 3 | 4 | 5 |
| 15. | Difficulties using your hands in everyday tasks? | 1 | 2 | 3 | 4 | 5 |
| 16. | Having to cut down the amount of time you spent on work or other daily activities? | 1 | 2 | 3 | 4 | 5 |
| 17. | Problems using transport (e.g. car, bus, train, taxi, etc.)? | 1 | 2 | 3 | 4 | 5 |
| 18. | Taking longer to do things? | 1 | 2 | 3 | 4 | 5 |
| 19. | Difficulty doing things spontaneously (e.g. going out on the spur of the moment)? | 1 | 2 | 3 | 4 | 5 |
| 20. | Needing to go to the toilet urgently? | 1 | 2 | 3 | 4 | 5 |
| 21. | Feeling unwell? | 1 | 2 | 3 | 4 | 5 |
| 22. | Problems sleeping? | 1 | 2 | 3 | 4 | 5 |
| 23. | Feeling mentally fatigued? | 1 | 2 | 3 | 4 | 5 |
| 24. | Worries related to your MS? | 1 | 2 | 3 | 4 | 5 |
| 25. | Feeling anxious or tense? | 1 | 2 | 3 | 4 | 5 |
| 26. | Feeling irritable, impatient, or short tempered? | 1 | 2 | 3 | 4 | 5 |
| 27. | Problems concentrating? | 1 | 2 | 3 | 4 | 5 |
| 28 | Lack of confidence? | 1 | 2 | 3 | 4 | 5 |
| 29. | Feeling depressed? | 1 | 2 | 3 | 4 | 5 |

Appendix B: Hospital Anxiety and Depression Scale (HADS)

**Hospital Anxiety and Depression Scale (HADS)**

**Tick the box beside the reply that is closest to how you have been feeling in the past week.**
**Don't take too long over you replies: your immediate is best.**

| D | A | | D | A | |
|---|---|---|---|---|---|
| | | **I feel tense or 'wound up':** | | | **I feel as if I am slowed down:** |
| | 3 | Most of the time | 3 | | Nearly all the time |
| | 2 | A lot of the time | 2 | | Very often |
| | 1 | From time to time, occasionally | 1 | | Sometimes |
| | 0 | Not at all | 0 | | Not at all |
| | | | | | |
| | | **I still enjoy the things I used to enjoy:** | | | **I get a sort of frightened feeling like 'butterflies' in the stomach:** |
| 0 | | Definitely as much | | 0 | Not at all |
| 1 | | Not quite so much | | 1 | Occasionally |
| 2 | | Only a little | | 2 | Quite Often |
| 3 | | Hardly at all | | 3 | Very Often |
| | | | | | |
| | | **I get a sort of frightened feeling as if something awful is about to happen:** | | | **I have lost interest in my appearance:** |
| | 3 | Very definitely and quite badly | 3 | | Definitely |
| | 2 | Yes, but not too badly | 2 | | I don't take as much care as I should |
| | 1 | A little, but it doesn't worry me | 1 | | I may not take quite as much care |
| | 0 | Not at all | 0 | | I take just as much care as ever |
| | | | | | |
| | | **I can laugh and see the funny side of things:** | | | **I feel restless as I have to be on the move:** |
| 0 | | As much as I always could | | 3 | Very much indeed |
| 1 | | Not quite so much now | | 2 | Quite a lot |
| 2 | | Definitely not so much now | | 1 | Not very much |
| 3 | | Not at all | | 0 | Not at all |
| | | **Worrying thoughts go through my mind:** | | | **I look forward with enjoyment to things:** |
| | 3 | A great deal of the time | 0 | | As much as I ever did |
| | 2 | A lot of the time | 1 | | Rather less than I used to |
| | 1 | From time to time, but not too often | 2 | | Definitely less than I used to |
| | 0 | Only occasionally | 3 | | Hardly at all |
| | | | | | |
| | | **I feel cheerful:** | | | **I get sudden feelings of panic:** |
| 3 | | Not at all | | 3 | Very often indeed |
| 2 | | Not often | | 2 | Quite often |
| 1 | | Sometimes | | 1 | Not very often |
| 0 | | Most of the time | | 0 | Not at all |
| | | | | | |
| | | **I can sit at ease and feel relaxed:** | | | **I can enjoy a good book or radio or TV program:** |
| | 0 | Definitely | 0 | | Often |
| | 1 | Usually | 1 | | Sometimes |
| | 2 | Not Often | 2 | | Not often |
| | 3 | Not at all | 3 | | Very seldom |

Please check you have answered all the questions

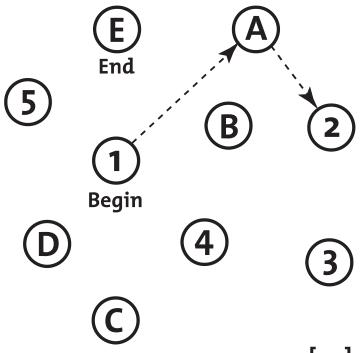
Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

Appendix C: Montreal Cognitive Assessment (MoCA)

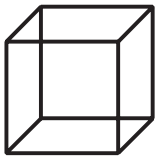
**MONTREAL COGNITIVE ASSESSMENT (MOCA)**

NAME :
Education : Date of birth :
Sex : DATE :

**VISUOSPATIAL / EXECUTIVE** — POINTS




Copy cube



[ ] [ ]

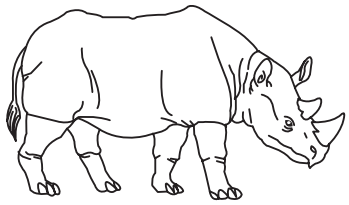
Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

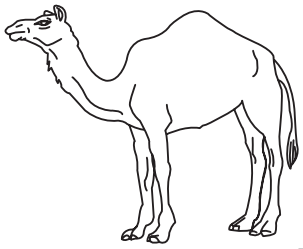
__/5

**NAMING**

[ ]



[ ]



[ ]

__/3

**MEMORY** — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

| | FACE | VELVET | CHURCH | DAISY | RED |
|---|---|---|---|---|---|
| 1st trial | | | | | |
| 2nd trial | | | | | |

No points

**ATTENTION** — Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

**LANGUAGE** — Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words)

__/1

**ABSTRACTION** — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

**DELAYED RECALL**

| | Has to recall words WITH NO CUE | FACE | VELVET | CHURCH | DAISY | RED | Points for UNCUED recall only |
|---|---|---|---|---|---|---|---|
| | | [ ] | [ ] | [ ] | [ ] | [ ] | |
| Optional | Category cue | | | | | | |
| | Multiple choice cue | | | | | | |

__/5

**ORIENTATION** — [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

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Normal ≥ 26 / 30

**TOTAL** __/30

Add 1 point if ≤ 12 yr edu

Appendix D: Interview Guide

1. **Symptomology**

**Introduction: First I would like to know a little about your experience living with MS.**

A. Can you start by telling me a little about your MS?

B. What symptoms have the greatest impact on you?

C. How do they impact your everyday life?

D. What would you like people to know about your experience living with MS?

2. **Health and lifestyle**

**Introduction: Next I would like to ask you some questions about your health and lifestyle.**

A. What do you think is important for maintaining a healthy life living with MS?

B. Do you use any of these strategies in your everyday life?

    a. Probes if needed:

        i. Do you take part in any exercise? (why/why not)

        ii. Do you take part in any social activates? (why/why not)

        iii. Do you make any choices about what you eat or don't eat? (why/why not)

        iv. Do you seek advice from doctors or other health care professionals about living with your MS? (why/why not)

        v. Are there resources that you wish you had access to improve your health that you don't currently have?

C. Do you think lifestyle choices can have an impact Multiple Sclerosis?

**3. Research Perceptions**

**Introduction: Last I would like to understand a little bit more what you think about MS research.**

A. How would you describe the importance of research for people living with MS?
B. Do you think you have a role to play in research about MS?
C. Have you participated in any other research projects? (If yes move to question 3. D, if no move to question 3. E)
D. Have any of these projects involved physical activity? (move to question 3. F)
E. Have you been invited to participate any other MS research projects?
F. How would you describe your overall experience with research participation?
G. Can you tell me what you remember about first being approached for the HITMS project in [the neurologist's] office? (if they remember continue to question 2. G; if no move to question 2. J)
H. What made you interested in participating?
I. What aspects of the project did you like?
J. Were there aspects of the project that you didn't like?
K. Do you remember being told about the physical profile that included walking and fitness tests? (if yes move to question 2.L; if no move to question 2.M)
L. Can you tell me more about why you chose not to take part in this aspect of the research?

M. (Probe, if needed) Sometimes aspects of people's lives make it hard for them to feel they can take part in research that involves exercise. Is there anything about your everyday life you would say contributed to your decision not to participate (** if they could not remember substitute**that would keep you from wanting to participate in research that involves exercise)?

    a. (Probes, if needed)

        i. Ask about family life

        ii. Ask about work life

        iii. Ask about aspects of physical health

        iv. Ask about stress and/or mental health

        v. Ask about resources such as transportation, social support, and financial barriers

N. Is there anything we can do to make it easier or more appealing for you to participate in the physical profile of HITMS?

**CLOSING REMARKS**

Is there anything else you would like to add that you think would help me better understand your experience living with MS or your opinions about research that involves exercise for people with MS?