Variation in Fatigue and its Relationship with Physical Activity in Multiple Sclerosis

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ABSTRACT

Various aspects of fatigue in multiple sclerosis (MS) are explained in the literature, however, there is inconsistent evidence regarding daily variation of fatigue and its association with physical activity. While there is evidence from randomized controlled trials (RCT) that exercise can reduce fatigue, the relationship between these variables is a "chicken or egg" phenomenon, and is not clear whether fatigue is a cause or consequence of physical inactivity.

The global aim of this study is to contribute evidence towards the daily variability in fatigue and to delineate the temporal sequence between fatigue and physical activity in people with MS.

This is a longitudinal predictive study over two time periods embedded in an RCT on exercise for MS (MSTEP). Fatigue was measured using 10 point visual analogue scale for 4 time points every day. Physical activity was recorded on accelerometer for two contiguous periods of 7 days, one period immediately after trial entry and assessment, and one period after the first exercise prescription, for maximum data points of 56 per person. Data was analyzed using Generalized Estimating Equations to adjust the variance for the clustering of measures within person. Odds ratio (OR) was used to identify peak times of the day for fatigue.

The results on 40 participants suggested that the odds of having maximum fatigue increased along the course of the day (lowest in morning, highest at night). Compared to 8:00 hours, the OR associated with having maximum fatigue at 16:00 hours was 2.56 (95% CI: +0.21, +1.67); and at 21:00 hours was 4.84 (95% CI: +0.88, +2.27).

At neither time period did end-of-day fatigue level impact on next day physical activity as measured by number of steps and the same null effect was observed between physical activity throughout the day and fatigue the next day.

In this sample of people with MS participating in an exercise trial, there was no evidence linking fatigue and physical activity, potentially breaking the myth that physical activity increases fatigue. This should be reassuring to people with MS who wish to increase physical activity but fear negative impacts on fatigue.

ABRÉGÉ

Divers aspects de la fatigue reliés à la sclérose en plaque (SP) sont expliqués dans la littérature. Cependant, les évidences sont inconsistantes concernant la variation quotidienne de la fatigue et son association avec l'activité physique. Bien qu'il y ait des évidences provenant d'essais randomisés contrôlés (ECR) démontrant que l'exercice peut réduire la fatigue, la relation entre ces variables est un phénomène de « l'œuf ou la poule » et il n'est pas clair sir la fatigue st une cause ou une conséquence de l'inactivité physique.

L'objectif global de cette étude est de contribuer à l'avancement des évidences concernant la variabilité de la fatigue et de délimiter la séquence temporelle entre la fatigue et l'activité physique chez les personnes atteintes de SP.

Il s'agit d'une étude longitudinale, réalisée sur deux périodes de temps et intégrée dans un ECR, sur liens prédictifs de l'exercice pour la SP (*MSTEP*). La fatigue a été mesurée quotidiennement à l'aide d'une échelle analogue de 10 points à 4 moments de la journée. L'activité physique a été enregistrée avec un accéléromètre pour deux périodes adjacentes de 7 jours, une période immédiatement après l'essai d'entrée et évaluation ainsi qu'une période après la première prescription d'exercices, pour un maximum de 56 points de données par personne. Les données ont été analysées par l'estimation d'équation généralisée afin d'ajuster la variance pour le regroupement des mesures au sein de la personne. Le rapport des chances (*Odds ratio* – OR) a été utilisé afin d'identifier les moments de la journée où la fatigue était le plus élevée.

Les résultats de 40 participants suggèrent que les chances d'avoir un maximum de fatigue augmente au cours de la journée (le moins élevé le matin, le plus élevé le soir). Comparé à 8:00 du matin, l'OR associé à un maximum de fatigue à 16:00 était de 2.56 (95% CI : +0.21, +1.67); et à 21:00 était de 4.84 (95% CI: +0.88, +2.27).

En aucun temps, le niveau de fatigue atteint en fin de journée a eu un impact sur l'activité physique du lendemain, tel que mesuré par le nombre de pas. Le même effet nul a été observé entre l'activité physique tout au long de la journée et la fatigue du lendemain.

Dans cet échantillon de personnes atteintes de SP participant à un essai sur l'exercice, il n'y a pas d'évidence que la fatigue et l'activité physique sont reliées, brisant ainsi potentiellement le

mythe que l'activité physique augmente la fatigue. Ceci devrait être rassurant pour les personnes atteintes de SP désirant augmenter leur activité physique, mais qui craignent les impacts négatifs sur la fatigue.

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PREFACE

Authors Contribution

Several steps were involved before completing this thesis.A research protocol was written by Shweta Selukar. It was approved by committee membersDr. Ross Andersenand Dr.Pierre Duquette,and supervisor Dr. Nancy Mayo.Following this an extensive literature review was conducted to find gaps in literature. The next step involved was data collection to targeted 40 people with MS. Then the collected data was analyzed and interpreted.This thesis was written by Shweta Selukar under the close supervision of Dr. Nancy Mayowithfeedback from committee members.

Organization of Thesis

The global aim of this thesis is to contribute evidence towards the variability in fatigue and its temporal sequence with physical activity in people with multiple sclerosis (MS). Specifically, the objects are: (i) to estimate the extent of variability in daily fatigue and identify the time of day where fatigue is the highest, and (ii) to estimate the temporal sequence between fatigue and physical activity.These objectives areaddressed in a manuscript.The manuscript willlater be submitted to scientific journals for publication.Following the regulations of Graduate and Postdoctoral Studies (GPS), this thesis contains several other chapters leading to Manuscripts.It is required by the GPS to include a literature review and conclusion that is separate from the manuscript. Thus, it is unavoidable to have redundancy of material in this thesis.

Chapter 1 is divided into four sections.

*Section one*gives a background of MS with its prevalence, aetiology, signs and symptoms, and management.

*Section two*describes perceived fatigue asone of the most debilitating symptoms in MS and its impact.It includes the taxonomy of fatigue, its types and causes, and the challenges with measuring and managing fatigue.

*Section three*provides an overview of physical activity in MS, ways of measuring it and reasons for decreased activity in this population.

Section four is a link between fatigue and physical activity. Itprovides a literature review on perceived fatigue, MS impairments, and physical activity.

Chapter 2 presents rationale and objectives of the Manuscript.This chapter provides current knowledge of diurnal pattern of fatigue in MS, its relationship with physical activity, and gaps in literature leading to the rational of this manuscript.

Chapter 3 consists of the manuscript. The objectives are (i) to estimate the extent of variability in daily fatigue and identify the time of day where fatigue is the highest, and (ii) to estimate the temporal sequence between fatigue and physical activity.Following this is the description of study population, procedure, and data analysis. Results are presented intablesand references are included at the end of the text.

Chapter 4is the concluding chapter of this thesis. It includes findings and implications from the manuscript. Following this the list of appendices and references is included.

CHAPTER 1

LITERATURE REVIEW

Section 1: Overview of Multiple Sclerosis

1.1.1 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, autoimmune, inflammatory, demyelinating disorder of the central nervous system [1;2]. It affects young adults between the ages of 19 to 50 years[3]. It leads to interference with work, leisure, daily activity andsub-optimal quality of life[4;5]. Based on 1994 data, a survey in the United States estimated that, the national annual cost for treatment of MS was $6.8 billion and the total lifetime cost per person was $2.2 million[6]. In Canada, the total cost was estimated to be $502.3 million attributing to the impairment, activity limitation, and participation restriction[6;7].

1.1.2 Epidemiology and Prevalence

MS is more common in North America, Australia, New Zealand and Europe [8]. In North America alone, 300,000 people are known to have MS [8]. The National Multiple Sclerosis Society estimates that 400,000 persons in the United States, and over 2 million worldwide have MS [9]. Canadians are known to have the highest prevalence of MS in the world with an estimate of about 240 per 100,000 individuals [10]. According to the Multiple Sclerosis Society of Canada in 2009, between 55,000 and 75,000 persons in Canada had MS[11]. Like other immune-mediated disease, MS affects women more than men, with a ratio that exceeds 3.2:1 in Canada

[12]. It typically targets young adults of the age group between 20 and 30 years, and rarely occurs before 10 years or after 60 years of age [13].

1.1.3 Aetiology

MS is an autoimmune disorder. The pathophysiology of MS has been studied extensively. Its cause is still a matter of debate withboth genetic and environmental factors playing a role[14]. Parents with MS have a 15% chance of passing it on to their children[15]. Vitamin D deficiency has been widely considered to have a causal association with MS [16]. Epstein-Barr virus, retrovirus, and infections especially mumps, varicella, and rubella are also implicated [17;18].Other environmental causesinclude some vaccines[19], cigarette smoking[20],and exposure toneuro-endocrine disruptors[21]. Altered lipid metabolism has also been proposed as a contributing factor[22].

1.1.4 Course of MS

MS has a chronic progressing course commonly with relapses and remissions depending on its type. There are four distinct diseasetypes [23]. *Relapsing Remitting MS (RRMS)*, as the name suggests, is characterized by an alternating course of relapses where the symptoms and disabilities exacerbate, followed by remissions where there is complete or partial recovery of symptoms (Figure1.1.1). Eighty percent of people diagnosed with MS initially present with RRMS. *Primary Progressive MS (PPMS)* is characterized by slow progression of symptoms without distinct relapses (Figure 1.1.2). About 10% of people with MS are affected by this

type,and it affects men and women equally. Eighty percent of people with RRMS eventually develop *Secondary Progressive MS (SPMS).* Unlike RRMS, the relapses are not very distinct with worsening of condition over time (Figure 1.1.3). Lastly,*Progressive Relapsing MS (PRMS)* is characterized by steady worsening of symptoms form the point of diagnosis, with distinct relapses but with or without remissions (Figure 1.1.4). This is a very rare type found in approximately 5% of people with MS. The course of MS can also be categorized as (i) *Benign MS,*where a person experiences few relapses but regains most of the neurological functions after 15 to 20 years, or (ii) *Malignant MS*, where a person experiences rapid worsening of the disease course within a short time after onset [24].

1.1.5 MS Signs and Symptoms

The most common signs and symptoms of MS are fatigue, weakness, incoordination, visual disturbance, bowel and bladder problems, gait problems, cognitive problems, sensory impairments, pain, tremor, spasticity and sexual dysfunctions [25;26]. Table 1.1.1 lists clinical manifestations of MS. No two people with MS will experience the exact same set of symptoms. Symptoms can vary according to the type and course of MS. For instance, persons with PPMS often present with slow worsening tremors and balance problems as the early symptom [24]. Early presenting symptoms in RRMS are proprioception changes, altered sensation, visual problems such as diplopia and optic neuritis [24;27]. Most common symptoms presented by all four types ofMS are visual disturbances (50% to 90%), fatigue (50% to 87%), balance problems (48% to 80%), and bladder problems (80%) [24;26]. There exists an interdependency between

several MS symptoms forming a vicious cycle[28]; for example anxiety or depression can be associated with sleep disorders or fatigue [28].

1.1.6 Medical Management

Advancement in pharmacotherapy post 1993 led to the production of disease modifying agents (DMA's) with immunomodulating properties. The United States Food and Drug Administration (FDA) approved production of interferon drugs: interferon beta-1a (Avonex, Rebif) and interferon beta-1b (Betaseron), which are now routinely prescribed medications for MS [29]. Early use of interferon beta-1a during the first demyelination episode slows down disease progression [30]. They reduce inflammation, proliferation, and swelling of T and B cells thus slowing down the autoimmune response [31]. They also prevent activated T cells from crossing the blood brain barrier, slowing down the demyelination process[31]. Other DMA's such as Copaxone and Novantrone are also immunomodulating and immunosuppressing agents in use [29]. Clinical trials in RRMS have shown these drugs to improve the course of MS by reducing relapse rate and improving quality of life [32]. These drugs also protect against CNS atrophy as seen on MRI[33].

1.1.7 Rehabilitation

While the above mentioned immunomodulating drugs help in decreasing the relapse rate, rehabilitation aims at improving function and quality of life. There is a growing body of evidence supporting that rehabilitation should be a key component of treatment for persons with MS.

According to the Medical Advisory Board of National MS Society, rehabilitation should be started whenever there is an "abrupt or gradual worsening of function, or an increase in impairment that has a significant impact on the individual's mobility, safety, independence, and/or quality of life" [24]. Rehabilitation is an integrated approach of therapies such as physical therapy, occupational therapy, therapy for speech and swallowing problems, cognitive rehabilitation, and vocational rehabilitation. A systematic review on 10 randomized controlled trial (RCT) indicated that, the multidisciplinary rehabilitation approach improves activity and participation of people with MS[34].

Rehabilitation permits people with disabilities such as MS to remain physically active as long as possible, within the constraints of their disability. The benefits of being physically active are well established. It helps in slowing down the disease progression, reduces fatigue, improves balance, strength and endurance, and hence, overall quality of life [35-37]. It provides a sense of well-being by reducing stress, anxiety, and depression [38;39].

1.1.8 The New MS

Prior to 1995, the medical treatment in MS was mainly targeted at reducing the severity of relapse and improving symptoms. For symptomatic treatment, the most commonly chosen drugs were steroids for relapses and baclofen for spasticity.

This trend changed after 1995 when new standards were established for diagnosis, namely the McDonald criteria[40]. Rather than depending on the clinical presentations, a non-invasive imaging technique, Magnetic Resonance Imaging (MRI), became a standardize procedure for diagnosis of MS. It not only helped in earlier diagnosis, but it also allowed us to understand the

clinical course depending on types of lesions seen on the MRI [41]. For example, in 1980s the time from symptom onset to diagnosis exceeded 7 years, and after 2000, the delay averaged 7.5 months[42].

At this time the therapeutic treatment of MS also reached a new milestone due to the introduction of Disease Modifying Therapies (DMT's). The first disease modifying agent (interferon beta) came to use in 1993 [43]. Following this, five more DMT became available [44-47]. Clinical trials have confirmed that these drugs improve the course of MS[31;32]. Due to these reasons, in 2008, Mayo et al in the article "Setting the Agenda for Multiple Sclerosis Rehabilitation Research" suggested that, the course of MS before 1995 is likely to be different from the course over last decade, as these diagnostic and therapeutic advances over past 10 years will allow people to have a smooth disease course and a better quality of life. Thus MS diagnosed after 1995 was termed "The New MS"[48].The new label was intended to applaud the advancements in diagnosis and treatment, and that should provide hope to people with MS for a different disease course than previous cohorts.

This section provided an overview of MS. In following sections, fatigue in MS will be reviewed in depth, followed by a review of physical activity, and the link between the two. Fatigue is the most common and distressing symptom experienced by a person with MS, as such, it is the topic of this thesis.

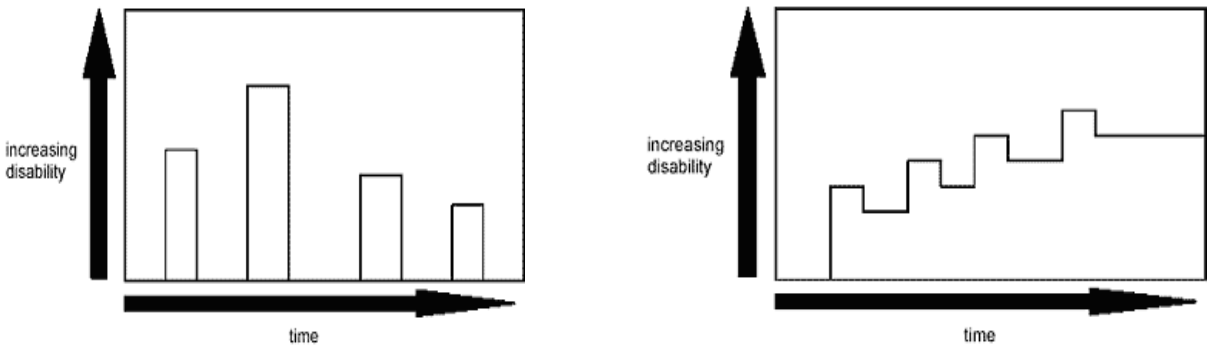

Figure 1.1.1. Relapsing Remitting MS: A) acute attacks followed by full recovery; B) acute attacks followed by partial recovery[11].

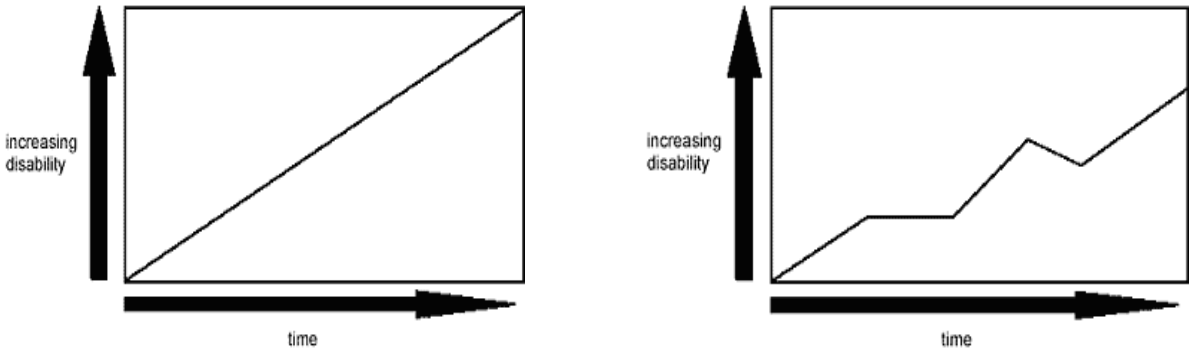

Figure 1.1.2. Primary Progressive MS: A) slow progression without relapses; B) slow progression with temporary minor remissions[11].

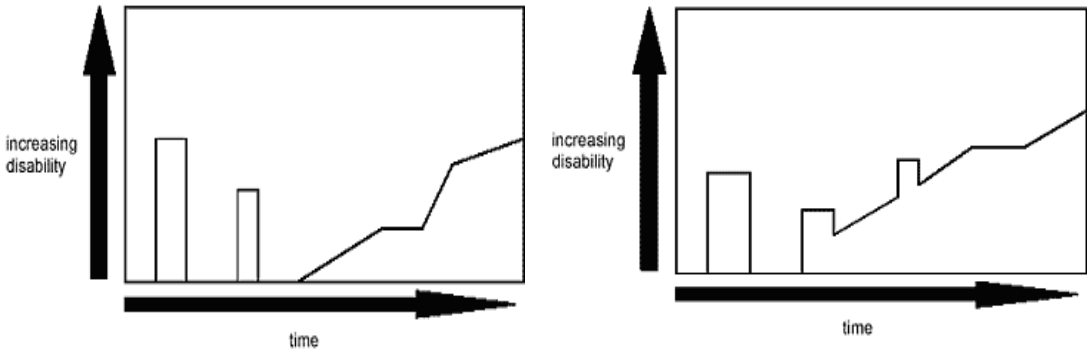

Figure 1.1.3. Secondary Progressive MS: Follows the course of RRMS with steady worsening over time, A) distinct relapse and remission; B) relapse with minor temporary improvement[11].

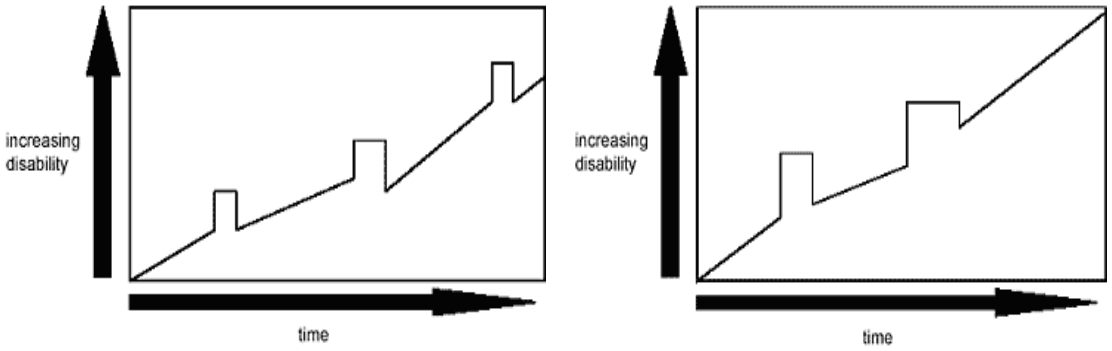

Figure 1.1.4: Progressive Relapsing MS: Steady worsening from the onset of disease with distinct relapse but with or without remissions[11].

Table 1.1.1. Clinical Manifestations of MS[49]:

Sensory Changes	Altered Sensations
	Anesthesia
	Paresthesias
	Disturbance in position sense
	Disturbance in vibration sense
Pain	Acute or chronic pain
	Trigeminal neuralgia
	Paroxysmal limb pain
	Headaches
	Dysesthesias
	Hyperpathia
	Chronic Neuropathic pain
Visual Changes	Optic Neuritis
	Marcus Gunn Pupil
	Nystagmus
	Ophthalmoplegia
	Diplopia
Motor Dysfunction	Weakness
	Fatigue
	Spasticity
	Balance and Coordination problems
	Ambulation and Mobility problems
Speech and Swallowing Dysfunctioning	Dysarthria
	Dysphonia
	Dysphagia
Cognitive and Affective Changes	Cognitive Impairments
	Depression
	Affective Changes
Autonomic Changes	Cardiovascular Dysautonomia
	Bladder Dysfunction
	Bowel Dysfunction
	Sexual Dysfunction

Section 2: Perceived Fatigue in MS

1.2.1 Introduction

Fatigue is identified as the most disabling symptom in MS.Over 40% of people experience it on a daily basis [50]. Approximately 80% of people with MS consistently report fatigue. Also 50 to 60% describe it as the worst symptom. It is one of the first symptoms a person complains of, manifesting even before a diagnosis of MS is made [51]. The James Lind Alliance and organization identifies research priorities jointly with patients, researchers and clinicians, ranked research on fatigue third among ten[52]. Fatigue is also identified as an important predictor of quality of life (QOL) [53-56].

People with MS describe fatigue as a feeling of restlessness, leading to an intense need to rest [9]. Presenting symptoms of fatigue are lack of energy, feeling of malaise, and inability to tolerate physical activity [9].

1.2.2 Fatigue versus Fatigability

There is inconsistencyin the terminologies used for fatigue. The term fatigue is used interchangeably with tiredness, exhaustion, or lack of energy. Also, there is no universally accepted definition of fatigue. Kluger et al proposed a unified taxonomy for fatigue [57]. They divided it into 2 domains, namely *perception of fatigue* and *performance fatigability*. Perception of fatigue can be defined as "A subjective lack of physical and/or mental energy that is perceived by the individual or the caregiver to interfere with usual or desired activity" [58]. Fatigability, on

other hand, is the decline in strength with prolong and repeated activity. In the cognitive domain, it is defined as increase in reaction time with continuous performance of task [59]. In the motor domain, it is defined as decrease in peak force with continuous activity [60]. Perception of fatigue and performance fatigability could mutually influence each other. Thus, the above mentioned taxonomy should be taken into consideration in the conceptualization of fatigue.

1.2.3 Types of Perceived Fatigue and its Causes

The cause of fatigue is still a matter of debate. Perception of fatigue in MS can be attributed to both central or peripheral mechanisms [50]. It can be divided in two broad categories: *primary fatigue (PF)* and *non-primary fatigue (NPF)*. PF is directly related to the disease mechanism and when no non-primary causes are found [61]. In MS, demyelination seems a reasonable explanation for development of fatigue due to longer central motor conduction time [62;63]. Also upper motor neuron dysfunctioning ensuing from demyelination, leads to hyperactive reflexes and impaired movements, increasing the effort required for daily activities[62;63].

NPF, also known as secondary fatigue, is secondary to the disease symptoms[64]. Forwell et al in 2008 concluded that, the most common factors leading to NPF are sleep problems (58%), mobility limitations (52%), and depression (40%) [61]. NPF is also associated with anxiety[65] and restless leg syndrome[66]. Other factors include medications, thermosensitivity, and infections.

There are various iatrogenic mechanisms which can lead to NPF. Medications for spasticity, pain, muscle tension, can increase fatigue, as can disease modifying drugs especially those made from beta interferon. Medications for allergy and psychological distress are known to induce

fatigue. Fatigue also depends on MS subtypes and its severity. People with the progressive subtype of MS are likely to have more severe fatigue [67]. Clear relationship exists between disability and fatigue. It shows a distinct pattern across disability levels measured on the Expanded Disability Status Score (EDSS) [68]and Patient Determined Disease Steps (PDDS)[69].

1.2.4 Distinguishing Features of MS Fatigue

Fatigue is common in general population, however, there are several unique features of MS fatigue. Krupp et al suggested that, in contrast to general population, MS fatigue is: (i) more severe and frequent; (ii) a greater impediment to sustained physical functioning; (iii) sudden in onset; (iv) longer to recover; (v) precipitated or accentuated by heat or humidity; (vi) sustained or chronic; and (vii) not always correlated with other MS symptoms [70]. Also according to the National MS Society, MS fatigue differs from general fatigue as it: (i) mostly occurs on a daily basis; (ii) can occur even after a peaceful night sleep; (iii) worsens as the day progresses; (iv) gets worse by heat and humidity; (v) can come suddenly;(vi) is severe than the normal fatigue; and (vii) interferes more with daily activities[9].

1.2.5 Management of Fatigue

Management of this symptom is a challenge because it is experienced differently across people and time. Fatigue is treatable but it takes a team approach with inputs from doctors, nurses, and physical and occupational therapists [71]. It is important when considering a treatment plan for

fatigue, to identify and treat the contributing factors such as anxiety, depression, stress, pain, spasticity etc.,as these factors could add to the fatigue experienced.

A scoping review by Branas et al on 15 studies, identified the most common interventions for treatment of fatigue, which included (i) behavioural advice; (ii) drugs (amantadine, pemoline, potassium-channel blockers and antidepressants); (iii) exercise and modalities such as cooling vests; and (iv) alternative therapies (acupressure and yoga) [72]. There is a substantial literature documenting the importance of physical activity in managing MS fatigue. In a 2012 meta-analysisof 39 randomized controlled trials, Kuspinar et al provided evidence that, aerobic exercises, strength training, and yoga reduces fatigue (ES=0.6) [73-77]. Also,in a 2013 meta-analysis of 17 randomized controlled trials, Pilutti et al provided evidence for the role of physical activity in reducing fatigue (ES= 0.45) [78].

The effectiveness of self-management in MS fatigue is well-documented in literature. Plow et al in a scoping review identified 27 self-management interventions from 1980 to 2008. Twelve out of these 27 interventions were directed towards fatigue management [79]. Energy management has shown to be a useful self-management tool[80]. Finlayson et al delivered 70 minutes energy conservation program through teleconferenceon 28 individuals with MS. This qualitative study concluded that, energy conservation helped people to deal with the challenges of fatigue, and to learn new skills to manage this symptom[81]. Following this, they also conducted a pilot study on 29 people with MS,and showed that energy conservation program significantly reduced fatigue impact and severity ($p<0.01$; ES=0.31) [82]. Thus, educating people about monitoring their fatigue levels, its causes, patterns, and treatment response is very important. Techniques such as evaluating energy levels, prioritizing tasks, activity pacing, good nights sleeps,

temperature control, planning the day in advance, scheduling rest, and practising proper body mechanics are effective self-management strategies [83;84].

1.2.6 Measuring Fatigue

Fatigue is a multidimensional concept. It can be operationalized as "A subjective lack of physical and/or mental energy, that is perceived by the individual or the caregiver to interfere with usual or desired activity"[58]. It has proven to be a difficult concept to define, also very little is known about its aetiology. Due to its multidimensionality, fatigue is also difficult to assess.

Before measuring fatigue, it is important to distinguish perception of fatigue from performance fatigability. Performance fatigability is measured directly through submaximal voltage on muscles such as tibialis anterior[85], adductor pollicis, and first dorsal interosseus [86],or with tests such as tongue protrusion force[87].

Perceived fatigue, on the other hand can only be measuredby asking the person directly. Fatigue is one of the constructs that can only be measured using what are known aspatient-reported outcomes (PRO's). The United States Food and Drug Administration defines PROs as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" [88]. More than 30 different multi-item indices are available to measure fatigue[89].

There are number of challenges with measuring MS fatigue. There is no gold standard, nor there is ever likely to be. Current fatigue indices vary on how fatigue is conceptualized, and measure different aspects of fatigue experience: intensity, frequency, duration, impact, or bother. A

comprehensive assessment, of all these aspects is important but combining these into a single index may not be possible.

MS fatigue indices also differ on the number of response categories.The optimal number of response options is between four and seven[90]. Validity and reliability decreases with less than four response options, and increases with increase in number of options[90]. Another challenge is the frame of reference used to evaluate the magnitude. For example, the Modified Fatigue Impact Scale (MFIS) uses“frequency” as the frame of reference (never, rarely, sometimes, often, always).In contrast to this, SF-36 uses “time”as a frame of reference (all of the time, most, a good bit, some, a little, none of the time).

Multi-item indices impose a response burden and may seem to be boring and repetitive to respondents, but theyprovide detailed information on a construct [91;92]. Validity and reliability of these measures tend to be high owing to the number of items included[90].Another approach to measurement of symptoms is to use a single-item rather than a collection of items. The most common way of measuring using a single-item is to use a 0 to 100 (or 0 to 10) visual analogue scale. This method has been well validated[93].This approach is particularly useful to screen people for fatigue and then to administer a more comprehensive index as needed for the person and the context.

As there is considerable choice of measuring fatigue, the decision as to what fatigue measure to use will depend on the goal of measurement. Screening for fatigue would require one approach, such as a single item, but a detailed qualitative assessment is needed for the purpose of self-management or identification of causes of fatigue leading to treatment options, then a multi-dimensional measure would be required. For research purposes, a quantitative approach is

needed optimally with a valid global score. The psychometric properties must also be considered, particularly if change over time is the clinical or research context. Various reviews indicate that work still needs to be done in this area, as many of these measures are not reliable, valid, or responsive [94-97].

This section highlighted fatigue as one of the most disabling symptoms. Its aetiology remains unclear with no universally accepted definition. Its multidimensional nature poses several measurement challenges. Despite a vast literature on MS fatigue, there are still areas that need to be explored further,particularly factors that modify the course of fatigue. The next section will provide an overview of physical activity in people with MS, leading to a presentation of the role of physical activity in the fatigue experience.

Section 3: Physical Activity in MS

1.3.1 Recommended Physical Activity and its Benefits for People with MS

The World Health Organisation (WHO) defines physical activity as “any bodily movement produced by a skeletal muscle that requires energy expenditure” [98].

In the past, it was believed,that people with MS should not be a part of exercise programs. This was because of a concern that,increased body temperature could worsen MS symptoms [99]. It was also thought that physical activity could increase fatigue[99].

However, there are growing bodies of evidence supporting the fact that people with MS should be physically active. Like every other individual, physical activity is considered beneficial for people with MS. It is a strong non-pharmacological tool to manage MS symptoms. The Canadian Society of Exercise Physiology (CSEP) gives physical activity guidelines for people with MS [100]. Adults aged 18 to 64 years, with mild to moderate disability, are recommended to perform aerobic exercises for 30 minutes, and strength training (10 to 15 repetitions) twice per week [100]. These guidelines are targeted to reduce fatigue, improve mobility, andquality of life [100].

Beneficial effects of exercise are well documented in literature. Motl et al conducted a meta-analysis including 13 studies with 484 people with MS. The results indicated that physical activity is associated with increased quality of life (ES=0.31)[35]. A recent meta-analysis by Kuspinar et al on 39 randomized controlled trials, indicated that aerobic exercises, strength training, and yoga reduces fatigue (ES=0.6) [73-77]. A review by White et al indicated that exercise programsimprove muscle strength, mobility, cardiorespiratory fitness, and overall

quality of life [36]. It also improves activity level[101], walking capacity [102;103], health perception[37], and overall fitness[104].

1.3.2 Measuring Physical Activity

Physical activity can be operationalized as "any bodily movement produced by skeletal muscles that require energy expenditure" [105]. There are various ways to obtain information on physical activity. It can be measured through self-report or direct measures. The most commonly used method to measure physical activity is through patient report. This includes self-report of physical activity by means of questionnaires such asInternational Physical Activity Questionnaire (IPAQ), Godin Leisure-Time Questionnaire (GLTEQ), or a simple daily activity diary [106;107]. They are widely used due to their low cost, low participation burden, practicality, and general acceptance. One major drawback of using this type of measure is that participants cannot accurately estimate their true levels of physical activity [108]. Questionnaires that ask individuals about their physical activity over past weeks are more susceptible to response and recall bias [108]. Further, use of diary/logs have shown high subject burden [108]. Lack of rigorous methods to measure physical activity is considered a major study limitation[109].

Direct measures on other hand remove recall bias and report accurately, but can only sample time. These measures include instruments such as doubly labelled water (DLB), calorimeter, and motion sensors and monitors, such as accelerometers and pedometers (table1.3.1). Direct calorimeter measures heat produced by body during physical activity [110]. Indirect calorimetermeasuresexchange of respiratory gases during controlled physical activity [110].

DLW also measures oxygen uptake and carbon dioxide production, along with cardiopulmonary parameters giving the true estimates of energy expenditure [111]. DLW and calorimeter are regarded as the "gold standard" to measure energy expenditure. Heart rate monitor is a convenient indicator of duration and intensity of activity. Heart rate recordings can be saved and downloaded later to calculate energy expenditure and VO_2[112].Pedometer, more commonly known as "step counter", is among the simplest wearable motion sensor giving information on step counts [112]. Accelerometers, as the name suggests, measure acceleration along a given axis. It could be uniaxial, biaxial, or triaxial [112]. The accelerometer has several advantagesover the pedometer.The accelerations produced are proportional to the external force, thus they reflect intensity and frequency of movement. It also provides information on energy expenditure in free living environment.

Direct measures are more reliable as compared to self-reportof physical activity[113]. They are immune to recall and response bias and are, thus, considered to be the optimal way to measure physical activity[113]. Literature also suggests that instruments such as pedometers and accelerometers can measure physical activity as well as walking mobility, whereas self-report instruments measure either one of them[114]. These technological advancesare also known to promote physical activity. Wearing an activity monitor can increase physical activity by acting as a "cue to action". Studies have shown that use of pedometers with a step count goal not only increases physical activity, but also decreases body mass index and body weight [115].

Physical activity from self-report and direct methods of measurement correlate only weakly. Motl et al in 2006 through a cross-sectional study on 30 people with MS, showed that there was a strong correlation between self-reported physical activity measures such as GLTEQ and 7-day physical activity recall (7dPAR) ($r=0.84$, $p<0.05$), and between direct measures such

aspedometers and accelerometers ($r=0.93$, $p<0.05$). However, there wasa weak correlation between the scores of self-reported and direct measures ($r=0.48$, $p<0.05$)[116]. Practical issues such as cost, comfort, and need for technical expertise should be considered before deciding on the choice of instrument to measure physical activity.

1.3.3 Overview of Physical Activity in MS

To date, evidence suggests that people with MS are less physically active than their peer group. The most compelling data on physical activity and MS comes from Motl et al, who pooled locally available data from 13 studies with 2360 people with MS. They showed that individuals with MS are less physically active than people without MS, but have a level of activity similar to people with chronic fatigue syndrome or chronic obstructive pulmonary disease (ES= -0.60, $p<0.0001$)[117]. These results were confirmed in several other studies [118-120]. Decrease in physical activity may lead to sedentary lifestyle with added risk of developing fatigue, muscle weakness, obesity, and osteoporosis [121].

There can be various reasons for compromised physical activity in MS. It could be attributed to thedisease subtype. For example, people with PPMS experience more severe symptoms and motor impairments, making it difficult to engage in physical activity [122]. Decreased physical activity in this population could result from one or more MSsymptoms, and can be attributed to fatigue, sleep disturbance, depression, anxiety, and pain[64].

Muscle weakness is one of the most common factorslimiting physical activity in people with MS. MS associated demyelination leads to chain of events, starting from increase incorticomotoneuron conduction time, leading to a decrease in firing rate, and inadequate

transmission. These events lead to balance impairment, atrophy, and muscle weakness. (Figure 1.3.1) [123-127]. Impairments in balance and coordination also affect physical activity[128] along with altered sensation, pain, visual and cognitive impairment which could also affect balance and in turn the activity levels[129-131].

This section provided a background of physical activity in people with MS. To sum up, people with MS are less active than recommended. There could be various reasons for this, not all related to the MS impairments. The next section will presentthe literature review onthe association between physical activity, fatigue, and other MS symptoms.

Figure 1.3.1: Chain of events leading to decrease in physical activity:

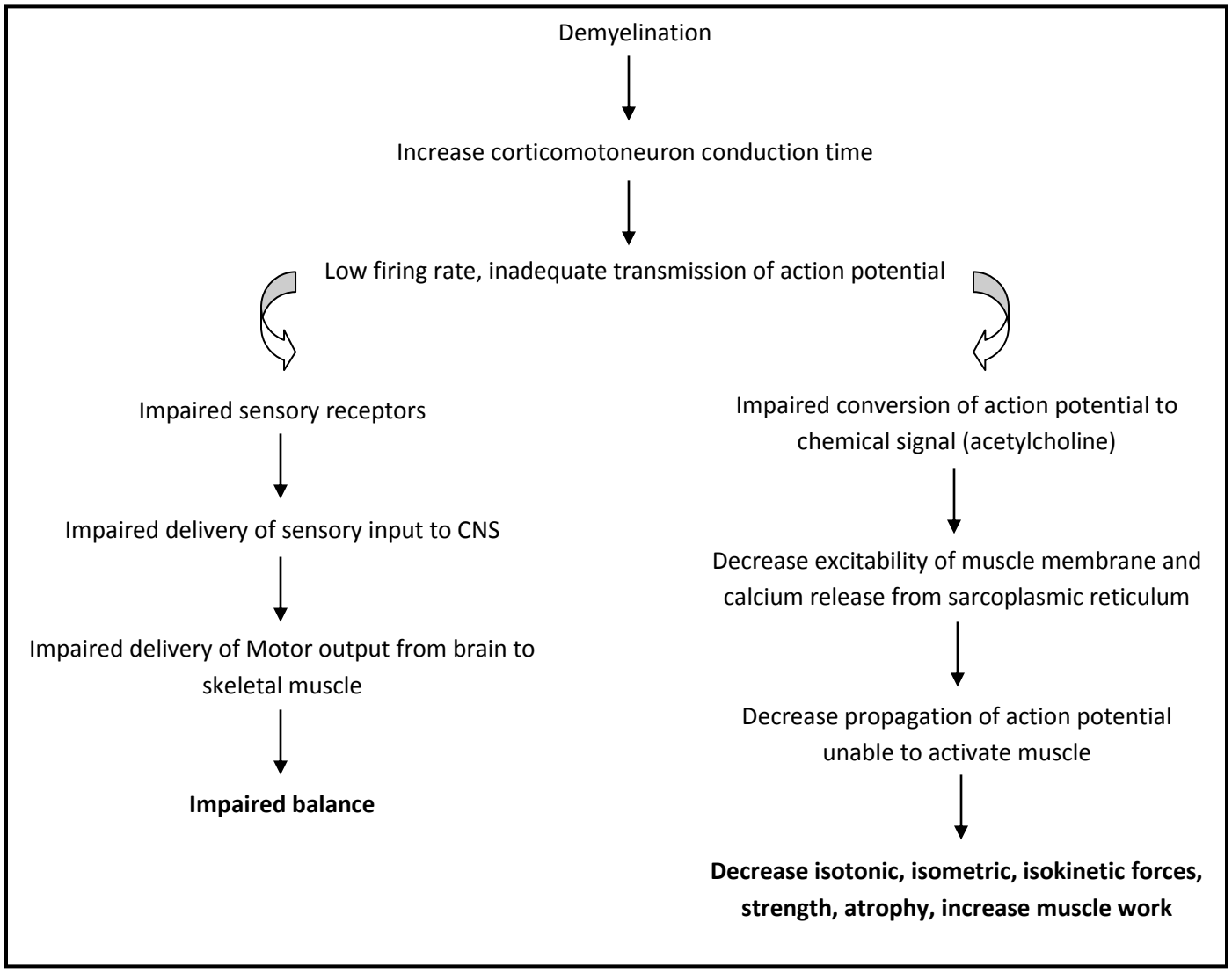

Table 1.3.1: Overview of direct measures of physical activity:

	Measurement	Outcome	Psychometric Property	Advantages	Disadvantages
Room Calorimetry [110;132]	CO_2 and VO_2 production	EE	Reliability: 0.92 Concurrent Validity: Good Excellent accuracy	Moderate response burden	Expensive, require technical expertise, requires laboratory setting
Indirect Calorimetry [110;132]	CO_2 and VO_2 production	EE	Reliability: 0.92 Concurrent Validity: Good	Low response burden	Expensive, require technical expertise, requires laboratory setting
Double Labelled Water (DLW) [111;133]	CO_2 production	EE	Reliability: 0.78 Concurrent Validity: Good	Suitable for all population, good precision, moderate response burden	Expensive, does not provide information on intensity, duration, frequency, not suitable for large studies
Heart Rate Monitors [134;135]	Heart Rate	EE	Reliability:0.75-0.85 Concurrent Validity: Good	Suitable for all population, No laboratory setting required, Low participant burden	Expensive, affected by external factors such as temperature, humidity, hydration, emotional stress
Accelerometry [134;136]	Acceleration of body in one or more direction	Step Counts EE	Reliability: 0.85-0.90 Concurrent Validity: Good	Suitable for all population, high acceptability, less response burden	Expensive, highly accurate for triaxial but accuracy is less for uniaxial and biaxial, underestimates energy cost of walking
Pedometry [134;137]	Number of steps	Step count	Reliability: 0.80 Concurrent Validity: Good	Inexpensive, Suitable for all population, Less response burden.	Unable to measure non-locomotor movements and intensity

Section 4: Link between Fatigue and Physical activity

In previous sections, the extent and impact of fatigue and low physical activity were presented, outlining measurement challenges for both.In this section, the link between fatigue and physical activity will be illustrated considering that other MS impairments likely mediate the effect.

1.4.1 Association between Perceived Fatigue, MS Impairments, and Physical Activity

To identify what had been done in this area, a systematic search was conducted using databases CINHAL and Medline. Keywords included "multiple sclerosis, physical activity, exercise, fatigue, exhaustion and tired". Table 1.4.1 lists studies (n=12)which investigated the association between fatigue,various otherMS impairments, and physical activity.Except for one, all studies were cross sectional in nature with sample sizes ranging from 44 to 312.

The results of the studies in the first part of Table 1.4.1showthat perceived fatigue ismoderately correlated with anxiety, sleep,and MS severity, and is highly correlated with depression.The studies in the second partof Table 1.4.1are all from Motl et al, and present results linking MS impairments and physical activity. Across studies, increasing levels of MS impairments are associated with lower physical activity and this hold for both self-report and direct measures of physical activity.

Only few studies were found on relationship between individual MS symptoms and physical activity. This is due to the interdependency between various MS symptoms.In literature this was described as*the theory of unpleasant symptoms*. According to this theory, a symbiotic relationship between multiple concurrent symptoms, is likely to have a stronger impact on physical functioning as compared to an individual symptom[138]. Motl et al in a longitudinal

study on 292 people with MS,suggested that symptom clusters have a common precursor (e.g., personal, environmental, or psychological factors), and they together have a strong negative impact on physical activity [64;138]. The symptom cluster of fatigue, pain, and depression was found to be the most important for physical activity[64].

The third part of table 1.4.1 presents literature linking perceived fatigue and physical activity. Five of the six studies measured physical activity using a direct measure. However, regardless of how physical activity was measured, (directly or through questionnaires) association was weak.

These weak results were attributed to the presence of symptom clusters. Also the relationship between fatigue and physical activity is likely to be bidirectional. Thus the interaction between these two variables needs to be clarified[139-141].It is well documented that physical activity reduces fatigue,[73-77]but there is not enough evidence on how fatigue influences physical activity.

1.4.2 Limitation in Measurement

A number of measurement inconsistencies contribute to the weak association found above (see table 1.4.1).

First, the timing of fatigue assessment is likely important. A multi-centre trial by Feys et al on 102 people with MS, measured fatigue three times throughout the day(9:00, 12:00, 15:00 hours),using the Rochester Fatigue Diary. They showed that people reported higher fatigue at 12:00 and 15:00 hours as compared to 9:00 hours ($F=38.1$; $p<0.0001$)[142]. This diurnal change of self-reported fatigue has been confirmed in several clinical trials [143;144]. However, it is

uncertain from literature if this diurnal variation of fatigue has been accounted for, while trying to explore its relationship with physical activity. Many of the above studies have administered fatigue questionnaires one time in a day, not taking into account this daily variation of fatigue. It is conceivable that perceived fatigue and dynamic activity outcomes are not stable but time dependent, and sensitive to daily or weekly variation.

It is also known that fatigue is not unidimensional. At the very least, this construct has components of*perception of fatigue* and *performance fatigability.* Perception of fatigue is lack of physical or mental energy, whereas performance fatigability is decrease in muscle strength with continuous task performance. Perception of fatigue can only be assessed through self-report and not directly using a specific test, as one may do for measuring performance fatigability [85-87]. Thus, the relationship between perceived fatigue and physical activity could depend on types of questionnaires used, as different questionnaires evaluate different underlying constructs. Perceived fatigue has proven to be a difficult concept to define and measure clinically. More than 30 different questionnaires have been developed to measure fatigue, but we yet do not have a definitive measure or a gold standard. For its comprehensive assessment, it is therefore important to take into account the intensity, frequency, duration, and impact.

Self-reporting of physical activity is also a problem. The most common self-report measures of physical activity include questionnaires, logs/diaries, and interviews [106;107]. These measures are frequently used due to their practicality, low cost, low participation burden, and general acceptance [108]. Although these measures are useful to gain insight into physical activity, participants have tendency to over or underestimate their true levels [108]. They also have an issue of response and recall bias [108]. Motl, in his meta-analysis on physical activity in MS, reviewed 13 randomized controlled trials, and showed that there was a moderate or small mean

effect size (ES= -22) when physical activity was measured using self-reported measures. In contrast to this, there was a large mean effect size (ES= -12.89) when physical activity was measured using direct measures[117]. He therefore suggested that, self-reported measures in this population could be less accurate due to cognitive impairments, affecting areas of memory coding and retrieval. Thus, direct measures of physical activity provide more precise estimates and remove the issues of response and recall bias [113].

Our literature review revealed that few studies used accelerometers to measure the actual level of physical activity, and these were all cross-sectional in nature [139;140;145]. Given that fatigue and physical activity are time dependent, cross-sectional studies will not sort out the temporality. Longitudinal studies are needed to link changes in one variable, say fatigue, to changes in other variable(physical activity).They are the only design that can provide supporting evidence for cause-and-effect relationship, which is a limitation of the cross-sectional studies [146]. Researchershave recognized the limitation of thecross-sectional study design and have recommended using repeated measurements overtime to help unravel this longitudinal relationship, as to whether fatigue is an antecedent or consequence of physical inactivity [139;147].

The statistical analysis, if not optimized forthe data structure, can also result in poor estimation of the effect. Several studieshave used simple regression for analysis (see Table 1.4.1). This model is best suited for one outcome and one exposure at one time point, as when other variables are included, they are adjusted for each other making interpretation difficult.In case of MS, there are multiple impairments which usually act in combination to affect physical activity.When there are more timepoints, more complex models are needed as for the problem understudy here.

This section reviewed literature on perceived fatigue, MS impairments, and physical activity.Several measurement and methodological drawbacks were identified in these studies.To date, studies have found, only a weak association between perceived fatigue and physical activity in MS.Thus the relationship between these variables needs further clarification.

Table 1.4.1: Relationship between perceived fatigue, MS impairments, and physical activity (all studies are cross-sectional in nature unless specified otherwise):

Reference (Year)	n	Exposure	Outcome	Results
		MS impairments and perceived fatigue		
[148] (2006)	312	Depression MS severity	Perceived fatigue	r=0.74, 95% CI= 0.68 to 0.78 r=0.32, 95% CI= 0.21 to 0.41
[149] (2008)	140	Anxiety Depression	Perceived fatigue	OR= 5.12, 95% CI= 1.08 to 24.12 OR= 3.15, 95% CI= 1.14 to 8.71
[139] (2011)	80	Sleep MS severity	Perceived fatigue	r=0.42, 95% CI= 0.22 to 0.58 r= 0.38, 95% CI= 0.17 to 0.53
		MS impairmentsand physical activity		
[150] (2010)	269	MS impairments	Physical activity: *Accelerometer*	β= -0.24 95% CI= -0.34 to -0.12
[151] (2006)	196	MS impairments	Physical activity: *Self-reported and Accelerometer*	β= -0.24 95% CI= -0.36 to -0.10
[152] * (2008)	51	MS impairments	Physical activity: *Self-reported*	F(1,41)=4.53, p=0.04
		Perceived fatigue and physical activity		
[153] (2006)	133	Perceived fatigue	Physical activity: *Self-reported*	r= -0.26, 95% CI= -0.41 to -0.09
[139] (2011)	80	Perceived fatigue	Physical activity: *Accelerometer*	r= - 0.17, 95% CI= -0.37 to 0.05
[147] (2012)	75	Perceived fatigue	Energy cost of walking: *VmaxST system*	β= -0.18, 95% CI= -0.39 to 0.04
[141] (1997)	50	Perceived fatigue	Physical activity: *Accelerometer*	r= -0.16, 95% CI=-0.41 to 0.12
[140] (2011)	45	Perceived fatigue	Physical activity: *Accelerometer*	β= -0.02, 95% CI= -0.31 to 0.27
[154] (2012)	44	Perceived fatigue	Energy cost of walking: *Open circuit spirometry*	r=0.31, 95%CI=0.01 to 0.5

****Study Design: Longitudinal.***

CHAPTER 2

Rationale and Objectives for Manuscript

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disorder of central nervous system. It is a leading cause of disability in young adults aged 19 to 50 years [1]. The signs and symptoms of MS are fatigue, weakness, incoordination, visual disturbance, bowel and bladder problems, gait problems, cognitive problems, sensory impairments, pain, tremor, spasticity and sexual dysfunctions [25;26]. Out of all, fatigue is the most common symptom experienced on a daily basis by over 40% of people with MS [50]. It is estimated that everyone will have fatigue at some point after diagnosis.Fatigue can be either physical, mental or both. It interferes with people's personal and social life resulting in psychological distress [155]. Thus it is an important predictor of quality of life (QOL) [53-56].

Innumerable studies have been conducted over the years to understand this symptom. While much has been uncovered, several areas are still understudied in MS fatigue. One such area is the diurnal pattern of fatigue in MS. The course of fatigue has been studied across several other populations such as cancer and chronic fatigue syndrome, however, the studies are lacking in MS. A limited number of studies have tried to identify this pattern in MS, but the evidence is inconsistent.

There has been a tremendous development in quality of care for managing MS fatigue. One such advancement is the routine use of self-management strategies. It works best given that fatigue is experienced differently across people and over time. This makes it difficult to suggest a standard management program for all. Self-management provides a framework for the person with MS to

evaluate his or her daily energy stores and guidance as to,how to spend thisstore wisely. In order to do so, it is very important to understand patterns of fatigue throughout the course of the day.

The fact that people with MS are less physically active is well documented in literature[117]. One well identified reason is MS fatigue. Fatigue was identified among the top three barriers keeping people away from engaging in physical activity [156]. Fatigue also leads to lack of motivation in participating in exercise programs [156]. Wessely and colleagues further mentioned that person in presence of fatigue have tendency of avoiding physical activity [157]. According to these authors, when a person experiences any symptom, like fatigue or pain, and finds out that physical activity aggravates the symptom, they try to prevent these symptoms by avoiding physical activity. This inactivity leads to physical deconditioning, and as a result that symptom emerges at progressively lower levels of physical activity [157]. This set up a vicious cycle where fatigue decreases physical activity, and this decrease in physical activity may further lead to fatigue.Fjeldstad et al showed that people report needing tomake an additional effort to perform even the slightest activity, when they have feelings of asthenia (fatigue at rest) and pathological fatigability (fatigue upon physical loading) [158]. Feelings like these can keep people away from participating in physical activity programs. Thus it is clear that fatigue and physical activity are mutually influenced by each other, however it is unclear how these variables relate to each other over time.

This study has two objectives:

1. To estimate the extent of variability in daily fatigue in people with MS

   Specific Questions: (i) To estimate the extent to which fatigue varies over time, and (ii) To identify the time of day where fatigue is the highest

2. To estimate the temporal sequence between fatigue and physical activity

   Specific Questions: (i) The extent to which fatigue at the end of the day, predicts physical activity the next day, and (ii) The extent to which physical activity throughout the day, predicts fatigue the next day.

PREFACE TO MANUSCRIPT

The next chapter is the manuscript entitled Variation in Fatigue and its Relationship with Physical Activity in Multiple Sclerosis. The data for this manuscript comes from the Randomized Controlled Trial (RCT) "The Role of Exercise in Modifying outcomes of People with Multiple Sclerosis"[159], a multi-site study with a total sample size of 240, with an exercise prescription for 12 months.The first 14 days of the study period was used to link daily assessments of fatigue to physical activity.

Fatigue is an exposure variable and its severity was measured using a 0 to 10 (0: no fatigue, 10: highest fatigue) Visual Analogue Scale (VAS). Fatigue is operationalized as, "A subjective lack of physical and/or mental energy that is perceived by an individual or the caregiver to interfere with usual or desired activity" [160].

There is some evidence that fatigue increases along the course of the day [144]. Knowing its diurnal variation, it becomes difficult to capture the true levels of fatigue by just administering a questionnaire at one time point in a day, as done in many of the studies [139;140;147]. Thus the best way of measurement will be to administer a questionnaire several times as the day progresses. Schreurs et al, in a study on 98 people with MS over a course of one year concluded that, rather than measuring fatigue cross-sectionally, it should be measured longitudinally, as its relationship with physical and mental health changes over time [161]. Considering this, we measured fatigue four times every day for seven days pre- and seven days post-exercise prescription.

Unidimentional scales have good internal consistency and test-retest reliability. A 0 to 10 VAS has an ability to detect changes in self-reported fatigue over a 24 hour period [128]. Also, single

item measure has an advantage of face validity as compared to multiple item measure, as it is immediately clear to respondents which construct is being measured [162]. VAS has shown to have good psychometric properties [163]. Reliability on Interclass Correlation Coefficient ICC for all paired VAS scores was 0.97 (95% CI = 0.96 to 0.98) [164]. In MS, VAS for fatigue is equally correlated with other fatigue scales such as Fatigue Severity Scale (FSS) and Modified Fatigue Impact Scale (MFIS) [165].

Physical activity is an outcome variable and measured using accelerometer, seven days pre- and seven days post-exercise prescription.Physical activity is operationalized as, "Any bodily movement produced by a skeletal muscle that requires energy expenditure" [105]. Accelerometer as the name suggests, measures acceleration along a given axis/planes. It can measure these accelerations in one, two, or three orthogonal planes (anterior-posterior, medial-lateral, and vertical). This is done by piezoelectric sensors which generates voltage signal related to acceleration. The acceleration/deceleration signal is digitized by an analog to digital converter and numerically integrated over a pre-programmed epoch interval (i.e., discrete period of time for accumulating data)[114;136].

The population chosen reflects people diagnosed with MS in the post-1994 era. This was considering the technological advances after 1994, such as the standardized use of Magnetic Resonance Imaging for diagnosis of MS [166]. Also the disease modifying therapies (DMT) came into picture from this year onwards, reducing number of relapses and improving the course of MS [46;47;167].

Variation in Fatigue and its Relationship with Physical Activity in Multiple Sclerosis is presented in the next chapter.

CHAPTER 3

MANUSCRIPT

Variation in Fatigue and its Relationship with Physical Activity in Multiple Sclerosis

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3.1 INTRODUCTION:

Multiple Sclerosis (MS) is a chronic, inflammatory disease of the central nervous system, characterized by demyelinated white matter plaques in the brain and spinal cord[1;2]. It is a leading cause of disability in young adults [3]. It affects as many as 240 in every 100,000 Canadians [4], and women are three times more affected as compared to men [3;5].

People with MS show various clinical manifestations, however fatigue is one of the first and the most bothersome symptom [6]. The annual treatment cost for MS in Canada is estimated to be $502.3 million [7], and this was attributed to fatigue, pain and limited physical functioning [8]. Although fatigue is common in the general population, MS related fatigue can be sudden, sustained, and accentuated by heat or humidity[9].

Of the sequelae of MS, fatigue is probably the most studied symptom in terms of measurement, impact, and treatment. What has been less investigated is the pattern of fatigue over time, and what this may mean in terms of etiology, impact, and treatment. The Canadian Multiple Sclerosis Foundation provides this information to the MS constituency about fatigue: “Fatigue may be persistent but it is certainly not consistent. From one day to the next, or even one hour to the next, it can be impossible to predict what your level of fatigue might be” [10]. As fatigue is experienced differently across people and time, very few studies have tried to unravel its diurnal pattern. Thus, questions like; “When would fatigue set in?”, and “When is fatigue at its worst?”, still remains difficult for patients and clinicians to answer.

Gaps remain in understanding how fatigue varies on a daily basis in MS. In HIV/AIDS 318 people rated their fatigue twice a day for five days. The results revealed that, fatigue was significantly high in the evening (4.66 on 7 item Fatigue severity Scale) as compared to the

morning (2.89 on 7 item Fatigue Severity Scale) in this population (paired t[317]=15.3, p<0.001)[11]. In cancer, substantial evidence from longitudinal studies shows that there is a sharprise in fatigue after chemotherapy [12-14]. In chronic fatigue syndrome, Van der Werf et al, in a cross-sectional study among 164 people, found that fatigue increased along the course of the day (afternoon fatigue > morning fatigue, t=5.7, p<0.01 and evening fatigue > afternoon fatigue, t= -4.4, p<0.01) [15].

Fatigue is found to be one of the topmost reasons which prevent people from getting out, giving them a sense of isolation, and deteriorating quality of life [16-19]. Asano et al in 2013, through a cross-sectional survey on 417 people with MS, identified fatigue as one of the top three barriers to physical activity [20]. Similar results were showed by Kayes et al in 2010 through a qualitative study on 10 people with MS, who reported that they consider fatigue as a barrier in taking part in physical activity[21].

Knowing that there is not yet a cure for MS, its treatment focuses on slowing down the progression and managing symptoms. Disease modifying drugs havebeen shown to be effective for slowing down the disease progression [22], but they do not target specific MS symptoms.

Physical activity, either in form of aerobic or resistance training, has been shown to be effective to treat MS sequelae[23;24]. Exercise have shown to be effective in improving muscle strength[25], mobility[26], walking speed[26], coordination[24], functional impairment[23], and quality of life[24]. Although, several therapies have shown improvement in fatigue, there is a lack of truly effective treatment for this symptom. A meta-analysis by Kuspinar et al in 2012 on 39 randomized controlled trials, indicated that aerobic exercises, strength training, and yoga reduces fatigue (ES= 0.6)[27-31]. A meta-analysis by Pilutti et al in 2013 on 17 randomized

controlled trialsalso indicated that physical activity is associated with reduction in fatigue (ES= 0.45) [32].

The benefits of exercise are well established for people with MS. Despite, persons with MS show poor long term adherence in exercise programs. Theyare reported to have high drop-out rates [33] and low maintenance of activity at follow up[34]. Considering that people with MS consider fatigue as a barrier to take part in physical activity[21], the question still remains, as to whether, exercise programs should be directed to improve physical activity in order to reduce fatigue, or should consider treating fatigue first to improve physical activity.

Although, randomized controlled trialssuggest that exercise can reduce fatigue, the evidence for reduced activity as a contributor to fatigue in MS is inconsistent. The relationship between fatigue and every day physical activity is a "chicken or egg" phenomenon, it is not clear whether fatigue is a cause or a consequence of physical inactivity. Their relationship still remains unclear with both factors mutually influencing each other.

To identify what had been done in MS, a systematic search was conducted using databases CINHAL and Medline. Keywords included "multiple sclerosis, physical activity, exercise, fatigue, exhaustion and tired". There were only few studies identified (n=5) [9;35-38], also, estimating variability in pattern of daily fatigue was not the primary aim in most of these studies. First study was conducted in 1988, following which there were no studies till 2002. All of the identified studies were of short duration, with sample sizes ranging from 14 to 102. These studies have a number of methodological limitations as shown in table 3.1. Four of the five studies showed that fatigue was highest in afternoon, and in contrast one study reported that it was highest in morning. Although these studies confirmed the rise in fatigue from morning to

afternoon, it was difficult to predict a pattern, or the point of highest fatigue throughout the day based on these data. Thus in MS, there is an inconsistent evidence for diurnal pattern of fatigue.

Understanding this fluctuation of MS fatigue could have added benefits. The effectiveness of self-management in treatment of MS fatigue is well-documented in literature [39-41]. Evidence suggests that energy conservation can help reduce fatigue [39;40]. But as fatigue is experienced differently across people and time, it becomes difficult to follow a prescribed treatment protocol. Thus by identifying the daily pattern of fatigue, energy conservation techniques could be better targeted.

The current longitudinal study aims to estimate the daily variability in the pattern of fatigue,and contribute evidence towards the temporal sequence between fatigue and physical activity in people with MS. Specifically, the objectives are: (i) to estimate the extent of variability in daily fatigue and identify the time of day where fatigue is the highest, and (ii) to estimate the temporal sequence between fatigue and physical activity.

3.2 METHODS

Study Design:

This is a two-period longitudinal predictive study embedded within an ongoing randomized trial of exercise for people with MS "The Role of Exercise in Modifying outcomes of People with Multiple Sclerosis" [42]. Ethical consideration for this study was obtained from McGill University Health Centre (MUHC) at the Montreal Neurological Hospital.

Study Population:

This study is a secondary analysis of an ongoing Randomized Controlled Trial (RCT). Participants were recruited from two MS clinics: The Montreal Neurological Hospital and Centre Hospitalier de l'Université de Montréal. To be included, people had to be diagnosed with MS after 1994, aged 19 to 65 years, and capable of walking 100 meters without walking aid (PDDS stage: Early cane). Participants were excluded if theyhad (i) any additional illness that restricted their function; (ii) a relapse during the past 30 days (included only if they were stable for more than 30 days after relapse); and (iii) difficulty reading, understanding, or speaking English or French.

Persons who were diagnosed with MS only after 1994 were includedto have a more homogeneous group of people with respect to diagnostic criteria and access to disease modifying therapies (DMT) [43-45].

Measurement:

The demographic information such as age, gender, disability status was collected at baseline. The Patient Determined Disease Steps (PDDS) was used as a measure of disability (Appendix A). It ranks patient reported walking limitation on a nine point ordinal scale ranging from 0 (normal) to 8 (bedridden). It has been validated with other disability measures in multiple sclerosis [46].

Physical activity was measured using a uniaxial accelerometer.The ActivPAL accelerometer provided us with PC software which stores this data for all participants. Accelerometer has shown to have excellent psychometric properties in persons with MS[47]. It is identified as a feasible and acceptable tool to measure physical activity in this population. Acceptability is as high as 90% in people with MS, and they rated accelerometers "very comfortable" to wear [47]. Test-retest reliability on Interclass Correlation Coefficient (ICC) is 0.85 for vigorous activities, and 0.90 on rhythmic activities[47]. Information on average number of steps/day, energy expenditure, time spent sitting/lying, standing, stepping, number of transitions, and cadence for these time points was retrieved.

Fatigue was measured using a 0 to 10 (0: no fatigue, 10: highest fatigue) Visual Analogue Scale (VAS). VAS is a unidimensional single item measure of an attitude or characteristic, which ranges across a continuum of values, to capture intensity or severity of symptoms such as fatigue [48]. VAS is frequently used to assess such patient-reported outcomes because of its simplicity. The simplest form of VAS is a 10 centimeter horizontal line, anchored by word descriptors at each end which usually represents the extreme limits of the construct. VAS can be represented either horizontally or vertically [49]. Use of unidirectional scales such as VAS, due to their

simplicity, can be used repeatedly with less mental burden, thus giving us better understanding of the true fatigue scores.

To encourage long term adherence a simple daily fatigue diary (Appendix B, C) was provided to study participants. To reduce retrospective bias and track changes across the day, participants were asked to note down their fatigue on this fatigue diary four times every day: 8:00, 12:00, 16:00, and 21:00 hours for seven days, rather than requesting a global rating reflecting the fatigue for the entire day.

Procedure:

Eligible participants were identified from clinic records and mailed a post-card about the study. People either contacted the study centre directly or were telephoned by the research coordinatorto be informed of the study and, for those interested, an appointment was made for an assessment. At this first visit, the consent form was signed, questionnaires were completed, and assessement was made of their exercise capacity. After this first visit, an accelerometer was fixed to the thigh and a second appointment was made for 7 days later to attend for the exercise prescription. At this appointment, the accelerometer was retrieved, randomization was carried out, and the participants were given the exercise program. A second accelerometer was subsequently fixed in place to be worn for another seven days and then mailed back in a specially designed and addressed envelope. Thus, participants wore the accelerometer continuously, for the total of 14 days, 7 days pre-exercise prescription and 7 days after (Figure 3.1)

The accelerometers were pre-programmedto start at the desired time. Participants were instructed to continue their usual daily activities performed at home and outside. Along with theaccelerometer (ActivPAL), they were provided with an activity journal, to record their sleep time and reasons for removal of accelerometers in seven days (Appendix D, E). They were also provided with the fatigue diary (Appendix B, C) at the end of the session. Participants recorded their level of fatigue at four times every day- 8:00, 12:00, 16:00, and 21:00 hours, continuously for seven days, using a 0 to 10 Visual Analogue Scale (VAS). The procedure was repeated for the week post- exercise prescription.Participants were provided with a travelling compensation of $20 per visit. To ensure adherence in our study, the research coordinator followed up with the participants over telephone at regular intervals.

Data Analysis

Descriptive statistics were used to characterize the sampleon fatigue and on physical activity. For fatigue the maximum number of data points per person is 56 (2 time points X 7 days X 4 times of fatigue measurement every day- 8:00, 12:00, 16:00 and 21:00 hours). To summarize fatigue, mean values at 4 time points (averaged over days), pre- and post-exercise prescription were computed. The proportion of person-days of highest fatigue was calculated for each of the two time periods, pre- and post-exercise prescription.

The data was analyzed using Generalized Estimating Equation (GEE) considering that it is correlated within subject. GEE proposed by Liang and Zeger (1986) form the basis for regression methodology that accounts for correlated longitudinal data. They represent an extension of generalized linear model (GLM) that takes into account the dependence of observations within

an individual subjects over time, and also allows inclusion of subjects with missing data. It does not have any specific distribution assumption [50].

We used GEE with autoregressive correlation to estimate the pattern of fatigue for four time points, averaged over seven days, adjusting for within-person clustering. The estimates from GEE were used, to compute odds ratio (OR) along with its 95% confidence interval (CI). The time of the day where the fatigue was highest was identified and coded "one", and all other time points were coded "zero". The odds of fatigue at 12:00, 16:00, and 21:00 hours were estimated relative to the odds of fatigue at 8:00 hours. The final data is presented as OR and its 95% CI.

Distribution mean, standard deviation (SD), median, and range of the number of steps/day averaged for each time period are presented along with the distribution when log transformed. Following this, summary of all physical activity parameters at two time points is also presented.

GEE with autoregressive correlation was used to link fatigue to physical activity and vice versa, both pre- and post-exercise prescription. These models also included age, gender, and disability (PDDS). To estimate a longitudinal relationship between these variables, we computed estimates (β) along with its 95% CI. Single imputation was used for missing data and all statistical assumptions were accounted for.

In all the regression models, calendar time was considered as a continuous variable.Every observation in an individual was assumed to be equally correlated with other observations in that individual. All statistical analysis was carried out using Statistical Analysis System (SAS) Version 9.1, function 'SAS PROC GENMOD'.

3.3 RESULTS

A total of 40 participants with MS were assessed at baseline (pre-exercise prescription) and one week post-exercise prescription. The mean age of participants was 44 years and 80% were women. About 42% of participants had mild sensory symptoms, which did not interfere with their activity levels as seen on Patient Determined Disease Steps (PDDS). Also 25% had difficulty walking, and performing physically demanding activities.

Table 3.3 presents mean fatigue scores at four different time points during the day, averaged over seven days, pre- and post-exercise prescription. Across all persons, at all time points and days, the full range (0-10) of fatigue scores was observed. At 8:00 hours, the average fatigue pre-exercise prescription was 1.8 out of 10 (SD: 2.36). There was a trend for increasing fatigue over time, both pre- and post-exercise prescription. To express the increase in fatigue over time, the time period of highest fatigue was identified for each person-day, and expressed as a percent. With 40 participants and 14 days of data collection, the total number of person-days is 560 (40x14). The highest fatigue was reported at 8:00 hours for 15.2%. In contrast, the highest fatigue was reported at 21:00 hours for 34% of person-days. The odds of having highest fatigue at 12:00, 16:00 and 21:00 hours, relative to the odds at 8:00 hours increased with later time points. At 21:00 hours the odds ratio (OR) was 4.84 (95% CI: 0.88 – 2.27).

Table 3.4 shows the average steps/day pre- and post-exercise prescription, which was 6245 and 7317, respectively. The SD was large illustrating a non-normal distribution, and hence the median, 25%ile (Q1), 75%ile (Q3), and range are presented. To meet the assumptions of the regression analysis, the variable steps/day was log transformed and the values are presented. The median steps/day did not differ pre- and post-exercise prescription (902; 95%CI: -808, +1130).

Also shown are the other parameters of activity obtained from the accelerometer. Accelerometer does not differentiate between the time spent sitting and lying. In order to get a true value for time spent sitting, an average of 10 hours sleep and rest time was deducted from this value.The results showed that all parameters were stable over this short time period.

Table 3.3 showed that fatigue was highest at night. Therefore, regression analysis was carried out, linking end-of-day fatigue, age, gender, and disability to physical activity (log steps/day) the next day(Table 3.5). The estimates in this table show the logtransformed values for steps/day. Pre-exercise prescription, there was no effect of end-of-day fatigue on steps/day (95% CI: -0.02, +0.07). Participants, over 40 years walked an average of 5482 steps/day (SD: 3715), and those under 40 years, walked 6594 steps/day (SD: 4114). There was no difference in average steps/day by age (95% CI: -0.42, +0.53), nor gender (95% CI: -0.12, +0.48). However, for people with gait disability, the higher the fatigue the lower were the (log) steps/day (-0.48; 95%CI: -0.88, -0.08). Post-exercise prescription end-of-day fatigue did not impact on physical activity the next day (95% CI: -0.01, +0.11). Also there was no difference on steps/day by age, gender, and disability.

Table 3.6 presents the distribution of average fatigue, pre- and post-exercise prescription and the results of the regression analysis, linking physical activity throughout the day, age, gender, and disability to fatigue the next day.Pre-exercise prescription, there was no effect of physical activity throughout the day on fatigue the next day (95%CI: -0.00, +0.01). Participants over 40 years, had an average fatigue score of 2.47 (SD: 1.97), and those under 40 years had a score of 2.35 (SD: 1.86) out of 10. There were no differences in average fatigue by age, gender, nor disability. Post-exercise prescription, physical activity throughout the day did not impact on fatigue the next day (95%CI: -0.00, +0.01). Also the null effect of age, gender, and disability on fatigue levels was maintained.

3.4 DISCUSSION

This study confirmed that fatigue in MS varies during the day, being lowest in morning and highest at night. People with MS were much more likely to report their highest fatigue at 21:00 hours (OR: 4.84; 95%CI: +0.88, +2.27) than at 8:00 hours (see Table 3.3).

Few studies have addressed the longitudinal course of MS fatigue. Our literature review (see Table 3.2) revealed only five studies in this area, and the evidence was insufficient to establish a definite pattern in fatigue variability. Four out of five studies in the literature review concluded that fatigue was highest in the afternoon, and one study demonstrated that fatigue was highest in morning. In contrast to this, we found that fatigue is highest at night. These studies included individuals with higher disability levels on PDDS or EDDS. This could explain why participants reported higher fatigue early on in a day.

We did not see any change in fatigue scores one week post-exercise prescription. But the study was not designed to impact on fatigue, as data collection took place during the assessment and prescription period. The fatigue scores in this group ranged from 0 to 10 on VAS, but the mean fatigue scores from morning to evening were 2.4 out of 10. A study on comparison of different rating scales for MS fatigue showed that, a fatigue score of 6 out of 10 on VAS indicates sever fatigue, and impacts negatively on quality of life [51]. The mean fatigue experienced by our sample was comparatively low.

The second aim of our study was to estimate the temporal relationship between fatigue and physical activity. For this, we used an accelerometer worn for two periods of seven days, one period after enrolment in an exercise trial but before exercise prescription, and one period after exercise prescription. The accelerometer captured variety of physical activity parameters such as

average number of steps/day, energy expenditure, time spent sitting/lying, standing, stepping, number of transitions, and cadence.

The average step count values pre-exercise prescription was 6245 ± 3682. This was similar to the step count reported by Dlugonski et al on 645 people with MS (5903 ± 3185) [52]. Although the difference in average steps/day pre- and post-exercise prescription was not statistically different, out of 560 person-days, 212 person-days (38%) showed an increase in steps/day by more than 800, which is considered clinically meaningful in MS[53].

Overall, one week post-exercise prescription, physical activity did not increase significantly. Bravata et al, in a systematic review on 26 studies, concluded that wearing an activity monitor significantly increases physical activity[54]. In these 26 studies, the mean intervention duration was 18 weeks, and participants wore pedometers throughout. In our study, participants wore accelerometers only for one week. Thus, in long term, motion sensors could act as a cue to action, but it was not evident with its short term use.

The results did not show anyassociation between fatigue and physical activity over time indicating that in this sample of persons, fatigue at night was not associated with physical activity the next day and vice versa. Previous cross-sectional literature (see Table 1.4.1) showed similar results, but this was the first study to examine this temporal relationship longitudinally.

Evidence supports the role of physical activity in people with MS. In a meta-analysis on 39 randomized controlled trials, Kuspinar et al indicated that exercise reduces fatigue (ES=0.6). In contrast to this, it was previously believed that physical activity will induce fatigue due to rise in body temperature [55]. This study indicated that being physically active does not increase fatigue the following day.

Chapter one describes the methodological and measurement drawbacks in these studies. Taking these into account, the current study used a longitudinal design, fatigue was measured several times in a day, physical activity was measured directly, and appropriate statistical approach was used to deal with this non-independence of data.

This study has several limitations. According to the taxonomy presented in chapter one, fatigue has the components of perceived fatigue and performance fatigability. This study was only based on the measure of perceived fatigue. For future studies, it is recommended that performance fatigability should also be assessed while measuring perceived fatigue. This study followed up activity levels only after one week post-exercise prescription,for the purposes of looking at relationships before alteration with a new exercise program. These results should be confirmed with long term exercise programs.

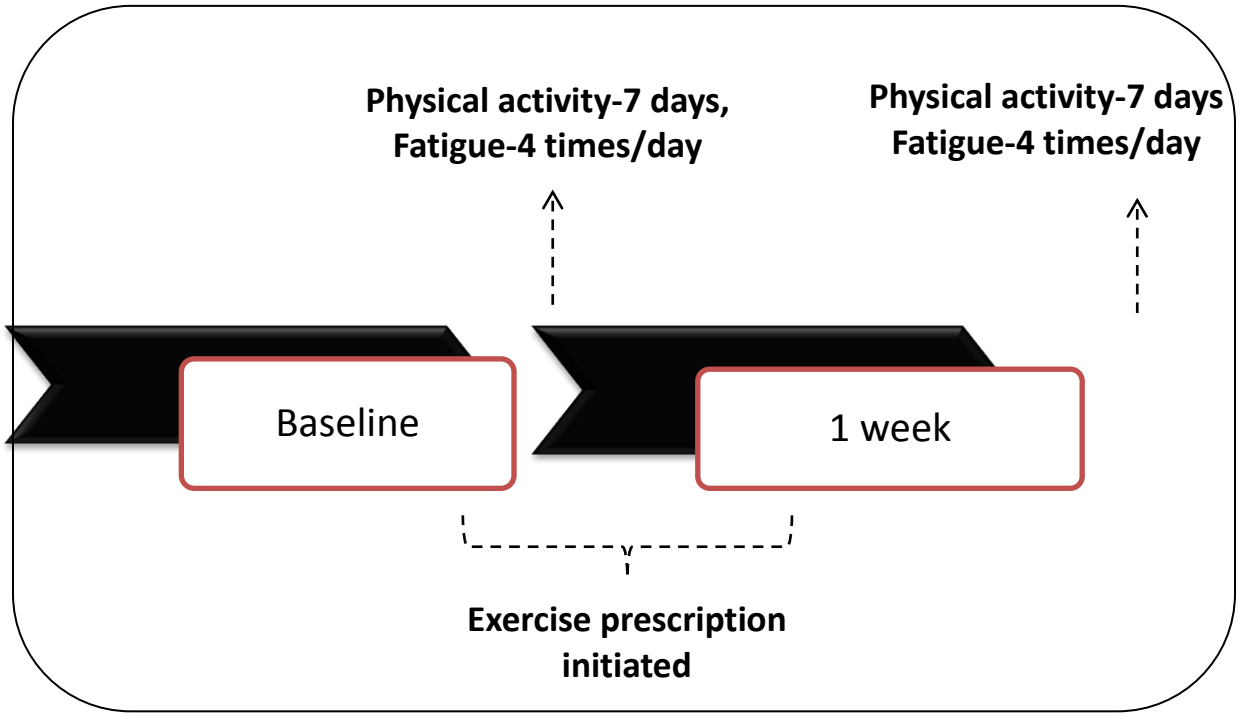
In conclusion, this study contributed evidence for variation of daily fatigue in people with MS. Fatigue is lowest in the morning, goes on increasing as the day progresses, and is highest at night. Our study concluded that, over this relatively short time-frame, fatigue and physical activity were independent of each other, breaking the myth that physical activity increases fatigue. This finding should be reassuring to people with MS who wish to increase physical activity but fear negative impacts on fatigue.

The current study has several clinical implications. For clinicians, knowing the pattern of daily fatigue could be beneficial to provide an idea as to when and how often should this symptom be assessed throughout the day. The above results are also beneficial for providing an effective self-management program. People with MS should be made aware of this pattern of fatigue. This would help them to effectively use techniques like energy conservation and activity pacing. Also

since this study confirmed the diurnal variation in fatigue it is recommended for future research that fatigue scores should not be averaged throughout the day as this might not provide true estimates of this construct. These results should be considered before designing a physical activity intervention, and people with MS should be recommended to participate in the exercise programs despite their levels of fatigue.With exercise, in long term follow up, it is anticipated that there would not only be an increase in physical activity, but also a reduction in fatigue.

FIGURES

Figure 3.1: Study Time points



TABLES

Table 3.1: Literature review on diurnal variation of fatigue in MS

Author (Year)	N	Fatigue measures	Results	Drawback
Krupp (1988)	32	Direct question (When do you experience your highest fatigue?)	Fatigue highest in afternoon	No analysis No measurement
Morris (2002)	14	Visual Analogue Scale (10:00 and 15:00 hours for one day)	Fatigue increases from morning to afternoon *(t[13]=-3.14, p=0.008)*	No recording of fatigue in evening or night
Schwid (2002)	23	Rochester Fatigue Diary (fatigue measured every hour for seven days)	High fatigue in morning and it decreases in afternoon	No analysis
Mills (2007)	40	Semi-structured Interview	Fatigue highest in afternoon	No measurement
Feys (2012)	102	Rochester Fatigue Diary (9:00, 120:00, 15:00 hours for one day)	High fatigue at 12:00 and 15:00 hours compared to 9:00 hours *(F[2,100]=38.1; p<0.0001)*	No recording of fatigue in evening or night

Table 3.2: Operationalization of variables

Type	Variables	Measurement Scale	Measure
Outcome	Physical activity	Continuous	Accelerometer
Exposure	Fatigue	Quasi-Continuous	Visual Analogue Scale (VAS)

Table 3.3: Mean values of fatigue at four time points (averaged over days), pre- and post-exercise prescription, and proportion of person-days per time point with highest level of fatigue

Time of measurement	Fatigue Pre-exercise prescription Mean (SD)	Fatigue Post-exercise prescription Mean (SD)	(%person-days of highest fatigue)	Odds Ratio*	95%CI
08:00 hours	1.8 (2.36)	1.7 (2.13)	15.2%	Referent	
12:00 hours	1.8 (2.03)	2.3 (2.21)	18.0%	0.78	-0.86, +0.35
16:00 hours	2.7 (2.35)	2.9 (2.38)	32.8%	2.56	+0.21, +1.67
21:00 hours	3.1 (2.78)	3.0 (2.57)	34.0%	4.84	+0.88, +2.27

*Odds ratioderived from GEE to account for repeated measures of fatigue
(SD: Standard deviation; CI: Confidence Interval)

Table 3.4: Steps/day (overall and log transformed), andmedian values for physical activity parameters, averaged over all days and time points, pre- and post-exercise prescription

Variables (n=40)	**Pre-Exercise Prescription (n= 262 person-days)**	**Post-Exercise Prescription (n= 238 person-days)**	
Overall Steps/day			
Mean (SD)	6245 (3682)	7317 (4314)	
Median	5846	6748	
Q1 – Q3	3486 – 8348	4182 – 9880	
Range	0 – 17656	0 – 20826	
Overall Log Steps/day			
Mean (SD)	8.58 (0.81)	8.56 (1.33)	
Median	8.69	8.82	
Q1 – Q3	8.22 – 9.03	8.37 – 9.20	
Range	1.79 – 9.78	0.69 – 9.94	
	Median [IQR]		*Difference (95% CI)*
Steps/day	5846 (4862)	6748 (5698)	902 (-808, +1130)
Energy Expenditure (MET.h)	32.9 (2.0)	33.4 (2.4)	0.5 (-0.66, +0.42)
Time spent			
Sitting (hours)*	8.2 (3.5)	7.8 (3.7)	- 0.4 (-2.24, +0.09)
Standing (hours)	4.2 (2.7)	4.4 (2.8)	0.2 (-0.75, +0.57)
Stepping (hours)	1.3 (1.0)	1.5 (1.1)	0.2 (-0.17, +0.14)
Transitioning (sit to stand)	53.0 (33)	55.0 (32)	2 (-3.68, +2.14)
Cadence (steps/min)			
Low (0-90)	2665 (2242)	2925 (2248)	260 (-623, +291)
Moderate (90-100)	1616 (1572)	1891 (1842)	275 (-301, +485)
High (110-140)	483 (1672)	972 (2562)	489 (-581, +494)

* Subtracted average of 10 hours for sleep and rest

Inter Quartile Range (IQR): is the difference between the value at the 25%ile (Q1) and 75%ile (Q3). E.g. the median for EE is 32.9 with IQR of 2.0. The 25%ile is 30.9 and the 75%ile is 34.9.

Table 3.5: Results of the regression analysis,pre- and post-exercise prescription, linking end-of-day fatigue,age, gender, and disability to physical activity (log steps/day) the next day

Parameter	**Steps/day Mean (SD)**	**Log (Steps/day) Mean (SD)**	**Estimates* (95%CI)**
		Pre-Exercise Prescription	
Fatigue			Referent
8:00,12:00,16:00 hours			
21:00 hours			0.02 (-0.02, +0.07)
Age			
>40 years	5482 (3715)	8.48 (0.89)	Referent
≤40 years	6594 (4114)	8.77 (0.55)	0.05 (-0.42, +0.53)
Gender			
Women	5710 (3984)	8.56 (0.87)	Referent
Men	6378 (3399)	8.62 (0.53)	0.17 (-0.12, +0.48)
Disability (PDDS)			
Normal	6662 (3924)	8.60 (0.62)	Referent
Mild disability	5583 (4261)	8.33 (1.83)	-0.22 (-0.81, +0.36)
Moderate disability	4939 (4859)	8.38 (0.68)	-0.11 (-0.62, +0.38)
Gait disability/early cane	5157 (2705)	8.40 (0.36)	-0.48 (-0.88, -0.08)
		Post-Exercise Prescription	
Fatigue			
8:00,12:00,16:00 hours			Referent
21:00 hours			0.05 (-0.01, +0.11)
Age			
>40 years	5990 (4204)	8.48 (1.36)	Referent
≤40 years	6695 (5714)	8.76 (1.24)	0.69 (-0.12, +1.51)
Gender			
Women	6486 (4611)	8.77 (0.67)	Referent
Men	5156 (5222)	7.68 (2.55)	-1.04 (-2.40, +0.30)
Disability (PDDS)			
Normal	6460 (4941)	8.45 (1.41)	Referent
Mild disability	5133 (5207)	8.19 (0.37)	-0.01 (-0.65, +0.63)
Moderate disability	8745 (5392)	8.53 (0.74)	0.25 (-0.40, +0.91)
Gait disability/early cane	5392 (3264)	8.51 (0.34)	0.38 (-0.54, +1.30)

*Estimates derived from GEE to account for repeated measure of steps/day; all estimates are adjusted for the other variables in the model.PDDS=Patient Determined Disease Steps

Table 3.6: Results of the regression analysis,pre- and post-exercise prescription, linking physical activity throughout the day, age, gender, and disability to fatigue the next day

Parameter	Mean (SD)	Estimates* (95% CI)
	Pre-Exercise Prescription	
1000 Steps/day		0.00 (-0.00, +0.01)
Age		
>40 years	2.47 (1.97)	Referent
≤40 years	2.35 (1.86)	-0.15 (-0.76, +1.06)
Gender		
Women	2.34 (2.05)	Referent
Men	2.44 (1.40)	0.11 (-0.64, +0.86)
Disability (PDDS)		
Normal	2.08 (1.76)	Referent
Mild disability	2.41 (1.87)	0.30 (-0.75, +1.35)
Moderate disability	3.32 (2.96)	0.69 (-1.21, +2.61)
Gait disability/early cane	2.58 (1.49)	0.03 (-1.04, +0.97)
	Post-Exercise prescription	
1000 Steps/day		0.00 (-0.00, +0.01)
Age		
>40 years	2.86 (1.92)	Referent
≤40 years	1.74 (2.03)	-0.79 (-1.80, +0.22)
Gender		
Women	1.71 (0.02)	Referent
Men	1.67 (1.83)	-0.43 (-1.52, +0.65)
Disability (PDDS)		
Normal	2.36 (2.08)	Referent
Mild disability	1.68 (1.91)	-0.38 (-1.53, +0.77)
Moderate disability	4.03 (2.14)	1.06 (-0.96, +3.09)
Gait disability/early cane	2.55 (1.57)	0.17 (-0.96, +1.30)

*Estimates derived from GEE to account for repeated measure of fatigue;all estimates are adjusted for the other variables in the model
PDDS: Patient Determined Disease Steps

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CHAPTER 4

Summary and Conclusion

Multiple Sclerosis is one of the most prevalent chronic neurological diseases.It has an unpredictable course. There has been an increase in prevalence of MS in various regions. It affects young adults[3], thus considerably reducing their quality of life[4;5]. Post 1995 there are increased possibilities of detecting MS early on, thus improving the course of disease[41].

Symptomatic management is an integral part of the treatment for people with MS. For this, it is important to understand the course of MS, along with its symptoms. One such debilitating symptom is MS fatigue. This thesis contributes towards the understanding of this symptom. Despite substantial literature in this area, there were certain gaps identified.Inconsistency was noted regarding variation of fatigue over time. This was addressed in the first objective.

There is a substantial amount of evidence suggesting that fatigue keeps people from being active. Despite the importance given to physical activity in MS, literature suggests that people with MSare sedentary. This builds up a strong need to study and understand how these variables influence each other over time.This was addressed in the second objective.

An extensive literature review was carried out to understand the existing literature on fatigue and its relationship with physical activity in MS. Despite the abundance of literature on MS fatigue, there was scarcity in studies exploring fatigue over time. Also innumerable trials for exercise programs were found in literature. However the relationship between fatigue and physical activity was not seen to be followed over time. The existing studies showed only a weak or no

association between these variables (Table 1.4.1).Thus the drawbacks or possible areas for bias in these studies were looked into to explore these variables further. Several measurement and statistical challenges were dealt with while designing this study.

One such challenge was measuringfatigue over time. Studies in past have measured fatigue using various measures.More than 30 instruments are available to measure this construct. In majority of studies, only average fatigue scores are recorded throughout the day. In few studies, fatigue measures were administered at multiple time points, but the scores were later averaged for analysis purpose. It is now known that MS fatigue is not stable throughout the day but varies across time and people. Thus the average fatigue scores will not account for the variability throughout the day. In this study, efforts were made to tract fatigue scores over time to understand the extent to which it varies throughout the day. Multidimensional measures are lengthy and time consuming. Hence a unidimensional measure was chosen to induce less participation burden.A user friendly fatigue diary with a visual analogue scale was designed to facilitate this (Appendix B,C).This gave us fatigue scores for four times/day, for total of seven days, pre- and post-exercise prescription.

As mentioned earlier, fatigue is not an easy construct to conceptualize. According to the taxonomy of fatigue provided by Kluger et al, fatigue can be divided into two domains, perceived fatigue and performance fatigability. Perceived fatigue is the subjective lack of physical or mental energy, whereas fatigability is decline in physical strength or reaction time with prolong and repeated activity. One limitation of this study was that it did not take into account the performance fatigability. There certainly is an overlap between these domains. Fatigability is known to influence the perception of fatigue. A recent cross-sectional study on 20 people with MS concluded that perceived fatigue is associated with performance fatigability (r^2:

0.45, p:0.01). They also proposed that fatigability is one of the underlying contributors to perceived fatigue. Clinically, attempts should be made to separate these components. It is not possible to eliminate fatigability while assessing fatigue, but atleast it should be documented.

Physical activity was measured using accelerometer. Accelerometer sums up physical activity thought parameters such assteps/day, energy expenditure, time spent sitting, lying, transitioning, cadence.This information is obtained almost for almost every min.This data was also obtained for a total of 7 days.This study did not document any significant increase in physical activity.However accelerometer datarevealed several interesting parameters which should be taken into consideration for future studies.Steps/day is considered to be one of the true estimates of physical activity.This is the most widely used parameter from accelerometer to sum up physical activity. Second most widely used parameter is energy expenditure (EE).EE can be defined as the amount of energy used for daily functioning of human body. The value for EE from Activpal accelerometer takes into account the energy spent during activity and rest, along with the basal metabolic rate (BMR).This parameter was fairlyconsistent and did not vary much over people and time.Thus attempts should be made to extract the exact energy spent during activity to understand its variation over time and correlation to other physical activity parameters.The speed of walking (cadence)could also be an important parameter for consideration. The speed of walking for normal adults is 90 to 100 steps/min. Cadence above 100 steps/min is indicative of fast walking. This parameter could be interesting to look at from future prospective. It is documented that people with MS are less physically active. So along with the amount of steps walked, it would also be of interest to know how fast people walked.

Data complexityand analysis of this correlated data was one of the biggest challenges. The above measures of fatigue and physical activity over time gave us as many as 56 data points per person.

When data is collected for more than one time point per person, the data is considered to be correlated. Most of the statistical analysisworks on the assumption of independent data. Thus to deal with this non- independence, generalized estimating equation was considered for analysis.

In conclusionperceived fatigue in MS follows a linear pattern. It is least in morning, increases as the day progresses, and is highest at night. The results showed that in long term, fatigue and physical activity are not related. Physical activity does not increase fatigue. On basis of these results, it is strongly recommended for people to understand that exercise does not induce fatigue and like everybody else, in long term exercise would benefit people with MS.

APPENDIX

A. Patient Determined Disease Score (PDDS)

B. Daily Fatigue Diary (ENGLISH)

C. Journal Quotidien de la Fatigue(FRENCH)

D. Activpal Journal (ENGLISH)

E. JournalActivpal (FRENCH)

F. Sample Size

G. Ethics and Confidentiality

H. Consent Form (ENGLISH)

I. Consent Form (FRENCH)

A. Patient Determined Disease Steps (PDDS)

Normal: I may have some mild symptoms, mostly sensory due to MS but they do not limit my activity.

Mild Disability: I have some noticeable symptoms from my MS but they are minor and have only a small effect on my lifestyle.

Moderate disability:I don't have any limitations in my walking ability but I do have significant problems due to MS that limit daily activities in other way.

Gait Disability:MS does interfere with my activities, especially walking. I can work a full day, but athletic or physically demanding activities are more difficult than they used to be

Early cane:I use a cane or some form of support for walking all the time or part of the time, especially when walking outside. I think I can walk 25 feet in 20 seconds without a cane or crutch. I always need a cane or crutch to walk as far as 3 blocks.

Late Cane: To be able to walk 25 feet, I have to use a cane or crutch. I can get around the house or other buildings by holding onto furniture or touching the walls for support.

Bilateral Support: Able to walk as far as 25 feet. I must have 2 canes, crutches or a walker.

Wheelchair/ scooter: My main form of mobility is a wheelchair. I may be able to stand and/or take one or two steps, but I can't walk 25 feet, even with crutches or a walker.

Bedridden: Unable to sit in a wheelchair for more than one hour.

B. <u>Daily Fatigue Diary (ENGLISH):</u>

For each day you are wearing the accelerometer, please indicate

1. **Your level of fatigue at the time points on a scale from 0-10 (0 being no fatigue and 10 being the worst fatigue)?**
2. **The time of day that you experienced your worst fatigue?**

Not at all fatigued 0 1 2 3 4 5 6 7 8 9 10 **Worst Fatigue**

	8 am *(level of fatigue from 0-10)*	***12 pm (noon)*** *(level of fatigue from 0-10)*	***4 pm*** *(level of fatigue from 0-10)*	***9 pm*** *(level of fatigue from 0-10)*	***At what time of the day did you experience your worst fatigue?***
Day 1					
Day 2					
Day 3					
Day 4					
Day 5					
Day 6					
Day 7					

C. <u>Journal Quotidien de la Fatigue (FRENCH)</u>

Pour chaque jour que vous mettiez l accéléromètre, s'il-vous-plait,

1. **Indiquez votre niveau de fatigue à chacun des différents moments de la journée sur une échelle de 0 a 10 (0 pas fatigue de tout et 10 la pire fatigue).**
2. **A quel moment de la journée avez vous ressenti votre pire fatigue?**

Pas fatigué du tout 0 1 2 3 4 5 6 7 8 9 10 **La pire Fatigue**

	8 am *(niveau de fatigue de 0-10)*	***12 pm(midi)*** *(niveau de fatigue de 0-10)*	***16h*** *(niveau de fatigue de 0-10)*	***21h*** *(niveau de fatigue de 0-10)*	*A quel moment de la journée avez vous ressenti votre pire fatigue?*
Jour 1					
Jour 2					
Jour 3					
Jour 4					
Jour 5					
Jour 6					
Jour 7					

D. <u>Activpal Journal(ENGLISH)</u>

Circle the day of the week that you first begin wearing the device, then **<u>fill in the date</u>**. In the table below, note the times, including "am" and "pm" that you got out of to bed and went to bed. Also indicate if or why and for how long the monitor was removed for any reason. *Pleasewear the device for 7*

Day Started: M T W Th F S SU

Date Started (MM/DD/YY): _____/_____/_____

	Got out of bed at:	Went to bed at:	Did you participate in any exercise while wearing the device?	Did you remove the device for any reason?	If Yes, during what times was the device off?	What was the reason why you took off the device?	Did you work during the time you wore the device?	What times did you work?
Sample	7:30am	10:45pm	Y N	Y N			Y N	9 am - 2pm
Day 1								
Day 2								
Day 3								
Day 4								
Day 5								
Day 6								
Day 7								

Write down anything else you would like to tell us about the device:

_____

_____

_____

E. Journal Activpal (FRENCH)

Premièrement, encerclez le jour de la semaine lorsque vous commencez le port de l'accéléromètre et **indiquez la date**. Ensuite, dans le tableau ci-dessous, notez l'heure à laquelle vous êtes sorti(e) du lit ("am" et "pm") et celle à laquelle vous vous êtes couchée(e). Veuillez également indiquer la ou les raisons de l'arrêt du port de l'accéléromètre ainsi que la durée de cet arrêt. S.V.P. Portez l'accéléromètre pendant 7 journées consécutives.

Jour de la semaine quand vous commencez le port du ActivPAL:

L – M – Mer – J – V – S - D

Début le (MM/JJ/AA)

_____/_____/_____

	Sorti(e) du lit :	Heure du coucher:	Avez-vous fait de l'exercice durant le port de l'accélromètre?	Avez-vous retiré l'appareil, sans raison particulière?	Si oui, à quel moment l'avez-vous retiré?	Notez les raison(s) de l'arrêt du port de l'accélromètre	Avez-vous travaillé(e) durant le port de l'accélromètre?	Notez les heures que vous avez travaillées?
Exemple	7:30am	10:45 pm	O N	O N			O N	9 h – 14 h
Jour 1								
Jour 2								
Jour 3								
Jour 4								
Jour 5								
Jour 6								
Jour 7								

Si vous avez des commentaires au sujet du port de l'accéléromètre, veuillez les indiquer ci-dessous ☺ _____

F. Sample Size

For sample size the issue is to identify the number needed to achieve reasonable power (80%) to detect clinically relevant effect sizes for the parameters under study, recognizing that the effective sample size is somewhere between the number of subjects (n) and the number of observations (n*t*days). The first objective is to estimate if there are specific times of the day when fatigue is higher. This is reported as an odds ratio (OR) and the desire was to detect an OR of at least 2.0 indicating a doubling of the probability of reporting particular time as having the highest fatigue relative to the first time of the day 08:00 (40% time2 vs. 20% time 0800). This requires a sample size of 164 independent observations. The design effect for this study is represented by the formula ***1+(n-1)r***[168]where n is the number of additional data collection opportunities and r is the estimated correlation between these data collection opportunities. As the plan was for 4 time points for two periods of 7 days, there are two separate design effects. For day, the design effect is calculated as 1+(6-1)r, and with r was set at 0.5, the design effect is 3.5. Thus, 162 independent observations can be generated from 47 people. An additional design effect is from time (4 time points) and this is calculated as 1+(3-1)0.5 or 2, indicating that a minimum of 28 people is required. As there is some expectation for missing data and as there are two (non-independent) time periods, the targeted sample size was 40 which would yield greater than 80% power, with an alpha level set at 0.05, to detect a minimum effect size of 2.0 (relative risk). This sample size would also permit consideration of covariates in the analysis.

G. Ethics and Confidentiality

As this is a secondary analysis, ethical approval was obtained from the McGill University Health Centre (MUHC) at the Montreal Neurological Hospital. Participation in our study is voluntary. Participants have rights to leave the study any time that want. Travelling compensation will be provided and also compensation will be given if they suffer from any kind of injury due to our study. All information in this study will remain confidential. Participants are represented by their ID numbers. All data is encrypted and password protected. Participants' files will be preserved in a locked cabinet in the department. After the analyses have been completed, all identifying information will be taken off and will be destroyed.

H. Consent form (ENGLISH)

PRINCIPAL INVESTIGATOR: Nancy Mayo BSc PT, MSc, PhDDivision of Clinical Epidemiology Royal Victoria Hospital Montreal Quebec

COLLABORATORS:Montreal Site **Y Lapierre**MD Department of Neurology and the MS clinic Montreal Neurological Hospital MUHC; **P Duquette** MD Department of Neurology Faculty of Medicine Centre hospitalier de l'Université de Montréal(CHUM) **F Grand'Maison**MD Director MS Clinic Rive Sud, **R Andersen PhD**Departement of Kinesiology and Physical Education Faculty of Medicine McGill University **S Bartlett PhD**Departement of Medicine Faculty of Medicine The Research Institute of the McGill University Health Centre

Toronto Site: **M Bayley** MD Director Neuro Rehabilitation Program Toronto Rehabilitation Institute- Faculty of Rehabilitation Medicine University of Toronto **P W O'Connor** MSc MD Director, Multiple Sclerosis (MS) Clinic and MS Research St. Michael's Hospital University of Toronto. **L Lee,** MSc MD MS Director Sunnybrook Health Sciences Centre MS Clinic Toronto, University of Toronto.

STUDY COORDINATOR: Carolina Moriello, BSc, MSc.(Rehabilitation Science)

FUNDING SOURCE: CIHR 2012-2015 grant #258309

Introduction

Despite the benefits of exercise and physical activity people with Multiple Sclerosis (MS) are relatively inactive. Physical activity is important for persons with disabilities to maintain physical function. A lack of physical activity can contribute to heart disease, osteoporosis,

obesity, and diabetes. At the moment, the best way for people with MS to exercise and be physical activity is unknown. People with MS report not knowing what to do. This is a barrier to exercise.

We are a group of researchers from McGill University, the McGill University Health Center, Centre Hospitalier de l'Université de Montréal and MS Clinic Rive Sud studying how exercise can help people with MS improve their function and quality of life. If you agree to participate, we will randomly assign you to one of two exercise groups. The decision on which group you will be in is similar to taking names out of a hat. The two groups are (1) an adapted approach similar to the exercise guidelines for people with MS; 30 minutes of moderate intensity exercise 2 times per week, strength training for major muscles 2 days per week; (2) an approach developed specifically for people with MS and spreads exercise out over 6 days a week and includes 2 days a week where you pushes yourself to perform at a higher intensity. No matter which group you are assigned to, you will be personally instructed on the exercise regimen by a trained exercise instructor or physiotherapist and you can have your exercise program revised as you progress

Procedures

The time period of the study is 2 years. We will assess your progress every 6 months for a total of 5 assessments.

You will be asked to undergo several different types of assessments at our lab at McGill University. A test of your exercise capacity where you pedal an exercise cycle for as long as you can while breathing into a tube held in your mouth. This measures how much oxygen you are using while exercising. This test is done 3 times, at study entry, at 12 months and 24 months.

1. An assessment of the muscle power in your legs which will be made on a special machine on which you sit and push against weights. This test will be done 3 times, at study entry, at 12 months and at 24 months. A body scan assessing body composition will be done at baseline and 12 months.
2. A second test of exercise capacity requiring you to go up and down a small step in time to a beat. This test will be done 3 times, at 3, 6 and 18 months.
3. A test of how far you can walk in 6 minutes and a test of balance. These tests will be done at every assessment.
4. Other tests of muscle strength to help design the exercise program for you. This is done at every assessment.
5. A test of your body's movements will be made by a small monitoring device attached to your thigh. You will wear this for one week before each of your five assessments. This device is very small and will not be noticeable to you or others

In addition, we will ask you to complete some questionnaires on your health and your usual activities. These will need to be completed 5 times over the 2 year period. You can fill them out over the internet, on paper, or over the phone, or in person at the time of the assessment, as you wish. You may skip any questions that make you feel uncomfortable.

Your exercise instructor will call you every two weeks for the first month to help with your exercise program and answer any questions you have. After the first month, your instructor will call once a month or you can email or call him or her every month. If you cannot come because you live too far away or do not feel well enough, we can come to your home.

Benefits

There is no guarantee that you will benefit directly from the program.

Compensation in Case of Injury If you suffer any injury following any procedure related to the research project you will receive the appropriate care and services for your medical condition without any charge to you. By accepting to participate in this project, you are not waiving any of your legal rights nor discharging the researchers, granting agency or the institution of their civil and professional responsibility.

Risks and Inconveniences

There are no serious risks involved in participating in this study. All evaluations will be supervised. If you require any assistance to ensure your safety, it will be provided.

There might be a small risk if you change your medication while you are in the study. Some medications can affect your motor performance either positively or negatively. One such medication is Fampyra (or the generic version) which your doctor might suggest to improve your walking speed. There is a risk of falling if your walking speed suddenly increases and you have not strengthened your leg and trunk muscles to support this extra speed. Fampyra also can affect balance directly and this might cause you to fall while exercising. To reduce this risk you could delay going on Fampyra until after the trial. If you chose to go on Fampyra you need to tell us because we would need to modify your exercise program to minimize the risk of a fall with Fampyra.

Confidentiality

Any personal information you provide (name, address, or health information) and any information that is collected from your assessments will be kept strictly confidential. This information will be kept safe in a locked filing cabinet within a secure space in a locked office in the Division of Clinical Epidemiology at Royal Victoria Hospital. We will put all the information into a computer and remove your name and any personal information. Then we will assign a number to your file, your name will not be on the forms. The information from the program will be in the form of statistical tables and summarized into graphs. No information from any individual will be released. The results of this research may be presented at meetings or in publications but your identity will not be revealed. Your name will not appear in any publication or report from this study. In the future, the information we gather may be used by other researchers to answer additional research questions about people with MS and for this reason all data will be kept for 25 years.

I agree to allow the data collected from this study to be used in future health research about people with MS, as long as I am not personally identified, and the same conditions concerning confidentiality and storage of data agreed to for the present study are adhered to.

Yes _____ □ No □

Voluntary Participation and Right to Withdraw

Your participation in this project is voluntary. You have the right to leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled including ongoing and future care. The investigator can end your participation in the project without your consent, if in his/her opinion it would be harmful for you to continue. We will communicate to you any information or relevant results that may affect your participation. To make sure this study follows the rules concerning research, a member of one of the MUHC-Research ethics Boards may contact you and /or review your research files.

Incidental findings

Any findings related to your medical care will be communicated to you and, if you wish to your doctor.

Compensation

You will not be paid to participate in this research study, but you will be reimbursed for parking or travel expenses, up to $20.00 per visit. If you cannot come because you live too far away or do not feel well enough, we can come to your home.

Contact Information

The person in charge of the research project is Dr. Nancy Mayo. If you have any questions about this study, please contact the research coordinator Carolina Moriello, who can be reached at 514-934-1934 ext. 36912. If you have any questions regarding your rights as a research subject and you wish to discuss them with someone not conducting the study, you may contact the Montreal Neurological Hospital, Patient Ombudsman at (514) 934-1934, ext. 48306. If you have any other

kind of comments or concerns, or need assistance regarding your participation as a research subject in this project, please contact the MNH Patient's Committee, room 354, tel. (514) 398-5358

Subject Consent Document

STUDY TITLE: The Role of Exercise in Modifying Outcomes for People with Multiple Sclerosis

PRINCIPAL INVESTIGATOR: Nancy Mayo BSc PT, MSc, PhD.

COLLABORATORS: P Duquette MD FRCP; Y Lapierre MD FRCP; F Grand'Maison MD FRCP; R Andersen PhD, S Bartlett PhD

STUDY COORDINATOR: Carolina Moriello, BSc, MSc.(Rehabilitation Science)

FUNDING SOURCE: CIHR 2012

STATEMENT OF CONSENT

I, _____, have read the above description with one of the investigators, _____. I fully understand the procedures, advantages and disadvantages of the study, which have been explained to me. I freely and voluntarily consent to participate in this study.

A copy of this consent form has been given to the person named below.

_____

(Printed) name of participant

_____ _____

Signature of participant Date of signature

_____

(Printed) name of person reading consent

_____ _____

Signature of person reading consent Date of signature

I. Consent form (FRENCH)

Titre de l'étude : Le rôle de l'exercice physique dans la modification des divers aspects de la santé chez les personnes atteintes de sclérose en plaques

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COORDONATEUR DE L'ÉTUDE : Carolina Moriello, B.Sc., MSc. (Science Réadaptation)

SOURCE DE FONDS : Subvention des IRSC 2012-2015 - n^{o} 258309

Introduction

Même si nous connaissons les avantages de faire de l'exercice et de l'activité physique, les personnes atteintes de sclérose en plaques (SP) sont relativement peu actives. Il est important de faire de l'activité physique pour les personnes ayant des incapacités afin de maintenir leurs capacités physiques. Le manque d'activités physiques peut contribuer aux maladies du cœur, à l'ostéoporose, à l'obésité et au diabète. En ce moment on ne connaît pas quel est le meilleur moyen pour les personnes atteintes de SP à faire de l'exercice et à être physiquement actif. Les personnes atteintes de la SP disent qu'ils ne savent pas quoi faire. Cela représente un obstacle à la pratique de l'activité physique.

Nous sommes un groupe de chercheurs de l'Université McGill, du Centre universitaire de santé McGill, du Centre hospitalier de l'Université de Montréal et de la clinique de SP Clinique Neuro Rive-Sud, qui étudions comment l'exercice peut aider à améliorer l'état et la qualité de vie des personnes atteintes de la SP. Si vous acceptez de participer à la présente étude, nous vous assignerons de façon aléatoire à un des deux groupes d'exercices. Cette façon de vous assigner à un groupe est comme tirer un nom d'un chapeau. Les deux groupes sont (1) une démarche adaptée du guide d'exercices pour les personnes avec la SP; 30 minutes d'exercices à intensité modéré 2 fois par semaine, entraînement avec des poids pour les muscles majeures 2 jours par semaine; (2) une approche développée spécialement pour les personnes atteintes de la SP qui étale les exercices sur une période de 6 jours par semaine, ceci inclut 2 jours par semaine où vous déployez des efforts de façon plus intense. Peu importe dans quel groupe vous êtes assigné, vous serez informé de façon personnelle sur votre programme par un entraineur physique ou un physiothérapeute spécialement formé et vous pourrez avoir votre programme d'entraînement révisé à mesure que vous progressez.

Procédures

La durée de l'étude est de 2 ans. Nous évaluerons votre progrès tous les 6 mois pour un total de 5 évaluations.

Vous serez soumis à différents types d'évaluation au laboratoire de l'Université McGill.

1. Un test qui mesure votre capacité physique où vous aurez à pédaler sur un vélo d'exercice aussi longtemps que vous pourrez tout en respirant dans un tube qui est maintenu dans votre bouche. Ceci mesure combien d'oxygène vous utilisez durant l'exercice. Ce test est fait 3 fois, à l'entrée dans l'étude, à 12 mois et à 24 mois.
2. Une évaluation de la puissance de vos muscles dans vos jambes qui sera faite avec une machine spéciale sur laquelle vous vous assoyez et vous poussez un poids. Ce test sera fait 3 fois, à l'entrée de l'étude, à 12 mois et à 24 mois. Une évaluation de la composition corporelle sera faite a à l'entrée de l'étude et à 12 mois.
3. Un deuxième test pour mesurer vos capacités physiques où vous aurez à monter et descendre une petite marche en suivant un rhyme donné. Ce test est fait 3 fois, à 3, 6 et à 18 mois.
4. Un test qui mesure quelle distance vous pouvez marcher durant 6 minutes et un test d'équilibre. Ce test sera fait à toutes les évaluations.
5. D'autres tests de force musculaire pour aider à créer un programme d'exercices pour vous. Ceci est fait à toutes les évaluations.
6. Un test des mouvements de votre corps sera fait à l'aide d'un petit dispositif de surveillance attaché à l'une de vos cuisses. Vous le porterez durant une semaine avant

chacune des 5 évaluations. Ce dispositif est très petit et ni vous ni les autres ne pourront le voir.

De plus nous vous demanderons de remplir quelques questionnaires sur votre santé et sur vos activités quotidiennes. Vous aurez à les remplir 5 fois sur une période de 2 ans. Vous pouvez les remplir de la façon que vous voulez soit sur Internet, sur papier, par téléphone ou en personne au moment de l'évaluation. Vous pouvez sauter toute question avec les quelles vous n'êtes pas à l'aise.

Votre entraineur vous appellera tous les 2 semaines durant le premier mois pour vous aider en ce qui a trait à votre programme d'exercices et pour répondre à vos questions. Après le premier mois, votre entraîneur vous appellera une fois par mois ou vous pouvez lui envoyer un courriel ou l'appeler tous les mois. Si vous ne pouvez venir parce que vous habitez trop loin ou vous ne vous sentez pas assez bien, nous pouvons aller à votre domicile.

Avantages

Il n'y a aucune garantie que vous profiterez directement de ce programme.

Dédommagement en cas de blessure

Si vous souffrez d'une blessure à la suite de toutes procédures reliées au projet de recherche, vous recevrez des soins appropriés et tous les services médicaux pour votre état médical gratuitement. En acceptant de participer à cette étude vous ne renoncez pas à vos droits légaux ni ne libérez les chercheurs, l'organisme de subventions ou l'établissement de santé de ses responsabilités civiles et professionnelles.

Risques et inconvénients

Votre participation à cette étude n'est associée à aucun risque sérieux. Toutes les évaluations seront sous supervision. Si vous avez besoin d'aide pour assurer votre sécurité, elle vous sera fournie.

Il pourrait y avoir un petit risque si vous changez votre médication pendant la durée de l'étude. Certain médicaments peuvent affecter vos performances motrices de manière positive ou négative. Un de ces médicaments est le Fampyra (ou son équivalent générique) que votre

médecin pourrait vous suggérer pour améliorer votre vitesse de marche. Il y a un risque de chute lorsque votre vitesse de marche augmente soudainement sans que vous n'ayez renforci vos jambes et votre tronc pour supporter cette vitesse supplémentaire. Fampyra peut également affecter voter équilibre directement et cela pourrait entrainer une chute pendant que vous faites vos exercices. Pour réduire le risque, vous pourriez attendre pour commencer le Fampyra après l'étude. Si vous décidez de commencer le Fampyra, il est important de nous en avertir afin que les modifications nécessaires à votre programme d'exercices soient apportées pour minimiser le risque de chute avec le Fampyra.

Confidentialité

Toutes les informations personnelles que vous donnerez (nom, adresse ou des informations sur votre santé) et toutes les informations recueillies à la suite des évaluations seront gardées de façon strictement confidentielle. Ces informations seront gardées de façon sécuritaire dans un classeur fermé à clé, situé dans un espace sécurisé à l'intérieur d'un bureau verrouillé, de la Division d'épidémiologie clinique de l'Hôpital Royal Victoria. Nous saisirons toutes les données dans un ordinateur, sans que ne figurent votre nom et vos informations personnelles. Puis nous assignerons un numéro à votre fichier et votre nom ne sera pas sur le fichier. Les informations venant du programme seront sous la forme de tableaux statistiques et résumées dans des graphiques. Aucune information provenant des individus ne sera dévoilée. Les résultats de cette recherche seront peut-être présentés à des réunions ou dans des publications mais votre identité ne sera pas révélée. Votre nom n'apparaitra dans aucune publication ou rapport provenant de cette étude. À l'avenir, les informations que nous avons recueillies seront peut-être utilisées par d'autres chercheurs pour répondre à des questions supplémentaires à propos des personnes atteintes de la sclérose en plaques. C'est pour ces raisons que les données seront gardées durant

25 ans.

J’accepte que les données recueillies lors de cette étude soient utilisées pour d’autres recherches sur la santé des personnes atteintes de la sclérose et plaques, en autant que je ne sois pas personnellement identifié et que les mêmes conditions concernant la confidentialité et l’entreposage des données qui s’appliquent à cette étude soient aussi remplies.

Oui _____ Non

Participation volontaire et droit de se retirer de l’étude

Votre participation à cette étude est entièrement volontaire et vous pouvez décider de vous retirer de l’étude à n’importe quel moment. Si vous décidez de vous retirer de l’étude, vous ne subirez pas de pénalité et ne perdrez pas les avantages aux quels vous avez droit incluant vos soins actuels et futurs. Le chercheur peut arrêter votre participation à ce projet sans votre consentement si selon elle /selon lui, il serait dangereux pour vous de continuer. Nous communiquerons avec vous toute information ou résultats pertinents qui pourraient influencer votre participation. Afin de s’assurer que cette étude suive les règles concernant la recherche, un membre du comité d’éthique de la recherche pourrait vous contacter et/ou vérifier votre fichier de recherche.

Découvertes fortuites

Toute découverte reliée à votre état médical vous sera annoncée à vous et si vous le désirez, à votre médecin également.

Compensation

Vous ne serez pas payé pour avoir participé à ce projet de recherche mais vous serez remboursé jusqu'à 20 $ par visite, pour vos dépenses de stationnement ou de voyagement. Si vous ne pouvez pas venir parce que vous habitez trop loin ou si vous ne vous sentez pas assez bien, nous pouvons nous rendre à votre domicile.

Personnes ressources

La personne en charge de ce projet de recherche est la Dre Nancy Mayo. Si vous avez des questions à propos de cette étude, veuillez contacter la coordonatrice de recherche Carolina Moriello. Vous pouvez la rejoindre aux 514 934-1934, poste 36912. Si vous avez des questions concernant vos droits comme sujet de recherche et que vous aimeriez discuter de vos droits avec quelqu'un qui ne mène pas de cette étude, vous pouvez contacter l'ombudsman de l'Hôpital neurologique de Montréal au 514-934-1934, poste 48306. Si vous avez d'autres commentaires à faire ou inquiétudes à exprimer ou si vous avez besoin d'aide concernant votre participation en tant que sujet de recherche de cette étude, veuillez contacter le comité des patients de l'Hôpital neurologique de Montréal (bureau 354 - n^{o} de téléphone : 514 398-5358).

Consentement du sujet de recherche

TITRE DE L'ÉTUDE : Le rôle de l'exercice physique dans la modification des divers aspects de la santé chez les personnes atteintes de sclérose en plaques

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COORDINATICE DE L'ÉTUDE : Carolina Moriello, B.Sc., M.Sc. (sciences de la réadaptation)

SOURCE DE FONDS : Subvention des IRSC 2012-2015 - n^{o} 258309

DÉCLARATION DU PARTICIPANT

Je, _____, ai pris connaissance de la description de l'étude susmentionnée avec l'un des investigateurs, _____. Je comprends entièrement les procédures, avantages et désavantages de cette étude qui m'a été expliquée. Je consens de manière libre et volontaire à participer à cette étude.

Une copie de ce consentement a été donnée à la personne nommée ici-bas.

_____

(En lettres moulées) nom du participant

_____ _____

Signature du participant (e) Date de la signature

_____

(En lettres moulées) nom de la personne qui a lu le formulaire de consentement

_____ _____

Signature de la personne qui a lu le formulaire de consentement Date de la signature

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